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Heterogeneous Catalysis in Organic Chemistry

Gerard V. Smith and Ferenc Notheisz



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Catalysis in
Organic Chemistry*

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Heterogeneous Catalysis in Organic Chemistry

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PREFACE

The primary aim of this book is to help the experimental organic chemist with heterogeneous catalytic methods for making and breaking bonds. This book has two intentions. First, it is intended to serve the graduate students in organic chemistry who need to round out their education and learn about heterogeneous catalysis and the mechanisms of organic reactions on surfaces. Second, it is intended to aid the bright organic chemists who have prepared the next compound that will greatly improve the position of their company but who have just been informed by their supervisors that they must make their synthetic steps into heterogeneous catalytic steps.

The need to demystify heterogeneous organic reaction mechanisms is vital. In no other field of organic chemistry are the reactions clouded with folklore. Nowhere is there a greater need to clarify a field that is gradually coming out of its empirical age and into its scientific age. But barriers exist. One barrier is the startling lack of any requirements by many journal editors to publish characterization information about the catalysts used in synthetic preparations. This need is ignored in spite of well-documented facts that the structure of the catalyst and its preparation and history influence its activity and selectivity. Not requiring such information propagates the idea that the catalyst is a “black box” about which we know nothing. In fact, without such information, it is impossible to draw complete mechanistic conclusions about surface reactions; consequently, part of the value of published experimental syntheses is irretrievably lost. Another barrier is uninformed and lazy academicians who have labeled this field “black magic,” so many bright students have been misled into believing that nothing is known about the mechanisms of heterogeneous organic reactions. In contrast, and in spite of the fact that this field is in its infancy compared with homogeneous organic reaction mechanisms, much is known. Especially much is known about the mechanisms of making and

breaking bonds between hydrogen and other atoms, and much progress has been made in understanding newly discovered selective oxidations with hydrogen peroxide and titanium-containing molecular sieves.

In a completely practical vein, heterogeneous organic catalysis represents a viable solution to chemical manufacturing pollution problems by accomplishing zero discharge. Only by efficient selective control of products can zero discharge be achieved. Homogeneous reagents may create residues and separation problems, but heterogeneous catalysts can easily be contained and recycled.

Over the years, practical problems in heterogeneous organic catalysis have been solved by an empirical approach guided by experience. Frequently, this approach is successful; however, such a trial-and-error approach is becoming less and less successful as processes become more and more complicated and zero discharge is sought. What is needed is a new generation of organic chemists who understand both the basics of heterogeneous catalysis and the mechanisms of organic reactions on surfaces.

Clearly, this goal will not be met overnight. Rather, a patient compilation and sorting of data coupled with reasonable and likely organic mechanisms must be presented to students to give them the tools with which to predict future processes and solve future problems.

This exciting field of heterogeneous organic catalysis is one of the best-kept secrets of organic chemistry. Regrettably, many bright people do not discover it before they must learn it on a crash basis to keep their jobs. We hope this book will help them and also encourage professors to include heterogeneous catalysis as part of the education of the next generation of organic chemists.

Before closing, we would like to acknowledge events and individuals contributing to this work. This book is an outgrowth of a series of lectures presented by Professor Smith as a short course on catalysis in fine chemicals in the summer of 1994 at Pohang University of Science and Technology (POSTECH) Pohang, Korea. The authors' collaboration started shortly after that and gained momentum during the summer of 1995 in Szeged, Hungary; more progress was made in the first half of 1996 during a sabbatical at POSTECH. For these POSTECH opportunities, Professor Young Gul Kim and his colleagues in the Department of Chemical Engineering and the Research Center for Catalytic Technology are gratefully acknowledged.

Each of us would like to acknowledge special individuals who have made significant contributions to our professional careers and to this book. Professor Smith gratefully acknowledges the advice, encouragement, and mentoring of Samuel Siegel, Robert L. Burwell, Jr., and Paul N. Rylander. Likewise, Professor Notheisz is indebted to Professor Mihály Bartók for his many years of advice, help, and encouragement; and Professor Smith acknowledges with deep appreciation the close scientific association, generous hospitality, and

many stimulating discussions with Professor Bartók. Both of us feel it is important to acknowledge the 18 years of close collaboration between the Department of Chemistry and Biochemistry at Southern Illinois University at Carbondale and the Department of Organic Chemistry of József Attila University in Szeged, of which Professor Bartók was head. Collaborators who have also contributed in different ways to this work are Árpád Molnár, Ágnes Zsigmond, and István Pálinkó from Szeged and Daniel J. Ostgard from Carbondale. Additional contributions to this book were made especially by Dr. R. Song, who identified many references and prepared much of the early material for the 1994 lecture on oxidation, which has been updated and expanded into Chapter 6. Also we acknowledge the help of J. Cheng, F. Shi, and Y. Wang, who along with Dr. Song helped identify and collect many of the references from *The Journal of Organic Chemistry* and *The Journal of the American Chemical Society*. These difficult-to-identify references were obtained the hard way, before computer help, by scanning every page in several years of journals. We acknowledge the valuable contribution of Dr. Ágnes Zsigmond to Chapters 4 and 7, and the technical assistance of József Ocskó. We appreciate Professor R. Bruce King's reading Chapter 7 and suggesting organizational details, and we appreciate readings and advice from Professor S. Siegel, Professor M. Bartók, and Dr. P. N. Rylander.

Of course, the work would likely never have been conceived were it not for the 18-year perfect-match collaboration between our laboratories. For keeping this alive, we acknowledge financial support granted by the National Science Foundation, the U.S.–Hungarian Science & Technology Joint Fund, and the Hungarian Academy of Sciences.

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Introduction to Catalysis

- 1.1. Definitions and Language of Catalysis
- 1.2. Special Considerations for Heterogeneous Catalysis in Liquids
- 1.3. Drawing and Naming Surface Species in Organic Reactions on Surfaces
- 1.4. Hydrogen Sources
- 1.5. Books on Heterogeneous Catalysis of Organic Reactions
- References

1.1. DEFINITIONS AND LANGUAGE OF CATALYSIS

In any field, certain definitions and language must be understood, and the field of catalysis is no exception. Thus we start with some definitions before describing organic reactions on surfaces.

1.1.1. WHAT IS A CATALYTIC REACTION?

A catalytic reaction is one in which more than one turnover or event occurs per reaction center or catalytically active site (that is, the turnover number [TON] is greater than 1). Thus a reaction is not catalytic if it is stoichiometric or if its TON is less than 1. A reaction might indeed involve a true catalyst and under some circumstances be catalytic, but if one or fewer turnovers occur per active site, it is not a catalytic reaction.

1.1.2. WHAT IS A CATALYST?

A catalyst is a substance that increases the rate of a chemical reaction without itself being changed in the process. That is, the substance called a catalyst is the same after the reaction as before. During the reaction, it may become a different entity, but after the catalytic cycle is complete, the catalyst is the same as at the start.

A catalyst is not light or heat or any sort of electromagnetic radiation. These are not substances in the ordinary sense and therefore are not catalysts.

What a catalyst does is change the reaction pathway to one with a lower energy; however, one must remember that the rate of a chemical reaction depends on two things: the rate constant, which contains energy terms (both enthalpy and entropy), and concentration terms.

$$\text{Rate} = k[\] [\]$$

Frequently overlooked is the fact that a heterogeneous catalyst concentrates reactants on its surface and therefore increases their concentrations. This alone causes a rate increase; however, it is not sufficient to call the material a catalyst simply because it concentrates the reactants. It is just something that catalytic substances do as a matter of course while acting as catalysts.

1.1.2.1. Kinds of Catalysts

A rather large array of heterogeneous catalysts have been made, and, undoubtedly, still more different kinds will be invented and made. In this section we mention the different kinds of catalysts and their forms and some of the language used to describe them.

In general, there are heterogeneous, homogeneous, and biological catalysts. This is a somewhat arbitrary division, but serves the purpose of condensing the range of kinds of catalysts. This range is shown in the Fig. 1.1.

1.1.2.2. Forms of Heterogeneous Catalysts

Heterogeneous catalysts come in different forms depending on their use. Some categories frequently referred to are:

- Metals alone
 - Colloidal metals, metallic sponges or blacks, skeletal metals, metal powders, evaporated metal films, electrodeposited films, wires, foils, gauzes
- Metals plus other components
 - Metal oxides, metal sulfides, metal nitrides, metal carbides, metal borides, metal alloys, metallic glasses, molecular sieves, salts, acids

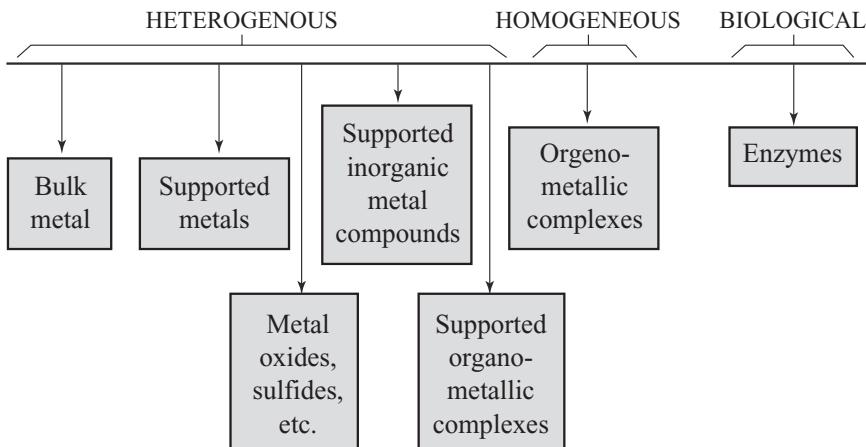


FIGURE 1.1 General kinds of catalysts.

- Supports (carriers)
 - High surface area ($>1 \text{ m}^2/\text{g}$)
 - Porous: natural clays, alumina, magnesia, activated carbon, silica, asbestos
 - Nonporous: silica-alumina, carbon black, titania, zinc oxide
 - Low Surface Area ($<1 \text{ m}^2/\text{g}$)
 - Porous: kieselguhr, pumice
 - Nonporous: ground glass, “alundum” ($\alpha\text{-Al}_2\text{O}_3$), silicon carbide
- Supported metals and metals plus other components
 - Pellets, granules, extrudates, monoliths, and special shapes

1.1.2.3. Preparations of Heterogeneous Catalysts

An excellent review of various catalyst preparation methods has been published,¹ and an earlier book devoted to patent literature preparations of hydrogenation catalysts is available.² Special studies of the formation of metal nanoclusters appeared in 1997 and 1998.^{3–5} What follows is a general summary of methods of preparation.

Colloidal metals are usually prepared by reduction of a salt with a reducing agent, such as phosphorus, acetone, tannin, or carbon monoxide. Platinum metals can also be prepared as finely divided very active “blacks” by reducing the metal salt in an aqueous solution of sodium or potassium borohydride.

Metallic sponges (or blacks) are coagulated colloids formed from the reduction of a salt in an alkaline solution with formaldehyde.

Skeletal metals are formed by leaching away one metal from an intimate alloy of two or more metals. The best example of this is Raney nickel.

Raney nickel, named for its inventor, Murray Raney, is widely used in the industry, chiefly because it is inexpensive and exhibits a wide range of catalytic activities. Essentially, it is prepared by an NaOH leaching of Al from a 50–50 alloy of Ni and Al. Various standard forms of Raney nickel are used, and discussions of these are readily available.^{6,7} Table 1.1 lists some essentials of the preparation.⁸ The Raney process is used to prepare several other metal catalysts.^{7,9,10}

Metallic powders are made several different ways. They can be prepared by reducing salts in a stream of a reducing gas, such as hydrogen; chlorides of metals are commonly used but oxides are used too. Thermal decomposition in a vacuum of metal carbonyls or metal salts of organic acids, such as formates, produces metal powders. Surface areas of such powders are around 1.5 m²/g. Powders can also be made from electrolytic reduction of salts in organic solvents and by atomization of the metal.

Evaporated metal films are prepared by “sputtering” metal wires in a vacuum. They have surface areas from 150 cm²/g up to several m²/g.

Metal sulfides may be prepared by simply passing a sulfur-containing compound over the metal in a stream of hydrogen. Such catalysts are fairly immune to typical nonmetallic poisons.

Nickel borides are usually prepared by reduction of nickel salts with sodium or potassium borohydride. Two types are used. P1 nickel boride is prepared by the reaction between aqueous solutions of nickel salts and a borohy-

TABLE 1.1 Different Raney Nickel Catalysts

Type	Addition temp (°C)	NaOH: Alloy (w/w)	Digestion (°C/time)	Washing process	Relative activity
W1	0	1:1	115/4 h	H ₂ O/EtOH	Lowest
W2	25	4:3	100/8–12 h	H ₂ O/EtOH	Medium
W3	-20	4:3	50/50 min	H ₂ O/EtOH	High
W4	50	4:3	50/50 min	H ₂ O/EtOH, H ₂	High
W5	50	4:3	50/50 min	EtOH	High
W6	50	4:3	50/50 min	H ₂ O, H ₂ /EtOH	Highest
W7	50	4:3	50/50 min	H ₂ O/EtOH	High
W8	0	1:1	100/4 h	H ₂ O/dioxane	Lowest

dride, and P2 is prepared from the reaction between 95% ethanol solutions of nickel salts and a borohydride.

Metallic glasses are alloys that have been cooled so rapidly that no crystal structure has had time to develop, for example, Pd-Si, Pd-Ge, Fe-Ge (Metglas). These materials are characterized by the absence of sharp lines in their X-ray spectra.

The most catalytically active metals are Ni, Pd, Pt, and Rh. Nickel is used extensively in hydrogenation. It is frequently used in skeletal form as Raney nickel (Ra-Ni or RNi). The hydrogenation of almost all hydrogenatable functional groups can be accomplished over some form of Ra-Ni. Ra-Ni is also useful for desulfurization of organic compounds, but this is a stoichiometric reaction, not a catalytic reaction.

Palladium is good for hydrogenations of most unsaturations except benzenes. It is frequently used by synthetic organic chemists for hydrogenolyzing off protecting groups. It is especially useful for the half-hydrogenation of acetylenes.

Platinum catalyzes the hydrogenation of most functional groups. It will not catalyze the hydrogenation of esters, acids, and amides.

Rhodium is good for the hydrogenation of most functional groups with a minimum of hydrogenolysis activity.

1.1.2.4. Characterizations of Heterogeneous Catalysts

Another term in the language of catalysis is *texture*. This a general term referring to a variety of physical characteristics. A simple definition is *the detailed geometry of the void space in the catalyst particles*. Essentially, it is manifested in seven measurements. These are:

1. Specific surface area (square meters per gram or square centimeters per gram): the sum of the external and the internal surface areas.
2. Specific porosity: the accessible pore void space per unit mass.
3. Pore shape: difficult to describe except in cases of regular structures such as zeolites.
4. Pore size distribution: the distribution of the pore volume versus the pore size.
5. Mean pore size: either the pore size distribution or the specific porosity divided by the specific surface area. Pores are divided into three categories: macro (30–50 nm), meso (intermediate size), and micro (less than 2 nm).
6. Shapes and sizes of agglomerates of particles: for example, pellets, granules, and extrudates.
7. Particle size distribution: for supported metals; sometimes measured from electron micrographs and sometimes calculated from the measured number of

surface atoms divided by the total number of atoms; expressed as percent dispersion (%D), percent exposed atoms, or fraction exposed (FE); perhaps the most widely cited data in the literature.

The effects of particle size on catalytic reactions are now well known and in part understood.¹¹ Boudart has defined two classes of heterogeneous catalytic reactions: structure sensitive, those whose rates per exposed atom (we are speaking of orders of magnitude here) depend on the particle size, such as hydrogenolysis of C–C bonds, and structure insensitive, those whose rates do not, such as the dehydrogenation of cyclohexane to benzene.¹¹ Since the relative populations of exposed atoms at vertices, edges, and planes of metal crystallites change as the particle size changes, structure-sensitive reactions are believed to occur on active sites whose populations change with the particle size. On the other hand, structure-insensitive reactions seem to occur on all (or most) exposed atoms, and therefore their turnover frequencies (rates per exposed atom) are not influenced much by particle size. (One theory suggests that a carbonaceous layer covers catalyst particles, and since this is uniform over all the catalyst particle, certain structure insensitive reactions occur on this layer and do not depend on the nature of the metal atom underneath.¹²) Because of this relationship between catalytic activity and particle size, it is easy to understand why some measure of particle size distribution is an important parameter in catalysis.

Measurements of particle size distributions can be made from electron micrographs by simply measuring the diameter of each individual particle in the micrograph. This is tedious, time consuming, and subject to some error. For example, the smallest particles, when slightly out of focus, may appear larger than they actually are. Unless the plane of the particle is exactly in focus, the particle will be slightly distorted. So electron micrographs may not give the best size data for the smallest crystallites on a supported metal catalyst.¹³

A more common measurement of particle size distribution is chemisorption. In this method a gas is allowed to adsorb on the exposed metal atoms and the number of gas atoms chemisorbed is divided by the total number of metal atoms. This gives an average ratio of the exposed surface metal atoms to the total metal atoms (N_s/N_t), assuming that the number of gas atoms chemisorbed per exposed metal atom is known. In the case of hydrogen chemisorbing on noble metals, one hydrogen per metal atom is assumed. Sometimes this ratio changes as the fraction of atoms exposed (FE) approaches 1.¹⁴ When chemisorbing hydrogen on Pd, care must be taken to eliminate the Pd– β -hydride phase. In the case of carbon monoxide chemisorption, the number of carbon monoxide molecules per metal atom depends on the conditions.

Once the FE, or percent dispersion, is known, a simple calculation converts dispersion to average particle size. However, this calculation is based on the

assumption that the particles have a certain regular shape, such as octahedral or cubooctahedral, which, of course, they do not. The best electron micrographs indicate that the smallest particles have spherical shapes, which means that a cubo-octahedron or a truncated octahedron approximates the likely shape of the smallest supported metal crystallites.¹⁵ An approximate particle size can be estimated by the inverse of the FE¹² (Fig. 1.2). That is, at 50% dispersion (FE) the particle size in nm is $1/0.5 \cong 2\text{nm} \cong 20\text{\AA}$. However, it must be remembered that these are only average values and do not reveal the distribution of particle sizes. As mentioned at the end of this section, certain small particles may be significantly more catalytically active than other sizes.

A variety of physical methods for characterizing catalysts have been developed. Descriptions of these and their meaning can be found in many books on catalysis and surface science. Most of them give information about the arrangements and nature of surface atoms but do not particularly identify or divulge information about the catalytically active site. The active site is where the chemical action takes place. It may be one atom or a cluster of atoms and, as some evidence suggests, may change its nature during the catalytic reaction.¹⁶

Ideally, those molecules that are involved in the catalytic reaction should be the best characterizers of catalytic sites. Indeed, the path of the development of organic reaction mechanisms is paved with clever examples of stereochemistry and isotopic substitution that reveal the nature of activated complexes and intermediates and allow the unambiguous interpretation of the stereorelations

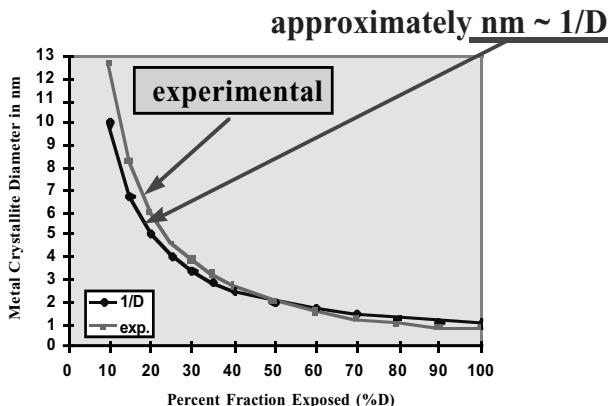


FIGURE 1.2 Estimation of particle size from the fraction exposed (FE). Dispersion (D) = percentage of atoms exposed, i.e., number of surface atoms/total number of atoms. Usually designated by %D, but sometimes by FE or %FE.

between each atom during the progress of many reactions. Not so in heterogeneous catalysis. Uses of such techniques are still in their infancy and offer great opportunities for enterprising chemists and chemical engineers. Chemical reactions for characterizing catalytic surfaces have just started to be developed.

What is now a classic example of the use of chemical reactions to characterize a catalytic surface is the work of Sinfelt and co-workers¹⁷ in which both structure-sensitive and structure-insensitive reactions were used to characterize Cu-Ni catalysts over their complete range of relative concentrations. As the Cu concentration in a Cu-Ni alloy increases to 100%, the rate of cyclohexane dehydrogenation (structure insensitive) remains constant until the very highest concentrations of Cu, whereas the rate of ethane hydrogenolysis (structure sensitive) continuously decreases. Since cyclohexane dehydrogenation presumably occurs on active sites of single Ni atoms, its rate remains constant until the concentration of Cu on the surface becomes high enough to severely dilute the Ni. On the other hand, ethane hydrogenolysis depends on active sites that are Ni clusters of a certain minimal size (the popular term for them today is *ensembles*). The population of these Ni ensembles on the surface becomes rapidly decreased as Cu atoms are incorporated into the surface.

Another way to characterize metal surfaces with a chemical reaction is the single turnover (STO) procedure of Augustine.¹⁸ Essentially this method uses the gas-phase hydrogenation and isomerization of 1-butene to measure different kinds of sites on noble metals. First the catalyst is “aged” by running the hydrogenation of 1-butene over it for some period of time. Then it is purged with flowing He and subjected to pulses of hydrogen sufficient to “saturate” the surface. This strongly adsorbed hydrogen is then abstracted by a pulse of 1-butene, the products from which are analyzed by gas chromatography. Any adsorbed butenes remaining on the surface are removed by a second pulse of hydrogen. Based on the mixture of products, 1-butene (presumably unreacted), *cis*- and *trans*-2-butenes, and butane, and also based on the assumption that hydrogen does not migrate on these metal surfaces, active sites are assigned to each product and are presented as fractions of the exposed metal atoms. Augustine and Thompson²⁰ attempted to correlate their data with Pt single crystal data of Somorjai and co-workers¹⁹ (Fig. 1.3) by running cyclohexane dehydrogenation studies on their supported Pt catalysts (Fig. 1.4). Indeed, catalysts that gave the highest amount of cyclohexane dehydrogenation also gave the highest amount of hydrogenation, so the conclusion is that the same sites catalyze both reactions. Further analogy to the single crystal work suggests that these sites are corner sites. The sites are labeled according to the nomenclature introduced by Siegel and associates.²¹ Corners are labeled 3M sites, edges, 2M , and planes, 1M . This nomenclature has been expanded by Augustine to include 3M_l and 3M_R sites.

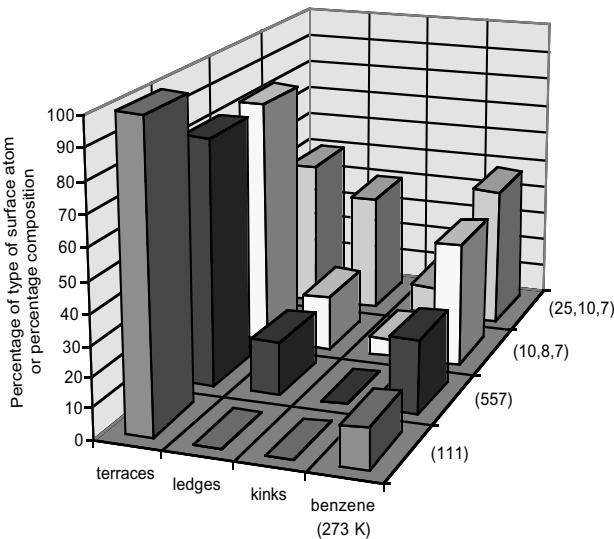


FIGURE 1.3 Data for dehydrogenation of cyclohexane to benzene over several Pt single crystals from reference 19.

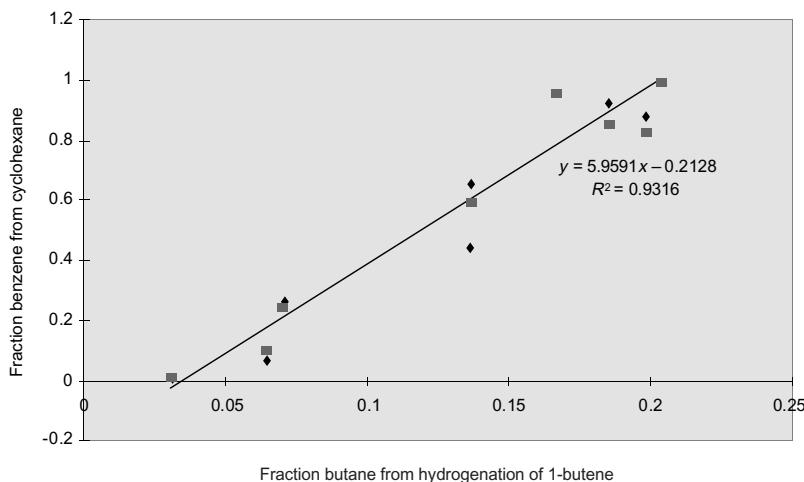


FIGURE 1.4 Benzene versus butane. Correlation of the percentage of benzene obtained from dehydrogenation of cyclohexane using 1-μl (◆) and 2.5-μl (■) slugs in a plug flow reactor to the fraction of butane obtained from 1-butene hydrogenation by the single turnover method over the same Pt catalysts supported on controlled pore glass. (Data replotted from reference 20. One point is omitted because the sum of sites adds to more than the fraction of exposed Pt.)

In Fig. 1.3,¹⁹ the relative rate of formation of benzene on ledge atoms is approximately 5.5 times as fast as the rate on terrace atoms, and on kink atoms it is approximately 23 to 27 times as fast. The classic mechanism for dehydrogenation of cyclohexane has been assumed to occur on terrace (plane) sites. In fact, cyclohexane dehydrogenation occurs slowly on terrace sites in the absence of either ledge (111) or kink (111) and (557) sites. But there does not appear to be a geometrical reason for the dehydrogenation to occur faster on either ledge or kink sites, and it may be that when ledge and kink atoms are adjacent to terrace atoms, or nearby, the abstracted hydrogen atoms may escape faster from the vicinity of the benzene. Such an explanation is reasonable in view of the fact that hydrogen dissociates much faster on defect-like sites such as steps (ledges) and corners (kinks)^{22–25} and the reverse process, desorption, occurs most readily on these sites too.²²

Still another way to characterize metal surface sites by a chemical reaction is with the unique molecules (+)- and (−)-apopinene (Fig. 1.5).^{25–28} The apopinenes are an enantiomeric pair of molecules with a double bond sterically hindered on one side by a *gem*-dimethyl group. During hydrogenation, each enantiomer may hydrogenate to the saturated symmetrical apopinane or isomerize to its enantiomer, which will have the same reactivity on a symmetrical surface (Scheme 1.1).

The ratio of double bond isomerization and addition occurring during the liquid-phase hydrogenation of both (+)- and (−)-apopinene has been mea-

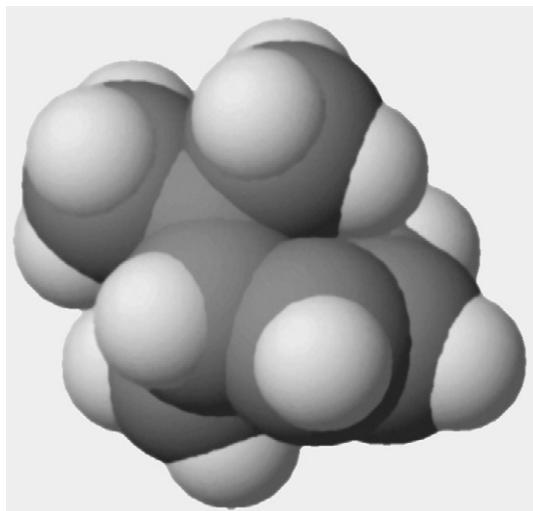
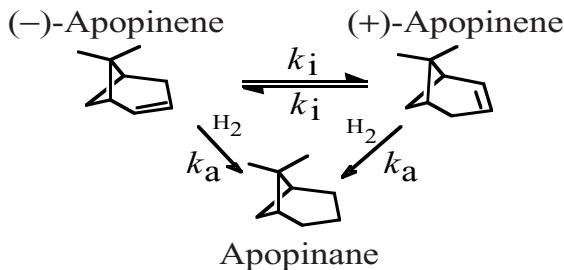
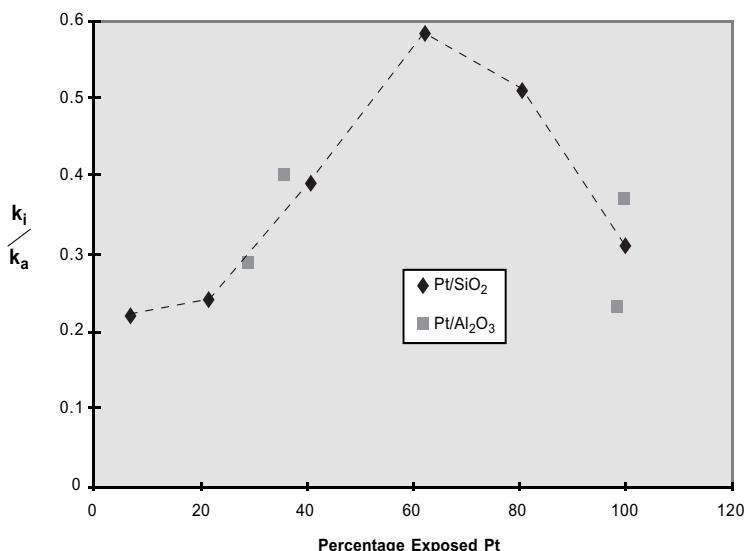


FIGURE 1.5 (−)-Apopinene.



SCHEME 1.1 Hydrogenation and double bond migration of apopinenes.

sured over a wide range of dispersed Pt and Pd catalysts and found to go through maxima around 60%D (Fig. 1.6). Since both isomerization and addition independently go through maxima at the same dispersion, and since edge sites go through maxima too, the conclusion is that edge sites and/or the sites nearby catalyze both addition and isomerization. The size of the 60%D crystallite (approximately 2.3-nm particle size) may be optimal for utilizing the maximal number of plane sites for hydrogenation or the maximal number of plane

FIGURE 1.6 Correlation of the ratio of isomerization to the addition of apopinenes with the fraction exposed (%D) Pt/SiO₂ and Pt/Al₂O₃.

sites for isomerization.²⁹ The rate at which hydrogen migrates onto planes after adsorption and dissociation on edges and corners^{22,24,26} may limit the hydrogenation ability of crystallites with large planes relative to edges and corners. On the other hand, the smaller planes on the crystallites with larger dispersion (smaller sizes) accompanied by more edge and corners are limited by the rate at which alkene can adsorb, hydrogenate, and desorb. So rate maxima as a function of particle size should be observed when the rate of the surface reaction is about the same as the rate of hydrogen adsorption–dissociation–migration. The position of the maxima depends on the balance between the rates of the reactions and the rate of hydrogen dissociation and migration.

Edge sites catalyzing addition appears to conflict with previously presented STO evidence, which concluded that corner sites catalyze addition. However, 60%D perfect cubo-octohedra (we do not believe that perfect crystallites exist in working catalysts; this example is for illustration) exhibit a (111) face similar to that shown in Figure 1.9 (Section 1.3), and every edge atom is adjacent to a corner atom as it is always adjacent to plane atoms, so too simple an interpretation of these results, such as postulating that only edge or corner atoms catalyze addition, should be avoided. Likely, combinations of these sites are more favorable to addition or isomerization than others, which do catalyze but not as efficiently. Also the STO and the apopinene conclusions appear to conflict with chiral modifier studies pointing to plane sites as enantioselective hydrogenation sites (Chapter 3). In this latter case though, the catalyst is poisoned by the chiral modifiers, so the results may not be comparable. On the other hand, carbonaceous deposits occur on step sites (ledges) during cyclohexane dehydrogenation³⁰ and may also occur during the aging process in the STO method. Likewise, carbonaceous deposits could accumulate during any of these processes, including hydrogenation of the apopinenes. Nevertheless, such conflicts show the complexity of the problem and the difficulty of characterizing active sites on surfaces. Probably, all the atoms on metal surfaces catalyze several phenomena at different rates during hydrogenation and the result is a confusing picture of the nature of the catalytic surface.

An interesting recent study sheds new light on the particle size effect in catalysis. This study involves Au, which has the interesting property of being a very poor catalyst in large particle sizes but a good catalyst in small particle sizes.³¹ Goodman and coworkers³² have shown that maximal catalytic activity of Au is associated with a quantum size effect that correlates with the thickness of the Au layer. A metal-to-nonmetal transition occurs at a two-atom thickness (particles 3.5 nm in diameter by 1.0 nm thick, approximately 300 atoms).³² A similar transition occurs in Pd (particles 3.0 nm in diameter by 1.0 nm thick, approximately 300 atoms),³³ which agrees with an earlier study in which Ni layered synthetic microstructures exhibited a rate maximum at a Ni thickness of 3.0 nm.³⁴ As metal particles become smaller, not only do their

fraction of edges go through maxima, but also a metal-to-nonmetal transition occurs (quantum size effect). This latter property may play an important role in catalysis.

1.1.2.5. The Chameleonic Surface

A quick survey of the literature reveals a confusing picture of the mechanism or mechanisms of surface reactions and the role or roles of the catalyst surface. A contributing factor is that different investigators are approaching surface reaction mechanisms from different points of view. In a very general way, there are three groups of investigators.

First there are the physical chemists, chemical engineers, and surface scientists, who study mainly nonpolar hydrocarbon reactions on clean and relatively clean metals and metal oxides. These have been the traditional studies formerly driven by the petroleum industry and now driven by environmental concerns. These workers typically treat the surface as a real entity composed of active sites (usually not identified, but believed in). These investigators typically, although not always, interpret mechanisms in terms of radical reactions on metals and in terms of acid-base reactions on metal oxides.

Second, there are the organic chemists, usually working in the fine chemicals and specialty chemicals industries but also working as students, postdoctoral fellows, or professors of synthetic organic chemistry in academia, who treat the catalyst as a reagent that is added to a reaction mixture to get it to proceed. In the synthetic organic chemistry laboratories of academia, the reactions are typically hydrogenolyses of polarized bonds. In the fine and specialty chemicals industries the reactions vary, but important reactions are hydrogenations, dehydrogenations, amoxidations, and oxidations. This group of workers tends to try to interpret mechanisms in terms of typical organic reaction mechanism with the catalyst acting as a sort of solvent. Hydrogenations are traditionally treated as radical reactions involving hydrogen atoms generated on the surface by homolytic dissociation of dihydrogen. Hydrogenolyses on metals, however, resemble typical S_N1 and S_N2 reactions, which means hydride ions may be involved.

Investigators in the third group come from all sorts of backgrounds and try to interpret surface reactions in terms of organometallic reaction mechanisms. They see many analogies between surface-catalyzed reactions (heterogeneous catalysis) and organometallic-catalyzed reactions (homogeneous catalysis). Therefore, their interpretations tend to view the active catalytic site on a surface as a single atom surrounded by other atoms, metal or nonmetal (such as oxygen); this resembles the ligands surrounding the metal atom of a homogeneous catalyst. Recent innovations by this group are the studies of metal clusters, which more closely resemble a very small metal crystallite.³⁵⁻³⁷

Of course, there is much overlap between these general categories of investigators, but the point is that the different investigators tend to view the catalytic surface from their own position. All the groups have valid points to make and their experimental data have meaning. Catalytic surfaces do seem to be capable of performing a variety of actions but one must use caution in transferring data from one experimental setting to another. In some ways what we have is the catalytic analogy of the description of an elephant by a group of blind people. One might ask, Is there consilience³⁸ in catalysis or does each viewpoint have truth in its own right³⁹ and, therefore, a unified theory of surface catalysis is unattainable? In many respects catalysts are like chameleons. They seem to transform their surfaces according to their environment.⁴⁰ Consequently, one of the big challenges of the next generation of catalytic scientists is to bring some order to descriptions of the chameleonic catalytic surface.

1.1.2.6. Substituent Effects in Heterogeneous Catalysis

A number of workers have investigated substituent effects and linear free energy relationships in heterogeneous catalysis, and an excellent review of this work has been contributed by Kraus.⁴¹ With respect to the effect of alkyl substituents on the rate of hydrogenation of C=C bonds, Lebedev and coworkers reported in 1925 that the rate is decreased by the number of substituents on the carbons.⁴² Most linear free energy relationship studies have been performed with alkyl substituents and good correlations have been found with σ^* ; studies with polar groups find only small electronic effects.⁴¹ This latter fact may occur because of the binding character of the double bond.

For example, in the deuteriumation of para-substituted styrenes, deuterium distributions in the resulting ethyl group vary little, as shown in Table 1.2.⁴³ Likewise, deuteriumation of pentafluorophenyl styrene and pentafluorophenyl α -methylstyrene yield virtually identical deuterium distributions as their perhydro family members.⁴⁴ Similarly, deuteriumation of *para*-nitrophenyl acrylate produces the same deuterium distributions as methyl acrylate.⁴⁵ Analogy to Zeise's salt suggests that the C=C bond may be bonded to the surface through a π -bond in which electronic effects are canceled by the two types of bonds, bonding and antibonding. A recent attempt to attribute polar effects to deuterium distributions⁴⁶ may also be interpreted in terms of an anchoring effect, which is, of course, merely a special substituent effect on surfaces.

1.1.2.7. The Anchoring Effect

The anchoring effect, which is also sometimes called the *haptophilic effect*, results from the fact that certain groupings increase the strength of adsorption of

TABLE 1.2 Effects of *para* Substituents during Deuteriumation of Styrenes

<i>p</i> -R-C ₆ H ₄ -CH=CH ₂ + D ₂ + catalyst → R-C ₆ H ₄ -C(H,D) ₂ -C(H,D) ₃ + catalyst			
p-R ^a	Catalyst	α-D	β-D
CH ₃ O-	Pd/C	1.47 ± 0.03	0.51 ± 0.02
H-	Pd/C	1.41 ± 0.02	0.58 ± 0.03
NO ₂ -	Pd/C	1.49 ± 0.06	0.51 ± 0.05
CH ₃ O-	Pt/C	1.34 ± 0.03	0.63 ± 0.02
H-	Pt/C	1.32 ± 0.04	0.68 ± 0.06
NO ₂ -	Pt/C	NO ₂ -reduces before C=C	
CH ₃ O-	Rh/C	1.43 ± 0.03	0.49 ± 0.03
H-	Rh/C	1.46 ± 0.01	0.54 ± 0.01
NO ₂ -	Rh/C	1.50 ± 0.02	0.50 ± 0.03

^a Hammett σ values: CH₃O-, -0.268; H-, 0.000; NO₂-, 0.778.

reacting organic molecules. Phenyl groupings as well as oxygen- and nitrogen-containing groupings seem to do this.^{44,47}

1.2. SPECIAL CONSIDERATIONS FOR HETEROGENEOUS CATALYSIS IN LIQUIDS

Most reactions run by organic chemists are in the liquid phase. Consequently, organic chemists of the heterogeneous catalytic variety have developed special techniques and apparatuses for running catalytic reactions in the liquid phase.

1.2.1. REACTION APPARATUSES

For organic chemical laboratory work, reaction apparatuses are designed to handle small amounts of reactants. Since the most frequently run catalytic reactions use hydrogen gas, these apparatuses are designed to contain and measure the hydrogen gas as well as contain the liquid components. The heterogeneous catalyst is kept suspended in the liquid phase by agitation. Various methods are used to agitate the reaction mixture and ensure intimate mixing of the three phases. This is critical for the production of meaningful results that can be interpreted in a chemical sense. Insufficient agitation results in

mass transfer problems that produce rates that are not due to the chemical reaction alone.

1.2.2. IDENTIFICATION AND CORRECTION OF RATE PROBLEMS

Many heterogeneous catalytic organic reactions are run in the liquid-phase, and liquid phase reactions present special mass transfer problems. Diffusion barriers exist between the gas and the liquid and between the liquid and the solid, so there are gas–liquid–solid diffusion barriers. When these barriers are too large, the true chemical rate at the surface is not observed.

A frequently overlooked situation in heterogeneous catalysis of organic reactions in the liquid phase is hydrogen deficiency at the catalytic sites. Deficiency of organic reactant at the active site is rare because its concentration in solution is high relative to that of hydrogen. Inadequate mixing and transfer of reactants between the gas, liquid, and solid phases can render experimental rate data meaningless.

Mass transfer problems can be addressed in several simple ways: by varying the stirring rate, varying the amount of catalyst, varying the temperature, grinding, and poisoning titration. Several of these are discussed in an article by Roberts.⁴⁸

Agitation, or stirring, can have a pronounced effect on mass transfer. Adequate mixing of reactants, gas, liquid, and solid is essential for observation of the chemical rate. Assurance of adequate stirring can be determined by running several experiments at different agitation rates. If no effect is observed (no rate change), then no significant gas–liquid transport problems are likely to exist. If some rate change is observed, then the reaction should be run under agitation rates that produce a constant maximal reaction rate as the agitation rate is increased. However, if reaction conditions are changed (temperature and/or pressure), the effect of the agitation rate must again be determined.

The amount of catalyst may influence the reaction rate because too much catalyst catalyzes the surface chemical reaction so fast that reactants are depleted in the liquid phase and diffusion of reactants controls the rate. Determination of the onset of diffusion control can be made by running several experiments at constant stirring rates with increasing catalyst weights. Initially, the rate increases in direct proportion to the catalyst weight (the increase in catalytic sites) until diffusion takes over. Then the rate per weight of catalyst levels off and becomes constant. The chemical rate is more likely to be observed at catalyst weights and stirring speeds in the region of the initial linear increase.

Measuring the rate of the catalytic reaction at different temperatures and determining the activation energy through an Arrhenius plot may reveal mass

transfer problems. In general, an activation energy less than 5 kcal/mol is strong evidence of diffusion control, either gas–liquid, liquid–solid, or both. On the other hand, an apparent activation energy of more than 10 kcal/mol is strong evidence of control by the chemical reaction at the surface. However, the importance of pore diffusion cannot be determined by this method.

The occurrence of pore diffusion can usually be determined by simply grinding the catalyst into smaller and smaller particles. If the rate per gram of catalyst increases as the particles become smaller and smaller, then pore diffusion is likely to be occurring. This effect is due to the fact that the pore lengths are decreased by the catalyst particles being ground into smaller and smaller pieces. Eventually, the pores become short enough that the reactants can readily diffuse in and out of them faster than the chemical reaction occurs on the surface.

Yet another way to detect mass transport problems is with a newly developed poisoning technique.^{24,26,49,50} This technique works for liquid-phase hydrogenations and possibly for other reactions that are poisoned by CS₂. It takes advantage of the fact that CS₂ poisons Pd and Pt linearly until all reaction stops. If mass transfer problems exist, the initial linear decrease in rate occurs at a slope less steep than the slope of the chemically controlled rate (Fig. 1.7). If no mass transport problems exist, the rate decreases linearly from the start with no change in slope. Therefore a plot of rate versus amount of CS₂ reveals the existence or absence of mass transport problems.⁴⁹

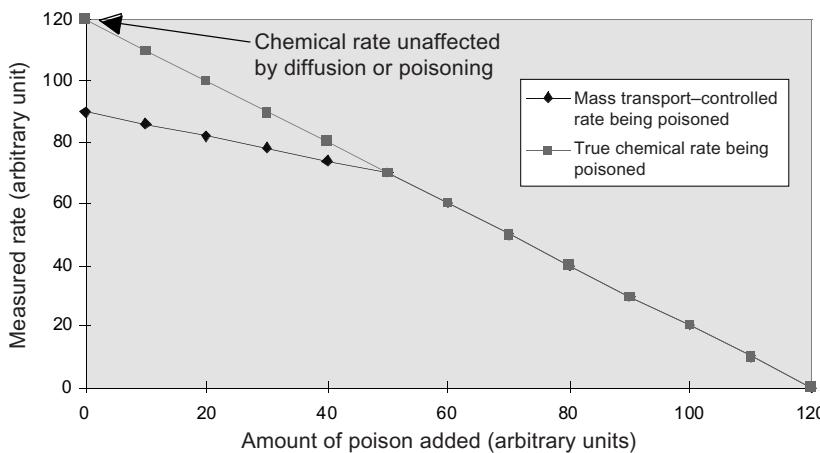


FIGURE 1.7 Effect of poisoning on the mass transport–controlled rate compared with the effect of poisoning on the true chemical rate.

1.2.3. SOLVENTS

Solvents regularly used in organic reactions are used in heterogeneous catalysis of organic reactions. When solvent information is known, it accompanies other reaction information in each chapter. It must be remembered, however, that the solvent may interact with the catalyst surface and be converted into something undesirable or may combine with or modify one or more of the reactants. The example in Table 1.3⁵¹ shows the rather minor effect of solvents on the stereochemistry of hydrogenation of the exo double bond in a spatane precursor.

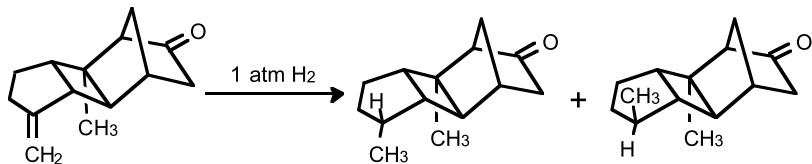
1.2.4. REACTION CONDITIONS

When reactions are run in the liquid phase, certain temperature limitations exist. However, if pressure is increased, temperature can frequently also be increased.

1.2.5. WHAT ABOUT POISONS?

One of the amazing things about heterogeneous catalysts is that they work in spite of the fact that the catalysts are exposed to all sorts of potential poisons in the laboratory atmosphere. Apparently, when hydrogen is introduced, it cleans the surface of the catalyst enough for the reaction to proceed.⁵²

TABLE 1.3 Influence of Solvent on Hydrogenation of an exo Double Bond



Solvent	Catalyst	Yield (%)	Yield (%)
Acetonitrile	PtO ₂	90	10
Ethyl acetate	PtO ₂	88	12
Ethanol	PtO ₂	86	14
Ethyl acetate	Pt/C	85	15
Acetic acid	PtO ₂	83	17
Benzene	(Ph ₃ P) ₃ RhCl	67	33

Occasionally, however, for no obvious reason heterogeneous catalytic reactions involving hydrogen (hydrogenations, hydrogenolyses) do not proceed. The usual excuse is that a poison is strongly adsorbing on the active sites on the catalyst surface and preventing reactions from occurring. Of course, physical possibilities, such as the temperature, pressure, and shaking rate, should be checked first. Sometimes a poison may be introduced into the reaction vessel or into the connecting lines. But typically the problem is caused by a poison present in the reactant. Sometimes it is possible to remove this poison by simply shaking the reaction mixture with the catalyst or with Ra-Ni before placing it in the reactor. In that strategy, the poison adheres to the catalyst and is removed from the reaction mixture. However, remember that Ra-Ni contains considerable available hydrogen (approximately 100 ml/g) so if only a small amount of reactant is available, shaking it with Ra-Ni might hydrogenate all of it. Sometimes just adding more catalyst will get the reaction going. In such case, the amount of poison is small and poisons only some but not all of the catalyst surface.

Avoiding poisons is aided by scrupulous attention to cleanliness.

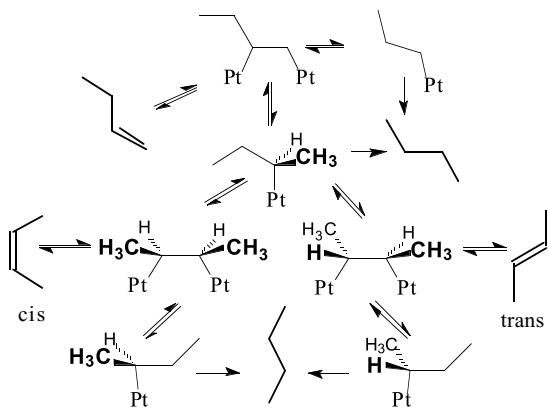
1.2.6. SAFETY

Many heterogeneous catalysts used with hydrogen may be pyrophoric. Especially, Raney catalysts, such as Ni, Co, and Cu, are pyrophoric if allowed to dry. So caution should always be used when filtering catalyst from a reaction mixture or when allowing a catalyst that has been exposed to hydrogen to come in contact with air or a source of oxygen. They may get very hot and ignite their surroundings. Instead, keep them wet with solvent or, better, with water.

Raney catalysts are usually shipped under water, so if water is an undesirable solvent, it must be displaced by appropriate washings with the desired solvent. Care should be taken when using ketones. Special care should be taken with nitrobenzene, which undergoes highly exothermic hydrogenation at room temperature (see Section 2.1.3).⁵³

1.3. DRAWING AND NAMING SURFACE SPECIES IN ORGANIC REACTIONS ON SURFACES

Without substantial artistic talent, depicting organic reaction mechanisms on surfaces is difficult. Over the years, a variety of methods have been invented and used with differing successes. Frequently used is an asterisk, an M, or sometimes the symbol of the metal catalyst to designate a surface catalytic



SCHEME 1.2 The classic mechanism of hydrogenation.

atom as shown in an example of the classic mechanism for hydrogenation in Scheme 1.2. Note that H is not shown.

However, such ambiguous schemes disregard the role of the metal surface and the steric relationship between the organic surface species and the surface atoms. Moreover, they suggest that only one or two surface atoms are involved in the reaction. This notion comes from analogy to homogeneous catalysis in which a single metal atom (surrounded by appropriate ligands) conducts catalysis. However, it is likely that groups of surface atoms are involved in heterogeneous catalysis.

Likewise, showing a generic surface such as a flat plane.⁵⁴ without emphasizing the individual atoms is awkward, as shown in Fig. 1.8.

Consequently, we favor a method that shows a view of organic molecules on a surface drawn as close as possible to their relative sizes. Two such surfaces, a face centered cubic (fcc) (111) and an fcc (100), are shown in Fig. 1.9, in which ¹M, ²M, and ³M represent plane, edge, and corner sites, respectively, according to the nomenclature invented by Siegel and associates.²¹ These are



FIGURE 1.8 Depictions of surfaces as generic flat planes.

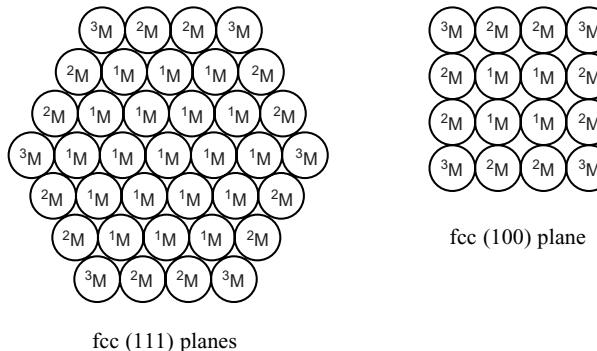


FIGURE 1.9 (111) and (100) faces of a face-centered cubic (fcc) regular cubooctahedron containing approximately 500 atoms with a dispersion of approximately 60%.

not the only surfaces active for catalytic reactions, but they seem to be the ones on which many activities occur. As can be seen, they exhibit edge and corner sites, which are implicated in certain reactions. Assuming these are Pt or Pd atoms, which are nearly the same size, C–C bonds are approximately 68% of their diameter. So adsorbed alkenes would fit as shown in the projections in Fig. 1.10 along with their suggested nomenclature.

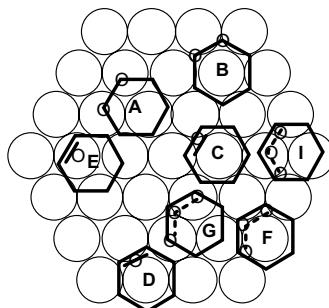
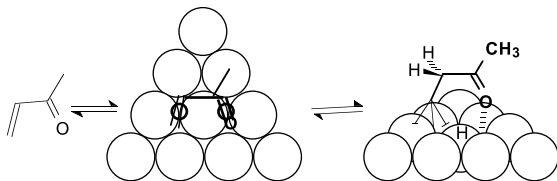


FIGURE 1.10 Various possible surface species on a Pt or Pd (111) surface. A and B represent possible locations of 1,2-di- σ -C_{1,2}-cyclohexane, and C, D, and E represent possible locations of π -complexed π-C_{1,2}-cyclohexene. Full complements of hydrogens are assumed at each angle and terminal that is not either σ - or π -bonded to a surface site as indicated by a small circle. Half-hydrogenated states, which are mono- σ -C_n-adsorbed species (where n is the number of the carbon attached to the surface), would be represented by one small circle at the carbon bonded to a surface site. F, G, and I represent possible locations of π-C_{1,3}-cyclohexene. F shows the three carbons of the π-allyl moiety adsorbed in three adjacent three-point hollow sites and G shows it over one three-point hollow site, whereas I shows adsorption over the approximate tops of three adjacent atoms. (Note: Label H is not used to avoid confusion with hydrogen, which is not shown.)



SCHEME 1.3 Possible three-dimensional depiction (right structure) of methyl vinyl ketone adsorbed as a butylidyne in one three-point hollow with the oxygen bonded at another three-point hollow.

Four kinds of adsorbed species are postulated to result from the adsorption of alkenes on noble metals, π -complexed double bonds, π -complexed π -allyl species, mono- σ -bonded alkanes, and di- σ -bonded alkanes. Distinguishing among these is difficult and has been the subject of much speculation. For example, alkenes may adsorb either by π -complexing or by di- σ -adsorption, and π -allyl species are thought to occur readily on Pd but not so readily on Pt.⁵⁵

Although these projections of organic molecules on surfaces deemphasize the stereochemistry of the adsorbed species, they are easy to draw and properly reveal the relative sizes and locations of surface atoms and organic species. When greater stereochemistry is desired, three-dimensional drawings may be made as shown in Scheme 1.3.

1.4. HYDROGEN SOURCES

1.4.1. GENERAL

To run a heterogeneous hydrogenation or hydrogenolysis, one must produce a hydrogen species on the surface. This is usually accomplished with dihydrogen gas, which dissociates on many catalytic surfaces to produce hydrogen atoms or ions by homolytic or heterolytic splitting. In addition to hydrogen gas, hydrogen may be obtained from various molecules that give up their hydrogens (undergo dehydrogenation) to a hydrogen-deficient surface. This hydrogen can then be used for hydrogenation or hydrogenolyses reactions. These hydrogen transfer reactions are discussed in Section 2.1.4.1 and can be useful when gaseous hydrogen must be avoided. One interesting aspect of this process is the use of a hydrogen-permeable membrane, usually Pd or a Pd alloy, to separate the hydrogen donor and the hydrogen acceptor (Section 2.1.4.2). In this configuration, hydrogen atoms are given up from the donor molecule on one side of the membrane and the hydrogens diffuse through the membrane to the other side, where they react with the acceptor molecules.

1.4.2. WHERE IS THE HYDROGEN?

Dihydrogen dissociates on the surfaces of many metals to form two adsorbed hydrogen atoms. The large energy of the bond between the hydrogens is virtually completely replaced with the energy of formation of the two hydrogen-to-metal bonds. Traditionally, these atoms have been considered attached atop surface metal atoms at locations of their “dangling bonds” called *coordinative unsaturations*. Plane, terrace, or face atoms, ¹M Siegel site, are envisioned as having one coordinative unsaturation; edge, ledge, or step atoms, ²M Siegel site, have two; and corner, kink, or vertex atoms, ³M Siegel site, three. This analogy comes from organometallic homogeneous catalysis, in which catalysis is usually carried out by a single metal atom surrounded by ligands, some of which may be displaced by solvent, reactants, and hydrogen atoms at different times during catalysis. On the metal surface the hydrogens are usually depicted as readily moving from atom to atom across the metal surface face.^{56, 57} However, at least one investigator assumes no movement.⁵⁸

The basis for the rapid movement depiction comes from rapid and extensive metal-catalyzed exchange between the hydrogens in hydrocarbons and deuterium gas and from the rapid exchange between hydrogen and deuterium over metals. The basis for nonmovement comes from temperature programmed desorption (TPD) studies of hydrogen adsorbed on various metals that reveal three separate desorption peaks.⁵⁹ In the former case, it appears that hydrogen and deuterium atoms can migrate so rapidly that the H–D pool on the surface is usually in dynamic equilibrium. On the other hand, the latter information suggests that at least three different sites exist from which hydrogens may recombine and desorb. These sites may be plane, edge, and corner sites.

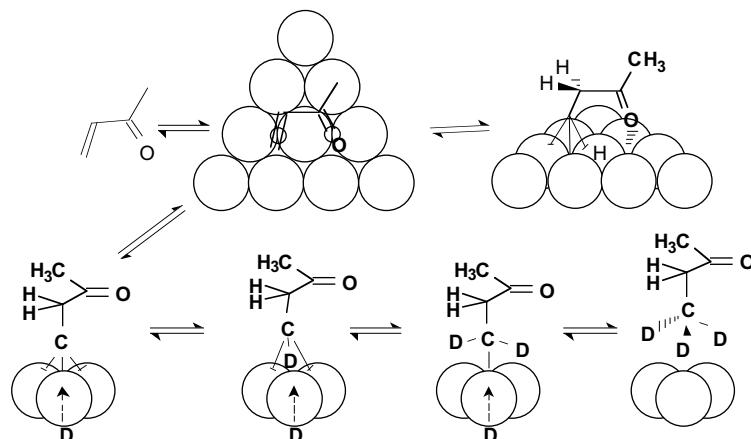
How can we rationalize these apparently conflicting assumptions? How can hydrogen and deuterium rapidly equilibrate between themselves and among the positions on hydrocarbons and still appear localized and immobile under TPD studies? The difference in the experiments reveals a possible explanation. First, during the TPD studies the catalyst is saturated with hydrogen at low temperatures and the temperature is ramped at a constant rate. Desorbed hydrogen is measured by a thermal conductivity cell or some other convenient device. Since desorption occurs first on the lowest bond energy sites, these sites become vacant and hydrogen attached to higher bond energy sites have little driving force to migrate to the less stable positions. Under such conditions, hydrogen migrates slower than desorption and three peaks are seen, presumably resulting from corners, edges, and planes.

On the other hand, removing hydrogen from the less active sites (higher bond energy) should result in hydrogen’s migrating in from the more active sites. Therefore, if hydrogenation takes place on the higher bond energy sites,

hydrogen migrates in from the lower bond energy sites. How fast hydrogen migrates depends on coverage. During liquid-phase hydrogenations, coverage is low, but during gas-phase hydrogenations, it is high.²⁵

Where are these hydrogen adsorption–desorption sites? King and co-workers^{22,60} have carefully examined this question by studying bimetallic catalysts composed of Cu, Ag, or Au alloyed with Pt, Rh, or Ru. They conclude that the “portals” of hydrogen adsorption and desorption are the edge and corner sites. Other evidence from CS₂ poisoning experiments also points to edges and corners.^{24,25}

But this picture of hydrogens sitting atop surface metal atoms is incomplete. In fact, hydrogen prefers to sit in more stable hollow site positions.⁶¹ And there is evidence that hydrogen can and does migrate, perhaps readily, along the subsurface layer of metal atoms just below the top layer.⁶² So the picture has changed somewhat to include this subsurface (bulk) hydrogen that can migrate subsurface and come up through the hollow sites to attack adsorbed species as shown in Scheme 1.4.^{62–64} If deuterium is placed on the surface, it exchanges with hydrogens in ethene but does not accomplish hydrogenation; subsurface hydrogen (bulk hydrogen) accomplishes hydrogenation of ethene,⁶³ cyclohexene,⁶⁴ and acetylene.⁶⁵ Additional evidence in support of this notion comes from studies with a Pd–Ni membrane in which the hydrogen dissociates on one side of the membrane and migrates (permeates) through to the other side. These studies show that surface hydrogen does not react with acetylene, but hydrogen permeating through the membrane accomplishes hydrogenation⁶⁶ (see also Section 2.1.4.2).



SCHEME 1.4 Depiction of deuterium attacking from the subsurface through a three-fold hollow site. The second (lower) layer of metal atoms is not shown.

1.5. BOOKS ON HETEROGENEOUS CATALYSIS OF ORGANIC REACTIONS

Not many books specifically address heterogeneous catalysis of organic reactions. The following list includes those whose aim is practical organic synthesis using heterogeneous catalysts and/or the fine chemicals industry. One, *Stereochemistry of Heterogeneous Metal Catalysis*, by M. Bartók and his faculty at The Department of Organic Chemistry at József Attila University in Szeged, Hungary, includes discussions of reaction mechanisms in many chapters. And the most recent addition, *Heterogeneous Catalysis for the Synthetic Chemist*, by R. L. Augustine, brings surface frontier molecular orbitals, chemoselectivity, regioselectivity, and stereoselectivity into discussions on reaction mechanisms on surfaces.

1.5.1. THE SERIES OF BOOKS PUBLISHED BY THE ORGANIC REACTIONS CATALYSIS SOCIETY

- Annals of the New York Academy of Sciences*, 145, pp. 1–206 (1967) [first conference on catalytic hydrogenation and analogous pressure reactions, J. M. O'Connor (Ed.)].
- Annals of the New York Academy of Sciences*, 158, pp. 439–588 (1969) [second conference, J. M. O'Connor (Ed.)].
- Annals of the New York Academy of Sciences*, 172, pp. 151–276 (1970) [third conference, M. A. Rebentrost (Ed.)].
- Annals of the New York Academy of Sciences*, 214, pp. 1–275 (1973) [fourth conference, P. N. Rylander (Ed.)].
- Catalysis in Organic Syntheses*, P. N. Rylander and H. Greenfield (Eds.), Academic Press, New York, 1976 [fifth conference].
- Catalysis in Organic Syntheses*, G. V. Smith (Ed.), Academic Press, New York, 1977 [sixth conference].
- Catalysis in Organic Syntheses*, W. H Jones (Ed.), Academic Press, New York, 1980 [seventh conference].
- Catalysis of Organic Reactions*, W. R. Moser (Ed.), Dekker, New York, 1981 [eighth conference].
- Catalysis of Organic Reactions*, J. R. Kosak (Ed.), Dekker, New York, 1984 [ninth conference].
- Catalysis of Organic Reactions*, R. L. Augustine (Ed.), Dekker, New York, 1985 [10th conference].
- Catalysis of Organic Reactions*, P. N. Rylander, H. Greenfield, and R. L. Augustine (Eds.), Dekker, New York, 1988 [11th conference].
- Catalysis of Organic Reactions*, D. W. Blackburn (Ed.), Dekker, New York, 1990 [12th conference].
- Catalysis of Organic Reactions*, W. E. Pascoe (Ed.), Dekker, New York, 1992 [13th conference].
- Catalysis of Organic Reactions*, J. R. Kosak, T. A. Johnson (Eds.), Dekker, New York, 1994 [14th conference].
- Catalysis of Organic Reactions*, M. Scaros, M. L. Prunier (Eds.), Dekker, New York, 1995 [15th conference].
- Catalysis of Organic Reactions*, R. Malz (Ed.), Dekker, New York, 1996 [16th conference].
- Catalysis of Organic Reactions*, F. Herkes (Ed.), Dekker, New York, 1998 [17th conference].

1.5.2. THE SERIES OF BOOKS PUBLISHED ORIGINALLY BY THE POITIERS (FRANCE) GROUP BUT EXPANDED TO GENERAL EUROPE

Heterogeneous Catalysis and Fine Chemicals (*Stud. Surf. Sci. Catal.*, 41), M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, C. Montassier, and G. Pérot (Eds.), Elsevier, Amsterdam 1988.

Heterogeneous Catalysis and Fine Chemicals II (*Stud. Surf. Sci. Catal.* 59), M. Guisnet, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, R. Maurel, and C. Montassier (Eds.), Elsevier, Amsterdam, 1991.

Heterogeneous Catalysis and Fine Chemicals III, M. Guisnet, J. Barbier, J. Barrault, C. Bouchoule, D. Duprez, G. Pérot, and C. Montassier (Eds.), Elsevier, Amsterdam, 1993.

Heterogeneous Catalysis and Fine Chemicals IV, H. U. Blaser, A. Baiker, and R. Prins (Eds.), Elsevier, Amsterdam, 1997.

1.5.3. THE SERIES OF BOOKS BY PAUL N. RYLANDER

Catalytic Hydrogenation over Platinum Metals, P. N. Rylander, Academic Press, New York, 1967.

Catalytic Hydrogenation in Organic Syntheses, P. N. Rylander, Academic Press, New York, 1979.

Hydrogenation Methods, P. N. Rylander, Academic Press, New York, 1985.

1.5.4. OTHER BOOKS

Catalytic Hydrogenation, Techniques and Applications in Organic Synthesis, R. L. Augustine, Dekker, New York, 1965.

Practical Catalytic Hydrogenation, M. Freifelder, Wiley-Interscience, New York, 1971.

Hydrogenation and hydrogenolysis in Synthetic Organic Chemistry, A. P. G. Kieboom and F. Van Rantwijk, Delft University Press, 1977.

Stereochemistry of Heterogeneous Metal Catalysis, M. Bartók, J. Czombos, K. Felföldi, L. Gera, Gy. Göndös, Á. Molnár, F. Notheisz, I. Pálinkó, Gy. Wittmann, and Á. G. Zsigmond, Wiley, Chichester, 1985.

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Hydrogenations

- 2.1. Hydrogenation of Carbon–Carbon Multiple Bonds
- 2.2. Hydrogenation of C=O Bonds
- 2.3. Hydrogenation of Nitrogen-Containing Multiple Bonds and Reductive Amination
- 2.4. Hydrogen Sources

References

A great deal of industrial heterogeneous organic chemistry involves the use of hydrogen. Making bonds between hydrogen and other atoms is a primary method for converting one functional group into another. This is typically called *hydrogenation* if hydrogen is added across a π -bond, but it is called *hydrogenolysis* if hydrogen is added across a σ -bond. Some authors use *hydrogenation* when they mean *hydrogenolysis*.¹ Sometimes the term *hydrogenative addition* is used for hydrogenolysis of small rings.²

Some organic chemists call hydrogenation *reduction*.³ This is a correct term, since, technically speaking, the atoms involved (C, O, or N) are converted from a higher to a lower oxidation state. However, *reduction* could suggest other processes, for example, reduction by di-imide,⁴ metal and acid,⁵ or hydrazine⁶ (which fits comfortably in the category of *transfer hydrogenation*, see Section 2.4.1). Granted, these reagents add hydrogen across π -bonds, but, just like hydrogen, they also reduce other things. Nevertheless, the specific reaction of hydrogen to reduce π -bonds is called *hydrogenation*, and that is the term we use.

If the addition of hydrogen across π -bonds is specifically called *hydrogenation*, what then should we call the addition of deuterium across π -bonds? Many authors call this *deuteration*,⁷ however, this term can be confused with processes in which protium is replaced with deuterium in any compound. Other terms used instead of *hydrogenation with deuterium* are *deuteriogenation*⁸ and *deuteriumation*.⁹ *Deuteriogenation* is clearly awkward and, besides, is inadequate on the grounds that no element or molecule of deuterioxygen exists. *Deuteriumation* is most desirable on the basis of its logical extension of the construction of the parent term, *hydrogenation*. *Hydrogenation* is constructed from *hydrogen* and *ation*; likewise, *deuteriumation* is constructed from *deuterium* and *ation*. So, in this book, the addition of deuterium to π -bonds (*hydrogenation with deuterium*) is called *deuteriumation*.

Fortunately, virtually everything said about hydrogenations is applicable to deuteriumations. Exceptions are certain rates and certain processes using metal and metal alloy membranes for hydrogenations (deuteriumations). Differences between the formation of the β -hydride and β -deuteride phases in these latter cases affect the reaction outcomes. Such differences between hydrogenations and deuteriumations are pointed out and discussed where appropriate.

This chapter addresses hydrogenation and Chapter 4 addresses hydrogenolysis. The reverse reaction, dehydrogenation, may be called either *dehydrogenation* or *oxidation*, depending on the method used for the conversion. As is the case with reduction, *oxidation* is a general term correctly used for dehydrogenation; however, *oxidation* in heterogeneous catalysis usually refers to the use of oxygen (frequently the addition of oxygen or the replacement of an atom of some other element with an atom of oxygen),¹⁰ either in the form of dioxygen or in combination with a metal. Sometimes an oxygen may be transferred from one molecule to another.¹¹ However, the term *dehydrogenation* specifically refers to the reverse of hydrogenation no matter how the transformation is accomplished. Dehydrogenation is addressed in Chapter 5 and oxidation is examined in different ways in Chapter 6.

2.1. HYDROGENATION OF CARBON–CARBON MULTIPLE BONDS

One of the most common heterogeneous organic reactions in the fine chemicals and the specialty chemicals industries is the hydrogenation of carbon–carbon multiple bonds. It is so common that an entire array of specialty catalysts has been developed to accomplish specific hydrogenation reactions. An important goal in this field is selectivity. However, when relatively large quantities of chemicals are produced, concerns also embrace economy, yield, and

zero discharge. Therefore, a wide variety of catalysts and conditions have been and will continue to be employed along with their accompanying folklore. Consequently, one of our goals is to convert these companions of descriptive science into mechanistic notions on which chemical reactivity can be predicted. In much of heterogeneous organic catalysis, this goal is difficult because of the absence of a description of one of the reactants, the active catalytic site; however, in the cases of hydrogenation and its accompanying reactions, considerable data exist on which to base discussions and understandings of mechanisms and, therefore, predictions of reactivities.

Before we examine the hydrogenation of each type of unsaturation, let us first take a look at the basic mechanism assumed to be operating on metal catalytic surfaces. This mechanism is variously referred to as the *classic mechanism*, the *Horiuti-Polanyi mechanism*, or the *half-hydrogenated state mechanism*. It certainly fits the *classic* definition, since it was first proposed by Horiuti and Polanyi in 1934¹² and is still used today. Its important surface species is a half-hydrogenated state. This mechanism was shown in Chapter 1 (Scheme 1.2) as an example of how surface reactions are sometimes written. It is shown in slightly different form in Fig. 2.1. Basically, an unsaturated molecule is pictured as adsorbing with its π -bond parallel to the plane of the surface atoms of the catalyst. In the original Horiuti-Polanyi formulation, the π -bond ruptures

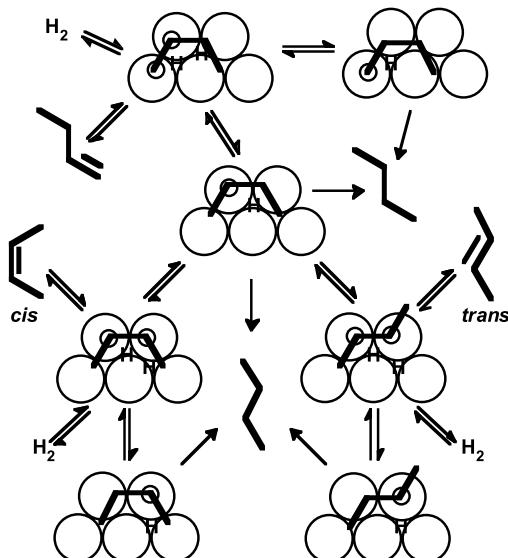


FIGURE 2.1 Classical Horiuti-Polanyi half-hydrogenated state mechanism for hydrogenation, double bond migration, cis-trans isomerization, and deuterium exchange.

and two σ -bonds are formed to two surface atoms. (A more recent formulation proposes that this adsorption may occur as a π -complex without rupturing the π -bond.) This is called *associative adsorption* as opposed to *dissociative adsorption*, in which a C–H (or O–H or N–H) bond is ruptured and two σ -bonds are formed between the catalyst and each of the formerly joined atoms. Following associative adsorption, one surface hydrogen adds to one of the atoms of the former π -bond, forming a half-hydrogenated state. These surface hydrogens are formed by dissociative adsorption of dihydrogen and are assumed to scoot around on the tops of the surface atoms of the catalyst. (In Section 1.4.2, we discussed other possible locations for the hydrogen, such as in the three-point hollows shown in Fig. 2.1.) Up to this point, each of the steps is assumed to be reversible; however, the next step, the addition of another hydrogen atom to the second atom of the former π -bond, is considered nonreversible because the resulting saturated molecule desorbs from the surface. Actually, this step is reversible (dehydrogenation) at higher temperatures and when favorable driving forces are present, such as in the dehydrogenation of cyclohexene to benzene. In summary, then, the classic mechanism involves associative adsorption to form a di- σ -adsorbed alkane, the addition of one surface hydrogen to one of the σ -bonds to form the half-hydrogenated state, the addition of a second hydrogen to complete saturation of the former π -bond, and desorption. Accompanying reactions such as double bond migration and *cis*–*trans* isomerization are readily accommodated by reversing the addition of the first hydrogen and by abstracting a different adjacent hydrogen either on a different or the same carbon, the latter preceded by rotation about the newly formed C–C single bond in the half-hydrogenated species. Deuterium exchange is readily accommodated by substituting deuterium for hydrogen on the surface.

2.1.1. HYDROGENATION OF ALKYNES

Hydrogenation of alkynes is important. First, it is important for the removal of traces of alkynes from alkene feed stocks in the polymer industry, and second, it is important for synthesizing *cis*-alkenes. Both of these processes involve the hydrogenation of only one of the two π -bonds of the alkyne; this is called *half-hydrogenation*. A related reaction, the half-hydrogenation of 1,3-dienes, shares many of the catalysts and conditions useful for half-hydrogenation of alkynes, but this reaction of 1,3-dienes exhibits some peculiarities of its own and is less common than the half-hydrogenation of alkynes. It is discussed in Section 2.1.2 and only half-hydrogenation of alkynes is addressed here.

Half-hydrogenations of alkynes are usually accomplished over poisoned Pd catalysts, but other catalysts also may also be used.¹³ Unpoisoned Pd sometimes does not give high stereoselectivity.¹⁴ One of the most mentioned Pd cat-

alysts for this purpose is Lindlar's catalyst.¹⁵ This catalyst gives high selectivity for half-hydrogenation to the *cis*-alkene.¹⁶ Although Lindlar's catalyst is prepared by a specific method, Pd/CaCO₃ poisoned with Pb acetate and quinoline, other partially poisoned Pd catalysts used for the half-hydrogenation of alkynes are erroneously called "Lindlar's catalyst." For example, Pd/BaSO₃ with quinoline¹⁷ and with pyridine,¹⁸ and Pd/CaCO₃ without quinoline,¹⁹ are referred to as "Lindlar's catalyst." In fact, Aldrich sells a 5% Pd/CaCO₃ poisoned with Pb but not quinoline,²⁰ catalog number 20,573-7, as "Lindlar catalyst," which partly explains the propagation of this erroneous terminology. The term has become so accepted in the synthetic literature that sometimes only "Lindlar catalyst"²¹ or "Lindlar conditions"²² is used to convey the idea of selective half-hydrogenation of an alkyne. As it turns out, almost any partially poisoned Pd catalyst will produce selectivity. Of course, not all such partially poisoned Pd catalysts are Lindlar's catalyst. But someday we may find chemists using a term like *Lindlar reduction* or its abbreviated form, *LR*, to mean half-hydrogenation of alkynes.

Other poisons (modifiers) used to create such selective Pd catalysts may be metals:²³ Zn, Cd, Zr, Ru, Au, Cu, Fe, Hg, Ag, Pb, Sb, and Sn; or solvents (organic modifiers):²⁴ pyridine, quinoline, piperidine, aniline, diethylamine, other amines, chlorobenzene, and sulfur compounds. Hydroxides have also been used to increase the half-hydrogenation selectivity of Pd.

In general, *cis*-alkene selectivity at the 91–98% level follow the order Pd > Rh > Pt > Ru ~ Ir as shown in Table 2.1.²⁵ Selectivity is achieved with other catalytic materials as well. Ni is effective (P2-Ni in ethylenediamine),²⁶ as are Pd-Si and Pd-Ge metallic glasses²⁷ and Si modified Pd.²⁸ A novel use of sol-gel technology to produce Pd-containing gels²⁹ and Rh/Cu-containing gels³⁰ creates heterogeneous catalysts that exhibit stereoselectivity for *cis* half-hydrogenation.

The mechanism of half-hydrogenation of alkynes is not fully understood, but some details are recognized. For example, it has long been recognized that alkynes adsorb more strongly than alkenes. During the half-hydrogenation of

TABLE 2.1 Order of *cis*-Alkene Selectivity from Hydrogenation of Alkynes²⁵

Catalyst	Ene selectivity	<i>Cis</i> stereoselectivity
Pd/C	0.998	0.978
Rh/C	0.810	0.956
Pt/C	0.900	0.925
Ru/C	0.860	0.917
Ir/Al ₂ O ₃	0.600	0.915

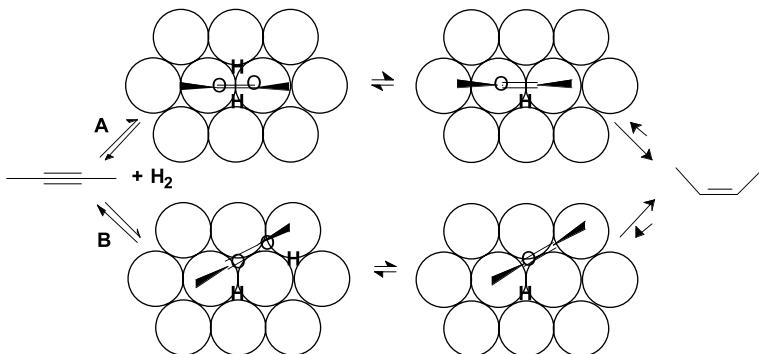


FIGURE 2.2 Mechanism of half-hydrogenation of alkynes showing two possible adsorption sites.

an alkyne, the corresponding alkene builds up with little or no formation of alkane until all alkyne is hydrogenated. After that, the reaction rate increases and alkene is hydrogenated. Individually the alkyne hydrogenates slower than the alkene. But the concentration effect of the catalyst plays an important role here. The surface concentration of the alkyne is large whereas that of the alkene is small. Consequently, in competition, the alkyne rate is much faster. In such a case, the noncompetitive relative rates of hydrogenation of the alkyne and alkene are inconsequential.

The kind of surface site catalyzing alkyne half-hydrogenation has been the subject of some speculation. Two possibilities are shown in Fig. 2.2. Certainly such a site should fit the evidence Burwell and associates obtained from the hydrogenation of di-*tert*-butyl acetylene (*2,2,5,5*-tetramethyl-3-hexyne).³¹ They proposed that the molecule dislocated a surface atom, pulling it up out of the plane of the surface (Fig. 2.3). That work concluded that hydrogenation

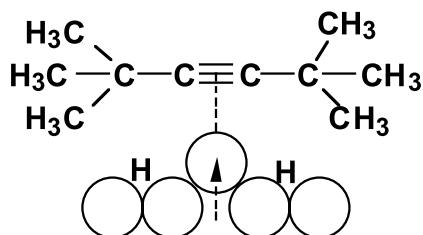
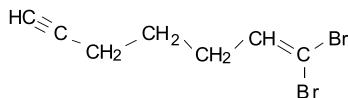


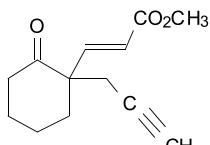
FIGURE 2.3 Burwell mechanism for hydrogenation of alkynes showing reconstruction of surface Pd atom.³¹

occurred on planes because the rate of hydrogenation appeared to be at least as large on plane atoms as on edge atoms.

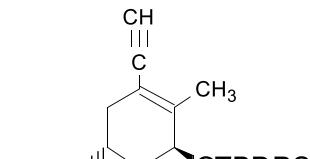
In support of this notion, evidence exists for the dislocation or dissolving of certain surface atoms when acetylenes are hydrogenated on Pd. For example, it has been found that terminal acetylenes produce a turbid solution when hydrogenated over Pd-Si metallic glasses in organic solvents. The turbidity disappears at half-hydrogenation.³² Also, when butadiene is industrially purified from vinylacetylene, the Pd dissolves when the vinylacetylene concentration is high, and a great effort has gone into preventing Pd dissolution by alloying it with other elements, such as Sb and Te.³³ Perhaps significantly, when Pd is poisoned with either pyridine or quinoline, no mention is made of Pd dissolving during the half-hydrogenation of 1,1-dibromo-1-heptene-6-yne (1),¹⁸ 2-(2'-carbethoxyvinyl)-2-(3'-prop-1'-ynyl)cyclohexanone (2),³⁴ or (3*S*, 5*R*)-3,5-bis[((*tert*-butyldiphenyl)silyl)oxy]-1-ethynyl-2-methylcyclohex-1-ene (3).^{20b} Therefore, one could conclude that these poisons protect Pd surface atoms from dislocating or dissolving.



(1)



(2)



(3)

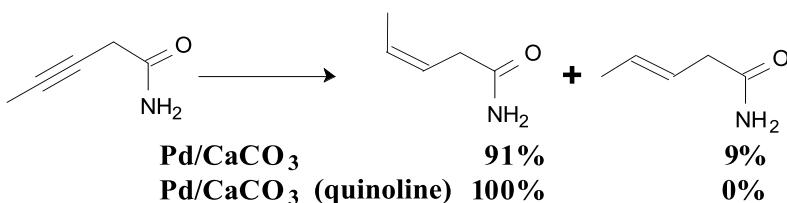


FIGURE 2.4

Introduction of a trimethylsilyl group on the triple bond seems to drastically lower half-hydrogenation selectivity¹⁹ even when the Pd is poisoned by pyridine.³⁵ In fact, silation of a terminal triple bond frequently protects it from being hydrogenated under mild conditions.³⁶ Sometimes silation in another part of the molecule inhibits hydrogenation,³⁷ but sometimes it does not;³⁸ however, fluorination does not appear to affect high selectivity.³⁹ So it seems that not only are the surface modifications important, but also the alkyne substituents are important for selective half-hydrogenation.

Full hydrogenation of the triple bond occurs over Raney nickel (Ra-Ni)⁴⁰ and even unpoisoned Pd/CaCO₃ will catalyze full saturation.⁴¹ Also, unpoisoned Pd/C will catalyze full saturation;⁴² however, pyridine poisoning⁴³ and molecules containing N⁴⁴ and S⁴⁵ instill half-hydrogenation selectivity. The poisons make a difference in selectivity even on Lindlar's catalyst; for example, hydrogenation of 3-pentynamide over Lindlar's catalyst without quinoline poisoning produced a 10:1 ratio of (*Z*)-3-pentenamide to saturated material, but with quinoline poisoning only the (*Z*)-3-pentenamide was produced (Fig. 2.4).⁴⁶

And finally, we point out that even poisoning may not produce exclusively the cis (*Z*) product. Hydrogenation of (\pm)-2-methyloctadec-7-yn-6-ol over 5% Pd/BaSO₄ poisoned with pyridine produced only an 87:13 ratio of *Z*:*E* isomers in 76% yield in 20–24 hours (Fig. 2.5).⁴⁷

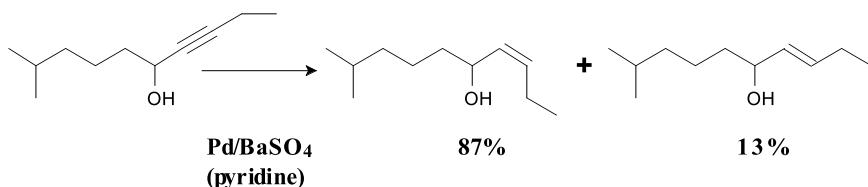


FIGURE 2.5

2.1.2. HYDROGENATION OF DIENES

Hydrogenation of dienes resembles hydrogenation of both monoenes and alkynes.⁴⁸ Allenes, 1,2-dienes, generally undergo first *cis* addition of hydrogen to the least-hindered side of the least-hindered double bond and then isomerization and/or hydrogenation of the second. For the cases of 1,3-dienes, over many catalysts both double bonds are hydrogenated with no evidence of sequential steps between the hydrogenation of the two double bonds.⁴⁹ However, over poisoned Rh⁵⁰ and over certain poisoned or otherwise modified Pd catalysts, and sometimes at low temperatures,⁵¹ the selective hydrogenation of one double bond may be accomplished followed by a decrease or cessation of rate of hydrogenation of the other. Solvents and the method of catalyst preparation may also affect the outcome.⁵²

For small-scale synthetic organic chemistry, the half-hydrogenation of dienes is sometimes useful. For example, at -10°C the half-hydrogenation by 1,4-addition of $(3\alpha,2a\alpha,5\beta,9a\beta)\text{-}2,3,3a,4,5,9a\text{-hexachydro-9a-hydroxy-3,5,8-trimethyl-1H-cyclopenta-cyclooctene-5-methanol}$ was accomplished (Fig. 2.6).⁵¹ Possibly, this is a hydrogenation of one double bond followed by isomerization of the other to the more stable position; however, in other experiments conducted by the authors, a position different from the one in the product appears to be more stable, so this may be an unambiguous example of 1,4-addition to a 1,3-diene.

After half-hydrogenation, migration of the remaining double bond (sometimes mistaken for 1,4-addition) can be inhibited by poisoning with CO.⁵³

Industrially, the half-hydrogenation of 1,3-dienes is important. So substantial work has gone into formulating catalysts and conditions for this. Hydrogen sulfide poisons Pd/Al₂O₃ for half-hydrogenation of 1,3-butadiene,⁵⁴ and Cr- or Ti-modified Pd⁵⁵ as well as colloidal Pd on a chelate resin⁵⁶ markedly inhibits hydrogenation of the second double bond in cyclopentadiene. Many industrial strategies involve simply poisoning Pd by circulating the feed or solvent over it

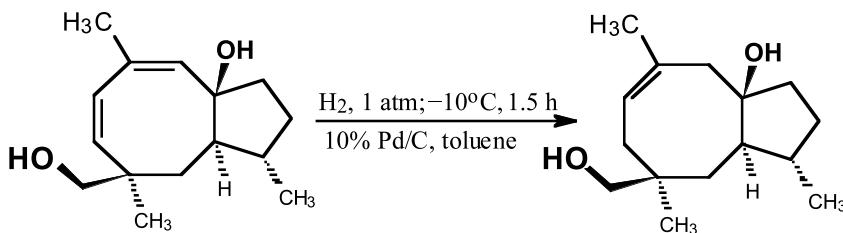


FIGURE 2.6

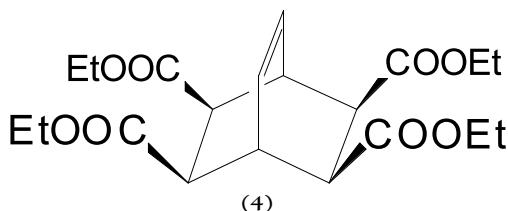
for some time before attempting half-hydrogenation of the 1,3-diene,⁵⁷ so this, as well as the low-temperature hydrogenation mentioned previously, would be a good strategy to try when attempting to selectively hydrogenate only one double bond of a 1,3-diene. By analogy, one might expect similar strategies to work for half-hydrogenation of alkynes.

2.1.3. HYDROGENATION OF ALKENES

Hydrogenation of carbon–carbon double bonds is frequently performed in laboratory and industrial organic syntheses. Usually it can be accomplished with little difficulty over a wide variety of catalysts. The ease of hydrogenation follows the order mono-, 1,1-di-, 1,2-di-, tri-, and tetra-substituted alkenes. Of course, the level of congestion at the double bond influences how it adsorbs on the catalytic surface and, therefore, influences the course of hydrogen addition. Although plane sites have been implicated in enantioselective hydrogenations (where enantiomeric modifiers likely poison the more active sites),⁵⁸ the most active site or sites for hydrogenation certainly appear to be edges and/or corners since some remarkably congested alkenes can be hydrogenated. For example, in their classic studies, Balandin and Klabunovskii and co-workers used sterically congested alkenes to determine the dimensions of active sites (which they called *multiplets*) and defined a site that today we might call an edge or a corner.⁵⁹

More recent examples of experiments with sterically congested molecules are Mylroie and Stenberg's hydrogenation of the sterically hindered substituted tryptocenes,⁶⁰ and hydrogenation of the double bond in tetraethyl bicyclo[2.2.2]oct-7-ene-2-syn,3-syn,5-syn,6-syn-tetracarboxylate (4) which occurs over 5% Pd/C in ethyl acetate at room temperature and under 1 atm of hydrogen in 48 hours.⁶¹

On the other hand, severe congestion and a lower temperature (20°C) prevent the hydrogenation of the propylidene double bond (tetrasubstituted but



DRAWING 2.4

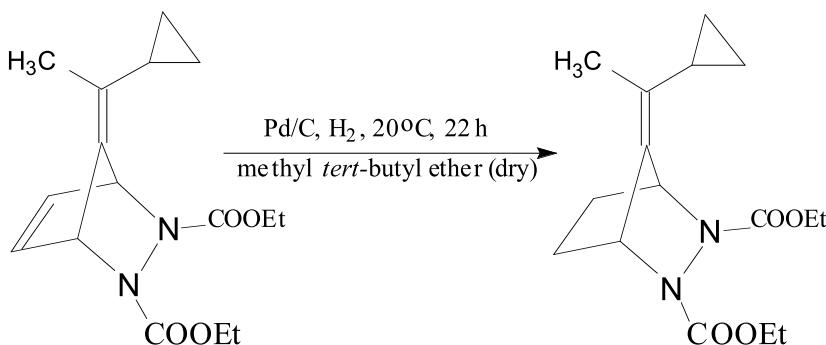


FIGURE 2.7

strained) in 2,3-dicarbethoxy-7-(2-cyclopropylpropylidene)-2,3-diazabicyclo [2.2.1]heptane over a Pd/C catalyst (Fig. 2.7)⁶² similar to that used in the previous example, and severe congestion appears to be the reason that the bicyclo-hindered double bond in the *cis,cis*-hexahydroanthracyl-substituted cyclohexene shown in Fig. 2.7 did not add hydrogen over Pd.⁶³ The slight

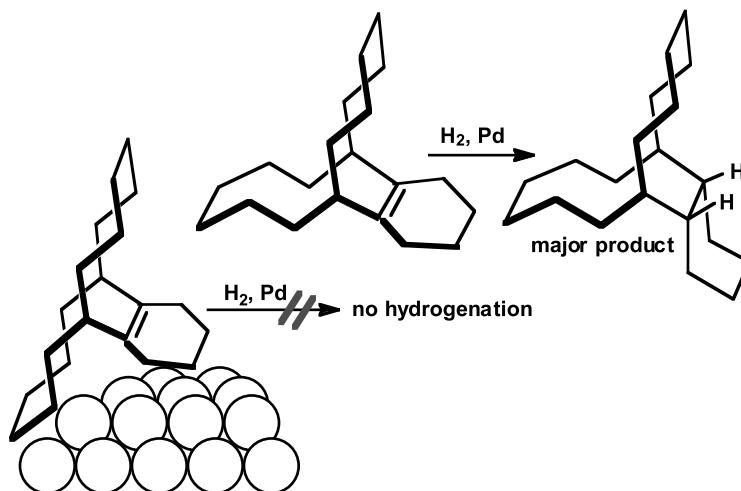
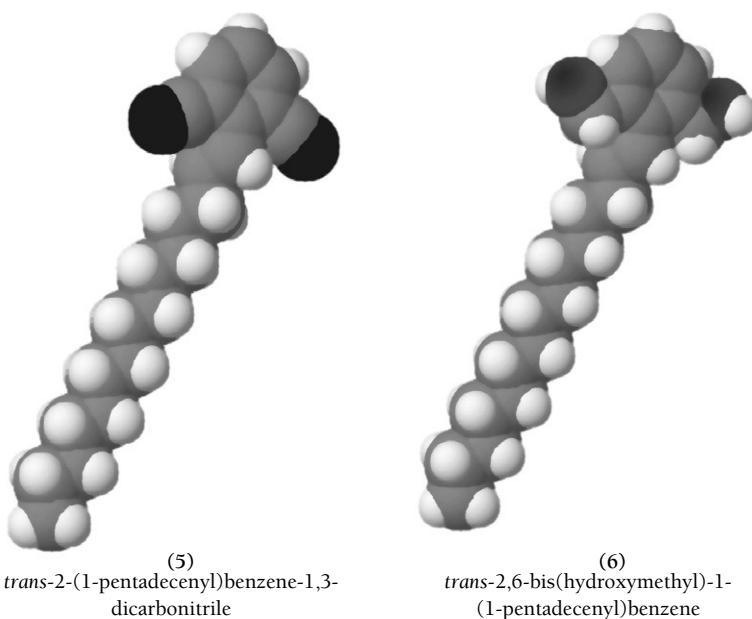


FIGURE 2.8

structural perturbations of this latter structure sometimes allow and sometimes disallow hydrogenation.⁶⁴

Interestingly, the ability of the double bond to lie flat on the surface doesn't seem to always be the predictor of whether or not hydrogenation will proceed readily. For example the disubstituted alkene in *trans*-2-(1-pentadecenyl)benzene-1,3-dicarbonitrile (5) does not hydrogenate over 10% Pd/C in THF–ethanol (1:1) at 1 atm hydrogen, but the corresponding diol, *trans*-2,6-bis(hydroxymethyl)-1-(1-pentadecenyl)benzene (6) does.⁶⁵ As the space-filling models show, the styryl C=C bond is almost perpendicular to the benzene ring in both molecules. The authors attribute the inability of the dinitrile to hydrogenate to electron-withdrawing effects; however, another possible explanation is that the dinitrile-substituted benzene ring is so strongly adsorbed onto the surface that the C=C bond cannot rotate into a position to which a surface (or subsurface) hydrogen can add to form a half-hydrogenated state. On the other hand, the oxygens of the dihydroxymethyl groups may adsorb and elevate the benzene from the surface enough to allow the C=C bond to rotate into a position in which a hydrogen atom can attack and form a half-hydrogenated state.



DRAWINGS 2.5–2.6

Congestion aside, most hydrogenations can be accomplished with ease, and the usual synthetic concern during hydrogenation of a carbon–carbon double bond is the resulting stereochemistry of the product. The reasonable assumption is that an alkene adsorbs horizontally to its plane either by π -complexing to active sites or by breaking its π -bond and forming two σ -bonds to active sites on the surface, and, further, that adsorbed hydrogen atoms add upward from the surface to the adsorbed side of the former double bond. This is syn addition (cis addition). Because other reactions usually accompany addition (cis trans isomerization and/or double bond migration followed by desorption and readsorption) the stereochemical outcome is not always certain. Moreover, the possibility of trans addition obfuscates predictions.

2.1.3.1. Apparent trans Addition

Apparent trans addition of hydrogen to a carbon–carbon double bond has been the subject of intense investigations and several mechanism have been proposed; the stereochemistry of hydrogenation of alkenes has been comprehensively reviewed by Siegel in 1966,⁶⁶ by Molnár in 1983,⁶⁷ and again by Bartók and Molnár in 1997,⁶⁸ so only a brief history is related here.

Early on, the concept of syn addition (cis addition) of hydrogen to carbon–carbon double bonds was well established by the pioneering analytical work of Linstead and associates,⁶⁹ and the later study by Siegel and Smith.⁷⁰ More examples continue to appear.⁷¹ This concept is now in most organic chemistry textbooks. However, what is not so well known is that evidence of *anti* addition (trans addition) exists. The *anti* additions are most obvious during the hydrogenation of tetrasubstituted alkenes. They occur in the hydrogenation of 1,2-dimethylcyclohexene⁷⁰ and several other molecules.^{72–75} This apparent trans addition is similar to the deuterium exchange of hydrogens on both sides of small-ring cycloalkanes, such as cyclopentane,⁷⁶ during one period of residence on metal surfaces and similar to the racemization and deuterium exchange of (+)-3-methylhexane over Ni⁷⁷ and Pd.⁷⁸ The basic problem is how hydrogen or deuterium can add or exchange on both sides of a molecule if the molecule is adsorbed flat on a surface and if the hydrogen (deuterium) approaches it only from the surface. Surely, only that face of an alkene that is toward the surface should add or exchange hydrogens (deuteriums). But the opposite face appears to be in on the action too. These phenomena have been explained by various processes, such as dissociatively adsorbed alkenes,⁷⁹ a rollover mechanism⁷⁸ (and the similar alkylidene species⁸⁰), a topside addition of hydrogen,⁸¹ a 1,3 hydrogen shift over the topside of an adsorbed alkene,⁸² and double bond migration followed by desorption and readsorption.⁸³

This last mechanism (Fig. 2.9) consists of known common reactions and appears to be the most widely accepted,⁸⁴ however, it appears to lack full

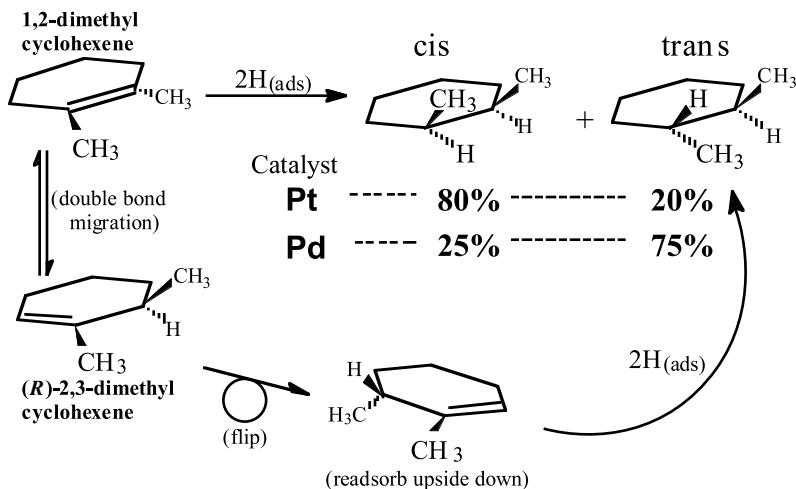


FIGURE 2.9

accounting of the formation of 20% *trans* product from the hydrogenation of 1,2-dimethylcyclohexene over Pt. The arguments for this are linked to the extent of double bond migration in different alkenes.

2.1.3.2. Double Bond Migration

Double bond migration occurs to different extents on different catalysts. On Pd it occurs readily, but on Pt it is slow compared with addition. The argument that *trans*-1,2-dimethylcyclohexane is formed from 1,2-dimethylcyclohexene on Pt by first double bond migration, then desorption, next readsorption on the opposite side of the ring, and finally, *cis* addition of hydrogen, requires approximately 70% incursion of this path to produce 20% *trans* product (2,3-dimethylcyclohexene itself yields only 30% *trans*).⁷⁰ Such a large amount of double bond migration from the more to the less stable isomer in the cyclohexene ring over Pt seem difficult to support by the available data. For example, deuteration of (R)-4-methylcyclohexene over Pt reveals only 2.6% double bond migration at 33% addition.⁸⁵ Thus, double bond migration in the cyclohexene ring is slower than for a *cis* double bond migration in a straight chain,⁸⁶ and slower still than in the strained ring system of (+)- and (-)-apopinene (Fig. 2.10).⁸⁷ Table 2.2 compares the relevant data^{9b}.

Although it seems clear that much of the apparent *trans* addition comes about through double bond migration, double bond migration seems unlikely

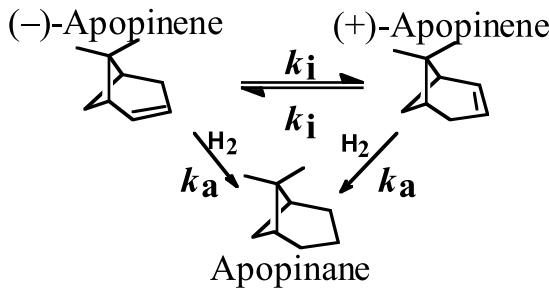


FIGURE 2.10

to fully account for formation of all of the *trans*-1,2-dimethylcyclohexane from the hydrogenation of 1,2-dimethylcyclohexene over Pt.

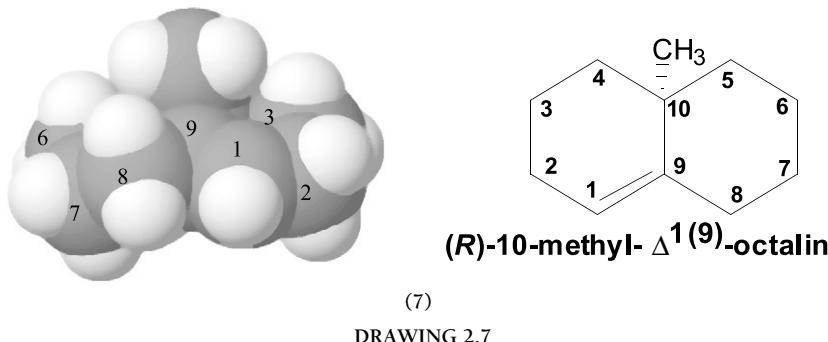
Moreover, a similar situation occurs during the hydrogenation of $\Delta^{9(10)}$ -octalin over Pt, in which *cis*- and *trans*-decalin are formed in approximately equal amounts. The isomeric $\Delta^{1(9)}$ -octalin does not isomerize to the more stable $\Delta^{9(10)}$ isomer.⁸⁸ A possible argument might be that the isomerization-desorption-flipping-readsorption is occurring in pores; however, if pore diffusion were allowing hidden double bond migration followed by readsorption and hydrogenation in the cases of 1,2-dimethylcyclohexene⁸⁹ and $\Delta^{9(10)}$ -octalin, then it also should allow it in the case of (*R*)-4-methylcyclohexene. But it does not.

Nevertheless, during hydrogenation of the dimethylcyclohexenes, the fact that the quantities of *trans* isomer increase with the double bond migration ability of the various catalysts⁹⁰ suggests that double bond migration sites (or the sites nearby) are involved in apparent *trans* addition.

To add another complication: recently, (*R*)-(-)-10-methyl- $\Delta^{1(9)}$ -octalin (7) has been prepared and its hydrogenation studied over Pt, Pd, and Rh catalysts.⁹¹ Like the apopinenes and the (*R*)-(-)-4-methylcyclohexene, this *R* enantiomer may undergo double bond migration to its *S* enantiomer, which

TABLE 2.2 Comparison of Relative Rates of Double Bond Migration on Platinum

Structural type	Relative rate migration	Migration/addition
Cyclohexene	1.0	0.078
Straight chain hydrocarbon (oleic acid, <i>cis</i> -)	3.7	0.28
Apopinene	7.9	0.61



will not displace the *R* enantiomer from a symmetrical surface. Therefore, double bond migration (racemization) may be detected by examining the starting enantiomer for a loss in optical rotation after different extents of hydrogenation. Apparently, the peculiar geometry of the molecule renders it unfavorable for double bond migration and hydrogenation. Over carbon-supported metals, hydrogenation proceeds very slowly and double bond migration not at all. Slight double bond migration occurs over $\text{Pd}/\text{Al}_2\text{O}_3$, which may be due to some acidic nature of the Al_2O_3 . Increasing slight racemization occurs over increasing dispersions of Pd/SiO_2 , which may signal a better fit on edges for this warped molecule. Examination of the model (7) reveals that the allylic hydrogens at C-8 that would be removed to form the $\pi\text{-C}_{1-8}$ -10-methyloctalin are unable to properly interact with the surface. For example, the axial C-8 hydrogen would be parallel to the surface if the molecule adsorbed on the side opposite the methyl. The equatorial C-8 hydrogen is correctly located if adsorption occurred at the same side as the methyl, except that the methyl probably creates so much steric interaction with the surface that the molecule cannot lay flat enough to allow the C-8 equatorial hydrogen to interact with the surface at an appropriate angle to be abstracted. Additionally, to form the $\pi\text{-C}_{1-8}$ -10-methyloctalin, substantial movement of C-7 would need to occur. These factors are not present in the apopinenes, in which double bond migration occurs readily.

On the other hand, the unexpected product is dominant. The *cis*-9-methyl-decalin is produced in larger amounts. This suggests that it is easier for the molecule to adsorb with the methyl toward the surface rather than away. In this adsorption the equatorial C-8 hydrogen is toward the surface, yet it is not abstracted. These results suggest that different steric requirements govern double bond migration (abstraction of an allylic hydrogen to form of a $\pi\text{-C}_{1-3}$ adsorbed species) than govern addition. A molecule may not be required to approach as close to the surface to add a hydrogen as to abstract a hydrogen.

Let us examine some of the other proposed mechanisms because they reveal how the various participants, physical chemists, surface scientists, chemical engineers, and organic chemists think. When proposals of a topside addition of hydrogen from an upper ledge onto an alkene adsorbed on a lower terrace were made in the 1960s,^{92,93} they seemed speculative, but in light of current understanding of catalytic surfaces and the movement of hydrogen thereon, they may have been prophetic. For, granting greater credence to this notion is the recent demonstration by McIntyre, Salmeron, and Somorjai that carbonaceous surface fragments may be removed by a scanning tunneling microscope Pt probe in a hydrogen atmosphere.⁹⁴ Presumably the hydrogen dissociates on the Pt probe and hydrogen atoms jump across the gap to the surface. Hydrogen atoms are known to add to the topside of cyclohexene adsorbed on Ni(111)⁹⁵ and Cu(100)⁹⁶. In both cases a deuterium atom from the gas phase initiates the reaction in a Rideal-Ely (top bombardment) mechanism, but in the case of the Ni(111) experiments, a hydrogen atom from the surface completes the addition whereas in the case of the Cu(100) experiments the geminal hydrogen is eliminated to the surface. Thus *trans* addition occurs, but the generation of hydrogen or deuterium atoms takes considerable energy and it is doubtful that these are present during liquid-phase hydrogenations. More likely would be the movement of a hydrogen atom from a ledge onto the top of an adsorbed alkene if the distance were not more than that of two hydrogen bonds. Hydrogen atoms are propelled out of the bulk of Ni with roughly 13 kcal/mol energy,⁹⁷ so a hydrogen atom coming from an adjacent wall might initiate *trans* addition as shown in Fig. 2.11. If that is the case, single crystals cut with steps at least two atoms high and predosed with hydrogen or deuterium should catalyze *trans* addition.

Since edges (and presumably ledges) are now associated with double bond migration,⁹⁸ and since apparent *trans* addition is a function of the double bond migration ability of various catalysts, perhaps such locations can produce both processes. The fact that tetrasubstituted alkenes hydrogenate much more slowly than tri-, di-, or monosubstituted alkenes would allow greater

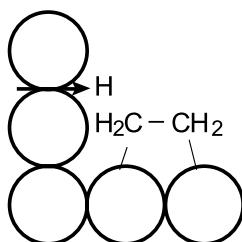


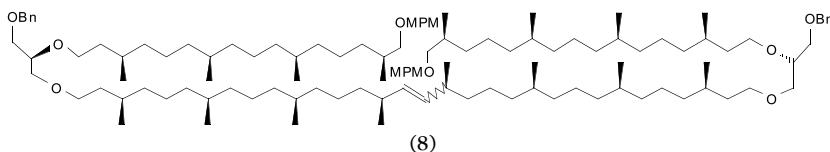
FIGURE 2.11 Possible mode of attack of bulk hydrogen to initiate *trans* addition.

occurrence of a slow process yielding apparent *trans* addition in the cases of tetrasubstituted alkenes.

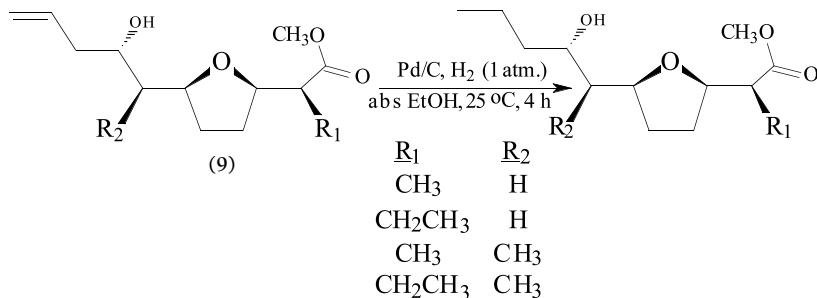
Nevertheless, aside from these cases of apparent *trans* addition, the dominant reaction involves the *cis* addition of hydrogen across the original double bond. But one must always be aware of the possibility and consequences of double bond migration, which may involve desorption and readsorption on the opposite face of the alkene-allyl system. Such double bond movements are not always apparent even though occurring, and, of course, many times they are of no consequence. However, when hydrogenating a double bond near a chiral center that contains a hydrogen (or deuterium), one must give careful consideration to the catalyst and procedure lest racemization occur.

Racemization occurred over Pd during the hydrogenation of $(-)$ -3,7-dimethyl-1-octene, $(+)$ -3-methyl-1-hexene,⁹⁹ and $3,3'-O-[(3R,7R,11S,15S,18S,22S,26R,30R)-3,7,11,15,18,22,26,30\text{-octamethyldotriacont-16-ene-1,32-diyl}] \text{bis} [1-O\text{-benzyl-2-O-}[(3R,7R,11S,15S)-16\text{-[}(4\text{-methoxybenzyl})\text{oxyl}]\text{-3,7,11,15-tetra-methylhexadecanyl]-sn-glycerol}$ ¹⁰⁰ (8), but to a lesser extent in $(-)$ -3-phenyl-1-butene.^{99,101} However, epimerization (or racemization) does not always occur even over Pd. For example, the hydrogenation of *trans*-4,5-dimethanoylcyclohexene over Pd/C in EtOAc produced 100% *cis*-1,2-dimethanoylcyclohexane with no apparent double bond migration accompanied by desorption, readsorption, and hydrogenation to form the *cis* isomer.¹⁰² Likewise, hydrogenation and hydrogenolysis of both 4(S),7-dibenzylxy-6(R)-methyl-1-heptene and 4(S),7(R)-dibenzylxy-1-decene¹⁰³ or the similar 4(S)-hydroxy-substituted 1-alkene¹⁰⁴ (9) and 4(R)t-butyldimethylsiloxy-5(R)-hydroxy-6(S)-benzyloxy-2-heptene¹⁰⁵ over Pd/C produced no evidence of double bond migration and accompanying racemization.

The reasons for the lack of double bond migration in these cases are not clear and likely unattainable because little if any experimental details are given. However, in some cases on Pd it is clear that hydroxide ion and nitrogen bases inhibit double bond migration⁹⁹ as they do alkyne half-hydrogenation. Examples of built-in nitrogen bases (and possibly nitrogen base contaminants) inhibiting double bond migration during hydrogenations over Pd exist in the synthetic literature.¹⁰⁶ On the other hand, the only ways to rationalize the formation of the *cis* ring junction and both $\alpha\text{-CH}_3$ and $\beta\text{-CH}_3$



DRAWING 2.8

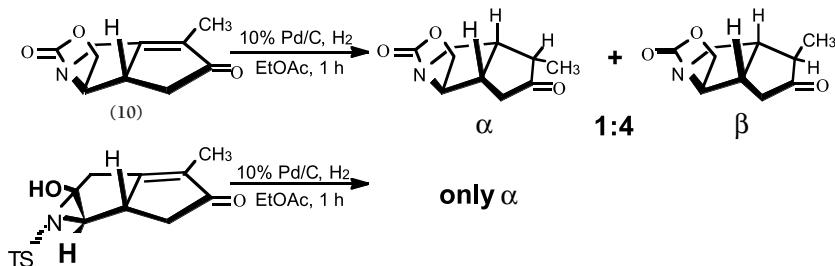


DRAWING 2.9

from the hydrogenation of **10** are either by double bond migration to the exo-ene (followed by desorption and readsorption at the opposite face) or by *trans* addition to the double bond in the ring.¹⁰⁷

Other factors that help reduce the relative rate of double bond migration are high pressures of hydrogen (50 psig or higher)^{106c} the catalyst (Ir > Os > Pt, Ru, Rh, >> Pd),¹⁰⁸ low temperatures,⁵¹ and possibly traces of water or oxygen.¹⁰⁹

This last possibility is suggested by the common use of a balloon of hydrogen to maintain 1 atm hydrogen pressure during a hydrogenation.^{110,111} Likely, these balloons are slightly permeable to oxygen and as long as the oxygen partial pressure does not build up above approximately 5%, they are safe from explosion. However, these traces of oxygen will form water and hydrogen peroxide on the surfaces of hydrogenation catalysts, especially in the presence of oxygen-containing organics.¹¹² Although the effect of oxygen on



DRAWING 2.10

the hydrogenation of carbonyl compounds is well established, studies of the effects of these molecules on selectivities of hydrogenations and on inhibition of double bond migration have not been made. But they are likely to strongly adsorb on the metal surfaces, possibly with dissociation, and occupy the more highly unsaturated sites, such as 3M and 2M sites.

An alternative mechanism for double bond migration has recently been proposed by Smith (Fig. 2.12).¹¹³ It is based in part on theoretical calculations,¹¹⁴ in part on the recent surface science work suggesting that hydrogen occupies threefold hollows,¹¹⁵ and in part on the experimental observation that during hydrogenation an allylic deuterium moves 1–3 across the bottom of an adsorbed allylic system without being exchanged.¹¹⁶

The theoretical calculations and the preservation of the allylic deuterium suggest movement of the π -allyl system over the top of the abstracted allylic deuterium rather than the usually suggested mechanism of moving the deuterium underneath the π -allyl system. The suggestion of a five-atom (quintet) edge site is based on the number of metal atoms required to accommodate the π -allyl movement and the abstracted deuterium. Of course, one of the end 2M edge atoms could be a 3M corner atom. This mechanism can also accommodate hydrogenation and deuteriumation if one assumes the hydrogen or deuterium is migrating subsurface and attacking the adsorbed alkene from threefold hollows as explained in Chapter 1 (Section 1.4.1) (compare with Fig. 2.1).

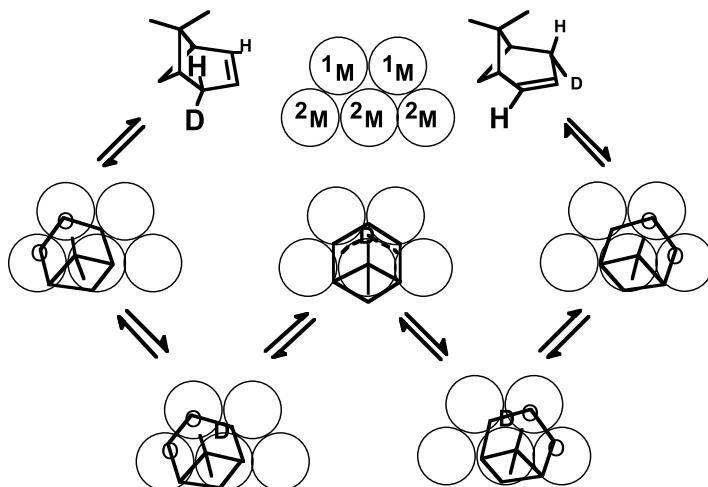


FIGURE 2.12 Mechanism of double bond migration on a quintet site.

2.1.3.3. Double Bond *cis*–*trans* Isomerization

Double bond *cis*–*trans* isomerization occurs during hydrogenation with a relative rate dependent on structure. The less stable double bond isomerizes to the more stable one, but, of course, kinetics and thermodynamics control the extent of isomerization. In a linear carbon chain, one can expect the *cis* alkene to isomerize to *trans* and vice versa if the thermodynamics are favorable. However, in a strained cyclic system, *trans* will isomerize to *cis* (Fig. 2.13).¹¹⁷

In principle, two mechanisms may lead to *cis*–*trans* isomerization: double bond migration along a linear carbon chain (Fig. 2.14A) or rotation about the former double bond in the half-hydrogenated state (Fig. 2.14B). Experimental data support the latter mechanism. For example, isomerization of the *cis* double bond in oleic acid under deuterium leads to relatively little movement of the double bond and forms *trans* isomers containing one deuterium per molecule (Fig. 2.15).¹¹⁸ Had double bond migration been an important pathway, much less deuterium would have been expected in the *trans* isomer. On the other hand, if isomerization occurs through the half-hydrogenated state (Fig. 2.14B), exactly one deuterium would be expected in the *trans* isomer because the rotation about the newly formed single bond places the added deuterium away from the surface, bringing the hydrogen on the original double bond in a position close to the surface where it can be extracted by the surface. Thus, the diadsorbed state is reformed and can desorb as the *trans* isomer.

Examples of this flipping mechanism are seen in *cis*–*trans* isomerizations from less stable to more stable isomers which when the reactions are carried out under deuterium. Already mentioned are the isomerizations of oleic acid. Additionally, methyl-(*Z*)-but-2-enoate isomerizes to its more stable *E*-isomer with incorporation of substantial amounts of deuterium during deuteriumation over Pd/C (Fig. 2.16). At the same percentage deuteriumation, the saturated product contains in its β -position 90% of the two deuteriums added to

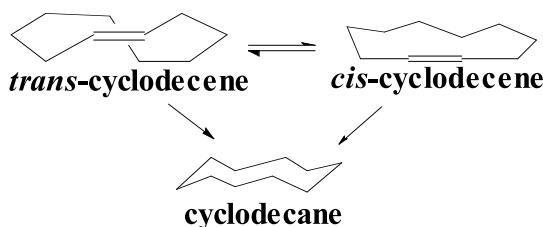


FIGURE 2.13

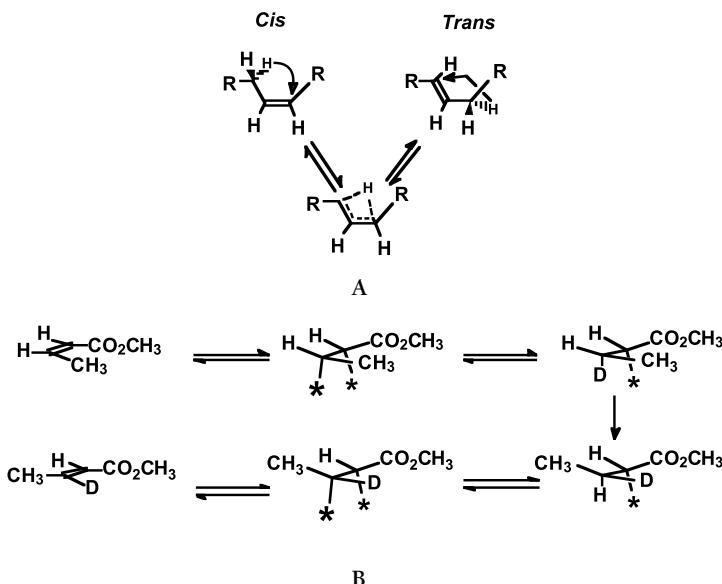


FIGURE 2.14 Two possible mechanisms for cis–trans isomerization. Mechanism A goes by way of double bond migration through a π -allyl surface species (hydrogen abstraction–addition) and mechanism B goes through the half-hydrogenated state (deuterium addition–protium abstraction).

the double bond. At complete saturation, more deuterium is in the β -position (Fig. 2.16).¹¹⁹ The simplest explanation is that the less stable *cis* isomer rotated about the former double bond in the half-hydrogenated state to the anti-eclipsed form, which continued to exchange its remaining hydrogen for

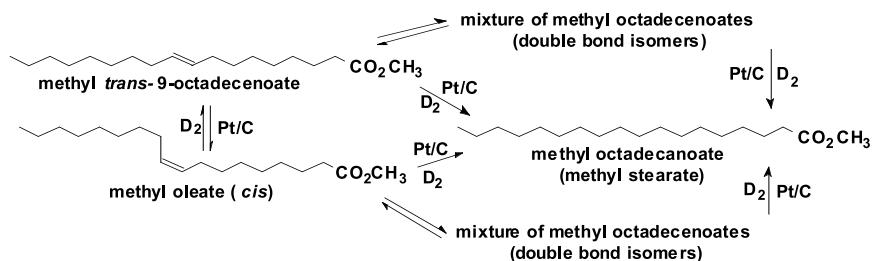


FIGURE 2.15

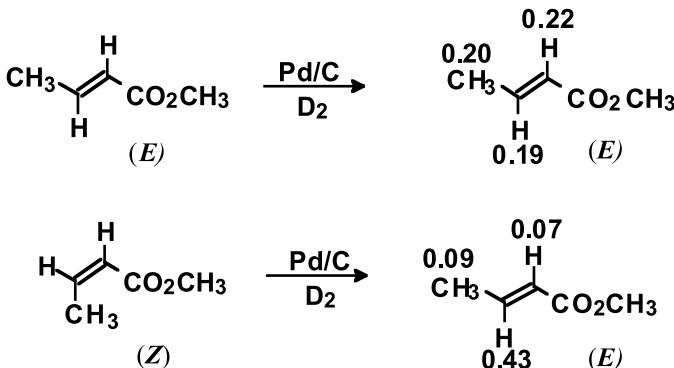


FIGURE 2.16 Partial deuteriumation of *Z* and *E* isomers of methy-but-2-enoate. Saturated products (d_n -methyl butanoate) not shown.¹¹⁹

deuterium until a hydrogen or deuterium added to the α -position. Because exchanged hydrogen had been placed on the surface, it was incorporated into the α -position when the final addition occurred. Apparently, on Pd this process is more rapid than surface diffusion of deuterium.

If the *cis-trans* isomerization is rapid compared with addition in the presence of deuterium, the exchanging alkene may exchange enough hydrogen onto the surface to dilute the adsorbed deuterium in the vicinity of the reaction site. Consequently, subsequent additions of surface hydrogen–deuterium will be rich in hydrogen rather than deuterium, so the saturated product obtained early in the deuteriumation will contain less deuterium than that obtained later. Overall, the amount of deuterium will average 2 because the surface hydrogen–deuterium exchanges very little with gas-phase hydrogen–deuterium during liquid-phase hydrogenations (Table 2.3). In the exchanged alkenes, the deuterium is conserved in the products and on the surface. As a result, deuterium may be distributed unsymmetrically between the two carbons of the former double bond. If one carbon of the double bond is more susceptible to addition–abstraction than the other, it may accumulate deuterium early in the reaction if it desorbs readily.

Sometimes *cis-trans* isomerizations occur slowly or not at all because certain groups anchor their end of the double bond to the surface and inhibit that end from flipping. Thus, phenyl groups and oxygen-containing groups tend to inhibit *cis-trans* isomerization (Fig. 2.17).¹²⁰

An example of this reveals an additional substituent effect (Fig. 2.18).¹²¹ Ordinarily, the phenyl and carboxyl groups anchor the double bond approximately equally (notice the sixth entry in Table 2.3 and cinnamic acid in Fig.

TABLE 2.3 Deuterium Distributions in Saturated Products at 100% Deuteriumation of α,β -Unsaturated Compounds¹¹⁹

X	a	t	c	Deuterium in saturate			
				Pd		Pt	
				α	β	α	β
CH ₃ O ₂ C-	H-	H-	H-	0.36	1.68	0.50	1.52
Ph-	H-	H-	H-	0.58	1.41	0.68	1.32
<i>tert</i> -butyl	H-	H-	H-	0.80	1.20	—	—
CH ₃ O ₂ C-	H-	CH ₃	H-	0.82	1.02	0.87 ^a	0.93 ^a
CH ₃ O ₂ C-	H-	H-	CH ₃	—	—	0.52 ^b	0.95 ^b
CH ₃ O ₂ C-	H-	Ph-	H-	1.00	1.00	0.99	1.01
CH ₃ O ₂ C-	CH ₃	H-	H-	0.15	1.82	0.34	1.72
Ph-	CH ₃	H-	H-	0.63	1.47	0.74	1.26
Ph-	Ph-	H-	H-	0.70	1.30	0.77	1.23

^a Deuterium in methyl = 0.22.

^b Deuterium in methyl = 0.42.

2.18); however, the presence of a *para*-methoxy group renders the phenyl group a better anchoring group than the carboxyl (Fig. 2.18).

An alternative, possibly parallel, mechanism for *cis-trans* isomerization¹²² has been resurrected by single crystal experiments.¹²³ During studies of double

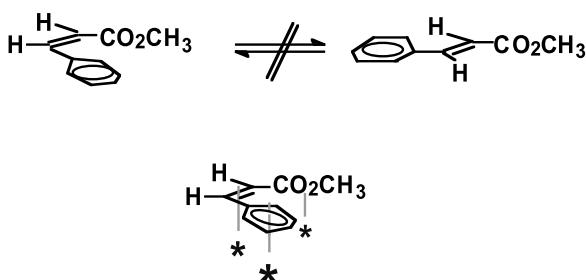


FIGURE 2.17 Phenyl effect.¹²⁰

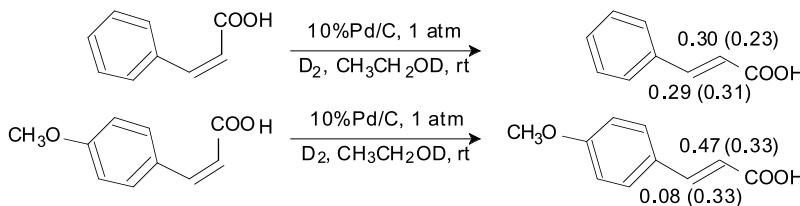


FIGURE 2.18 Partial deuteriumation of *cis*-3-phenyl propenoic acids showing the fraction of deuterium in olefinic positions of recovered *trans* isomers. Numbers in parentheses are over “Lindlar” catalyst.¹²¹

bond migration and *cis*–*trans* isomerization of *n*-butenes it was found that isomerization of *cis*- to *trans*-2-butene occurs twice as fast on a Pt(755) surface than on any of the other Pt surfaces examined, Pt foil, Pt(111), or Pt(100). Since the Pt(755) surface contains B₄ sites at one-atom-high steps, it has been proposed that *cis*-2-butene may adsorb at these sites such that metal atoms on both sides of the C=C double bond disrupt the π-bond enough to allow rotation about the remaining C₂–C₃ σ-bond¹²⁴ (Fig. 2.19). Such a mechanism

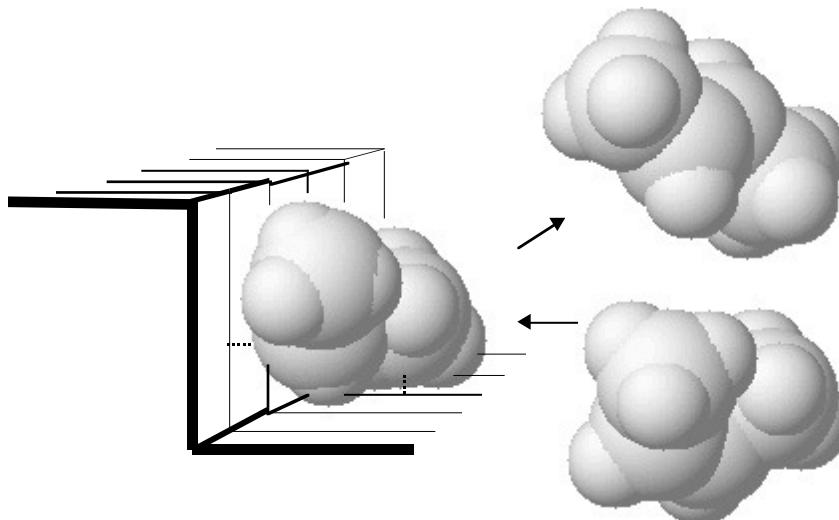


FIGURE 2.19 Adsorption of *cis*-2-butene at the B₄ site on Pt(755); metal atoms not shown.

would also help explain why so many light *trans*-alkene molecules are formed during deuteriumations of *cis*-alkenes.

2.1.3.4. Enantioselective Hydrogenation of C=C Bonds

The enantioselective hydrogenation of C=C bonds is included in Chapter 3, where the general nature of heterogeneous enantioselective hydrogenation is fully explored, so here we examine only the narrow subject. Enantioselective hydrogenation of C=C bonds occurs only on prochiral double bonds (at least one of the carbons substituted with two different groups other than hydrogen). A chiral environment is required.

The chiral environment is furnished by the catalyst as described in Chapter 3. Unfortunately, no general procedure now exists for uniformly producing highly enantioselective hydrogenations with heterogeneous catalysts. Several homogeneous and immobilized homogeneous chiral catalysts are highly enantioselective,¹²⁵ but there the prochiral double bond is bonded to the catalytic metal atom in close proximity to the chiral ligands and steric factors are well able to play an important part in orienting the incoming prochiral double bond. In contrast, chiral modification of metal surfaces has not yet been as successful and enantioselectivities generally have been low. Nevertheless, certain guidelines have emerged.

Generally, prochiral C=C bonds that produce the highest enantiomeric excesses (ee's; the difference between the enantiomers divided by the sum of the enantiomers) contain two or more anchoring groups. These anchoring groups are frequently phenyl and carboxyl, although carbonyls and basic nitrogens also play this role. For example, the highest ee (72%) obtained for any C=C bond is for (*E*)-2-phenylcinnamic acid, which contains three such anchoring groups. Table 2.4 lists most of the heterogeneous enantioselective hydrogenations of C=C double bonds.

2.1.4 AROMATICS

Hydrogenation of the aromatic ring is more difficult than that of either alkenes or alkynes. The reason is the resonance energy that must be surmounted. However, once the resonance energy is overcome, the molecule adds hydrogen rapidly. Several reviews have examined this field.^{138–140} Essentially, the relative order of activity for benzene hydrogenation is Rh > Ru > > Pt > Pd > Ni > Co.¹⁴¹ Originally, it was thought that the ring hydrogenated all at once. However, careful studies have shown that the benzene ring hydrogenates in steps. In fact, the intermediate mono- and dienes can and have been isolated.¹⁴² Con-

TABLE 2.4 Heterogeneous Enantioselective Hydrogenations of C=C Bonds

	A	B	X	Y	Catalyst/Support	Modifier	ee(%) ^a	Ref.
1	CO ₂ H	Ph	Ph	H	Pd/C	Cinchonidine	30	126
2	CO ₂ H	Ph	Ph	H	Pd/TiO ₂	Cinchonidine	72	127
3	CO ₂ H	CH ₃	Ph	H	Pd/SiO ₂	Borneoxysilyl	22.5	128
4	CO ₂ Me	CH ₂ CO ₂ Me	H	H	Pt/β-CDP	β-Cyclodextrin Polymer	4.8	129
5	CO ₂ Me	CH ₃ CO ₂ Me	H	H	Ru/β-CDP	β-Cyclodextrin Polymer	5.2	129
6	CO ₂ Me	CH ₂ CO ₂ Me	H	H	Rh/β-CDP	β-Cyclodextrin Polymer	4.8	129
7	CO ₂ Me	CH ₃	CH ₃	H	Pd/SiO ₂	Cinchonidine	0	130
8	CO ₂ H	CH ₃	CH ₃	H	Pd/SiO ₂	Cinchonidine	22	130
9	CO ₂ H	CH ₃	CH ₃	H	Pd/SiO ₂	Cinchonine	22	130
10	CO ₂ Et	CH ₃	CF ₃	H	Pd/SiO ₂	Cinchonidine	0	130
11	CO ₂ H	CH ₃	CF ₃	H	Pd/SiO ₂	Cinchonidine	15	130
12	CO ₂ H	CH ₃	H	C ₂ H ₅	Pd/SiO ₂	Cinchona	22	130
13	CO ₂ H	CH ₃	H	C ₂ H ₅	Pd/SiO ₂	Cinchonidine	20–27	130
14	CO ₂ H	CH ₃	C ₂ H ₅	H	Pd/SiO ₂	Borneoxysilyl	9	128
15	CO ₂ H	CH ₃	C ₂ H ₅	H	Pd/Al ₂ O ₃	Cinchonidine	52	131
16	CO ₂ Me	CH ₃	H	CH ₃	Pd/SiO ₂	Cinchonidine	0	130
17	CO ₂ H	CH ₃	H	CH ₃	Pd/SiO ₂	Cinchonidine	15	130
18	CO ₂ H	CH ₃	H	CH ₃	Pd/SiO ₂	Cinchonine	14	130
19	CO ₂ H	CH ₃	C ₂ H ₅	H	Pt/β-CDP	β-Cyclodextrin Polymer	3.3	129
20	CO ₂ H	CH ₃	C ₂ H ₅	H	Ru/β-CDP	β-Cyclodextrin Polymer	7.9	129
21	CO ₂ H	CH ₃	C ₂ H ₅	H	Rh/β-CDP	β-Cyclodextrin Polymer	2.1	129
22	CO ₂ H	CH ₃	C ₂ H ₅	H	Rh/β-CDP	β-Cyclodextrin Polymer	9.3	129
23	CO ₂ H	CH ₃	H	C ₂ H ₅	Pd/SiO ₂	Cinchonidine	65	130

continues

^a maximal ee (%).

TABLE 2.4 *continued*

	A	B	X	Y	Catalyst/Support	Modifier	ee(%) ^a	Ref.
24	CO ₂ H	CH ₃	H	C ₂ H ₅	Pd/SiO ₂	Cinchonine		130
25	CO ₂ H	C ₂ H ₅	H	C ₂ H ₅	Pd/SiO ₂	Cinchonidine	62	130
26	CO ₂ H	C ₂ H ₅	H	C ₂ H ₅	Pd/SiO ₂	Cinchonine	51	130
27	CO ₂ Na	Ph	Ph	H	Ra-Ni	Tartrate	17	132
28	CO ₂ H	NHAc	Ph	H	Pd, Ni, Ru	Poly-amino acid	6	133
29	C(O)OC(CH ₃)=N-B ^b		Ph	H	Pd	Silk fibroin	66	134
30	C(O)OC(CH ₃)=N-B ^b		Ph	H	Ra-Ni	Tyrosine	50	134
31	NHC(O)-B' ^c		Ph	H	Pd	Silk fibroin	23	134
32	CO ₂ Me	C(O)NH-A' ^c	H		Pt/C	Cinchonidine	11	134
33	CH ₃	N=CH-CH=CH-X ^b	H		Ra-Ni	Tartrate	5	135
34	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pt/C	(-)Dihydrovinpocetine	1.9	136
35	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Rh/C	(-)Dihydrovinpocetine	0.83	136
36	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Ru/C	(-)Dihydrovinpocetine	0.30	136
37	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Ir/C	(-)Dihydrovinpocetine	2.1	136
38	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd/C	(-)Dihydrovinpocetine	10	137
39	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd/C	Dihydrocinchonidine	3	137
40	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd/various	(-)Dihydrovinpocetine	16	136
41	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd black	(-)Dihydrovinpocetine	38	136
42	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd black	(-)Dihydrovinpocetine	40	137
43	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd black	Dihydrocinchonidine	20	137
44	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd powder	(-)Dihydrovinpocetine	19	137
45	CH ₃	C(CH ₃) ₂ CH ₂ C(O)-X ^b	H		Pd powder	Dihydrocinchonidine	10	137

^a maximal ee (%).^b connect in a cycle.^c two double bonds, that is, diamide of α -aminocinnamic acid.

ditions that favor partial hydrogenation of the benzene ring are Rh/C catalysts, low pressures (1 atm or less), and ambient temperatures.¹⁴³

2.2. HYDROGENATION OF C=O BONDS

Hydrogenation of carbonyl groups occurs readily over most catalysts.¹⁴⁴ However, care must be exercised in preventing hydrogenolysis of the resulting hydroxyl group.

2.2.1. ALDEHYDES

2.2.1.1. Saturated Aliphatic Aldehydes

Saturated aliphatic aldehydes are hydrogenated to the corresponding alcohols over platinum metal catalysts (Fig. 2.20) with little danger of overhydrogenation under ordinary conditions. Hydrogenation of saturated aliphatic aldehydes is relatively slow (compared with that of aromatic aldehydes), and elevated temperatures and pressures may be useful. Pt has been the most used catalyst, but from limited data it appears that Ru may frequently be a more active catalyst. Pd usually is a poor catalyst and can be used in those cases in which hydrogenation of another functional group is desired, leaving the aldehyde group unhydrogenated. However, if enough steric congestion occurs around the other functional group, for example, a highly substituted C=C bond, the aldehyde group will be hydrogenated preferentially (Fig. 2.21; see also Table 2.6, and Section 2.2.1.2).¹⁴⁵ Under elevated temperatures decarbonylation may occur (see Section 5.1).

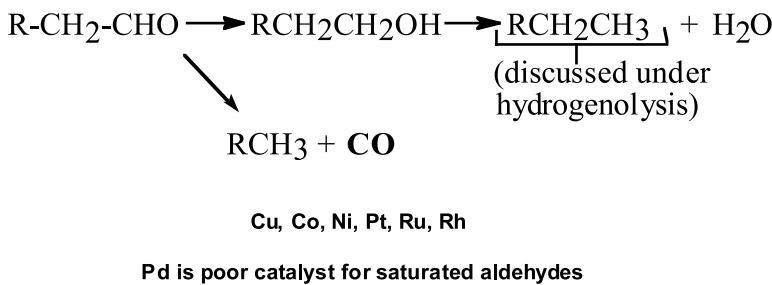


FIGURE 2.20

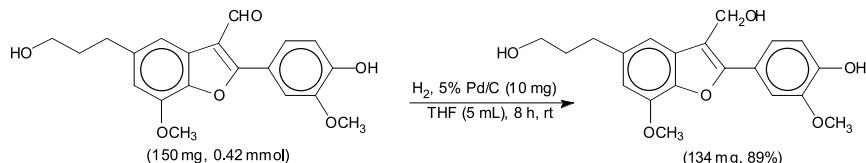


FIGURE 2.21

2.2.1.2. Chemoselectivity: Unsaturated Aldehydes

Frequently, hydrogenation of the aldehyde C=O bond competes with hydrogenation of a C=C bond. The challenge is to specifically hydrogenate one and then stop the reaction to obtain the desired product with the other double bond intact. Usually, unconjugated C=C and C=O bonds can be selectively hydrogenated (see Section 2.2.1.1); but if the two groups are conjugated, a variety of possibilities arise as depicted in Fig. 2.22. Therefore, α,β -unsaturated aldehydes occupy a unique position in the field of heterogeneous catalytic hydrogenation.

In general, over the more common catalysts hydrogenation of the C=C bond is favored over Pd and that of the C=O over Pt or Ru. However, steric hindrance around the C=C bond slows its hydrogenation and increases the probability of C=O hydrogenation. This can happen to such an extent that even over Pd, C=C bonds may be inhibited and C=O hydrogenation favored (see Section 2.2.1.1).

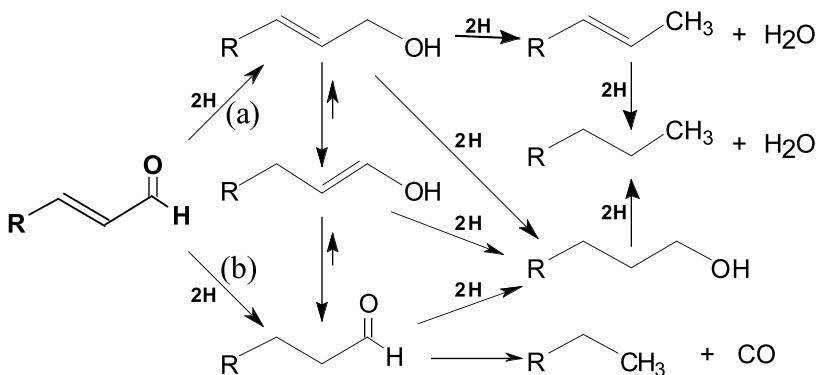


FIGURE 2.22

Considerable effort has gone into learning how to hydrogenate the C=O bond and retain the C=C bond to produce α,β -unsaturated alcohols (allylic alcohols), which are useful in the fine chemicals industry. Early works toward selectively hydrogenating the C=O bond have been reviewed and discussed.¹⁴⁶ An excellent review was published in 1995.¹⁴⁷

Table 2.5 lists some good catalysts and conditions to try for selective hydrogenation of the C=O bond in an α,β -unsaturated aldehyde.

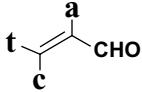
Under relatively mild conditions the Ru/C catalyst poisoned with Sn (lines 1 and 2), the Ir/C catalyst (lines 14 and 15), and the Raney-cobalt catalyst modified with CoCl₂ (line 19) seem likely systems to try when initiating a search for an effective method for selectively hydrogenating the C=O bond in an α,β -unsaturated aldehyde.

More recent work has focused on understanding the mechanism or mechanisms of selectivity. Some of these studies have been performed on well-characterized catalysts about which particle size information is available. Still others have been performed on single crystals. So conclusions may be reached about the effects on chemoselectivity of planes, edges, and corners that are related to particle size (structure sensitivity). A number of these studies, mostly on Pt, are summarized in Table 2.6. Since these studies have usually been performed in the vapor phase, information about solvent effects and their possible influence on chemoselectivity is unavailable.

In general, the results point to the edges and/or corners (small particles) favoring hydrogenation of the C=C bond whereas the planes (large particles) favor hydrogenation of the C=O bond. This seems to be true for all compounds on Pt (see Table 2.6, lines 10–27, and 29–30) and for cinnamaldehyde on Ru and Rh (see Table 2.6, lines 33, 34, 37, and 38); however, citral on Ru did not exhibit this effect (see Table 2.6, lines 35 and 36), according to the authors' statement. The reasons for this latter result are not clear. Why, for example should other alkyl-substituted α,β -unsaturated aldehydes exhibit this structure sensitivity and citral not? Clearly, other factors are also at play.

In addition to the metal, support, particle size, and substituents, other important factors are modifiers and solvents. (One must be aware that solvents should be considered modifiers too.) From early on, modifiers have played important roles in the selective hydrogenation of α,β -unsaturated aldehydes. The important ones are shown in Tables 2.6 and 2.5. Sn seems to be universally beneficial for selectively hydrogenating the C=O bond over the C=C bond (see Table 2.5, lines 1–3; Table 2.6, lines 3, 6, 9, 15, 17–19, and 28), but other metals and metalloids are beneficial too, as can be seen in Tables 2.6 and 2.5. Recently, Sn has been shown to preferentially bind to step sites,¹⁶⁷ which agrees with the generalization that these sites are involved in hydrogenation of C=C bonds. One interesting contradiction is the effect of the alkali metals, Na and K. Over Pt, Na causes a large increase in selectivity for hydrogenating the

TABLE 2.5 Some Successful Catalysts and Conditions for High Selectivity^a for Hydrogenating the C=O Bond in α,β -unsaturated Aldehydes

				Catalyst/ support	Modifier	Solvent	Temp. (°C)	Pressure (atm)	Ref.
	a	c	t						
1	H	CH ₃	C ₆ H ₁₁ ^b	2% Ru/C	Sn (20–40%)	EtOH (95%)	60	1	148
2	H	H	Ph	2% Ru/C	Sn (20–40%)	EtOH (95%)	60	1	148
3	H	CH ₃	C ₆ H ₁₁ ^b	Rh/SiO ₂	Sn (n-C ₄ H ₉) ₄	n-Heptane	67	75	149
4	H	H	CH ₃	5, 10, 30% Pt/C	Fe + Zn or Ag	EtOH	25	3.4	150
5	H	H	CH ₃	5% Pt/CaCO ₃	Fe-Zn	EtOH	25	3.4	150
6	H	H	Ph	PtO ₂	Fe-Zn	EtOH	25	3.4	150
7	H	H	Ph	5% Pt/C	Fe + Zn or Ag	n-Hexane	25	3.4	150
8	H	H	CH ₃	Re		Neat	145	152	151
9	H	H	Ph	Re		Neat	145	152	151
10	H	H	CH ₃	Re	Pyridine	Neat	110	174	152
11	H	H	Ph	Re	Pyridine	Neat	110	174	152
12	H	H	CH ₃	5% Os/C	—	2-Propanol	100	51–68	153
13	H	H	Ph	5% Os/C	—	2-Propanol	100	51–68	153
14	H	H	CH ₃	5% Ir/C	—	EtOH (96%)	Room	1	154
15	H	H	Ph	5% Ir/C	—	EtOH (96%)	Room	1	154
16	H	H	H	0.9% Re/CPG ^c	Re ₂ (CO) ₁₀ /CS ₂	Vapor phase	282	20.7	155
17	H	H	H	12% Re/C	CO	Vapor phase	119	2.45	155
18	H	H	H	Ag-Zn ^d	Fe ³⁺	Vapor phase	120	1	156
19	H	CH ₃	C ₆ H ₁₁ ^b	Co ^d	CoCl ₂	1-Propanol	30–65	1	157

^a Usually > 90% allylic alcohol, except for acrolein, which is usually \geq 70% allyl alcohol.

^b Citral (actually, a mixture of E and Z, likely E/Z \approx 2).

^c Controlled-pore glass.

^d Raney-type.

C=C bond (see Table 2.6, lines 1–2, 4–5, and 7–8), whereas over Ru, K exhibits just the opposite effect (see Table 2.6, lines 31–32). The effect of using NaOAc in the solvent system containing isopropanol and water is unclear (Table 2.6, lines 29–30). Additionally, typical catalyst poisons may improve

TABLE 2.6 Selectivities for Hydrogenation of Some α,β -Unsaturated Aldehydes

	Substituents			Catalyst/ support	Avg. size (nm) ^a	Modifier(s)	Temp. or solvent ^b	$C=O/C=C$ (surviving db) ^c	Ref.
	a	c	t						
1	H	H	H	Pt/SiO ₂	10.5	—	353 K	57.9	158
2	H	H	H	Pt/SiO ₂	8.5–15	Na	353 K	1077	158
3	H	H	H	Pt/SiO ₂	8.5–15	Sn, Ga, Fe	353 K	2.4–11.6	158
4	H	H	CH ₃	Pt/SiO ₂	10.5	—	353 K	3.8	158
5	H	H	CH ₃	Pt/SiO ₂	8.5–15	Na	353 K	6.9	158
6	H	H	CH ₃	Pt/SiO ₂	8.5–15	Ga, Fe, Sn	353 K	1.6–1.7	158
7	H	CH ₃	CH ₃	Pt/SiO ₂	10.5	—	353 K	0.83	158
8	H	CH ₃	CH ₃	Pt/SiO ₂	8.5–15	Na	353 K	2.8	158
9	H	CH ₃	CH ₃	Pt/SiO ₂	8.5–15	Fe, Ga, Sn	353 K	0.063–0.098	158
10	H	H	CH ₃	Pt (111)	SC	—	330 K	0.11 ^d	159
11	H	H	CH ₃	Pt ₈₀ Fe ₂₀	SC	Fe	330 K	0.15 ^d	159
12	H	CH ₃	CH ₃	Pt (111)	SC	—	330 K	1.27 ^d	159
13	H	CH ₃	CH ₃	Pt ₈₀ Fe ₂₀	SC	Fe	330 K	2.33 ^d	159
14	H	CH ₃	CH ₃	Pt (111)	SC	—	353 K	0.071	160
15	H	CH ₃	CH ₃	Pt (111)	SC	Sn (0.5 ML) ^e	353 K	0.063	160
16	H	CH ₃	CH ₃	Pt (553)	SC	—	353 K	0.36	160
17	H	CH ₃	CH ₃	Pt (553)	SC	Sn (0.5 ML) ^e	353 K	1.8	160
18	H	CH ₃	CH ₃	Pt (553)	SC	Sn (1 ML) ^e	353 K	0.33	160
19	H	CH ₃	CH ₃	Pt (553)	SC	Sn (2 ML) ^e	353 K	0.14	160
20	H	H	CH ₃	Pt/SiO ₂	11 ^f	—	EtOH	0.76	161

continues

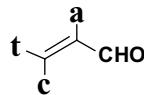
^a SC, single crystal; ND, not determined.^b Gas-phase reaction if temperature is indicated; experiments in EtOH were at room temperature, approximately 300 K.^c Saturated aldehyde divided by allylic alcohol; smaller numbers indicate greater selectivity for hydrogenation of C=O bond relative to that of C=C bond. This value does not reveal yield.^d Estimated from percentage allylic alcohol; percentages of saturated aldehyde and other products were not published, so relative amounts are uncertain and values are likely too large.^e ML, monolayer.^f Estimated from H/Pt data.^g Assumed value; only codes reported, not data.^h Citral (actually, a mixture of E and Z, likely E/Z ≈ 2).

TABLE 2.6 *continued*

Substituents			Catalyst/ support	Avg. size (nm) ^a	Modifier(s)	Temp. or solvent ^b	C=O/C=C (surviving db) ^c	Ref.	
a	c	t							
21	H	H	CH ₃	Pt/SiO ₂	5 ^f	—	EtOH	1.1	161
22	H	H	CH ₃	Pt/SiO ₂	2 ^f	—	EtOH	1.4	161
23	H	H	CH ₃	Pt/SiO ₂	1 ^f	—	EtOH	3.8	161
24	H	H	CH ₃	Pt/TiO ₂	5.8 ^f	—	EtOH	2.0 ^d	161
25	H	H	CH ₃	Pt/TiO ₂	1 ^f	—	EtOH	8.1 ^d	161
26	H	H	H	Pt/SiO ₂	3.2	—	353 K	79.9	162
27	H	H	H	Pt/SiO ₂	15	—	353 K	43.8	162
28	H	H	H	Pt/SiO ₂	15 ^g	Sn (10, 20, 25%)	353 K	2.73, 2.47, 2.66	162
29	H	H	Ph	3.6% Pt/C	1.3	NaOAc	2-C ₃ OH/ H ₂ O	0.26	163
30	H	H	Ph	3.6% Pt/C	5	NaOAc	2-C ₃ OH/ H ₂ O	0.031	163
31	H	CH ₃	CH ₃	Ru/SiO ₂	2.3	—	313 K	10.6	164
32	H	CH ₃	CH ₃	Ru/SiO ₂	2.3	K (10, 20%)	313 K	0.31, 0.24	164
33	H	CH ₃	Ph	0.5% Ru/C	3	—	EtOH	2.3 ^d	148
34	H	CH ₃	Ph	10% Ru/C	17	—	EtOH	0.66 ^d	148
35	H	CH ₃	C ₆ H ₁₁ ^h	0.5% Ru/C	3	—	EtOH	1.9 ^d	148
36	H	CH ₃	C ₆ H ₁₁ ^h	10% Ru/C	17	—	EtOH	1.9 ^d	148
37	H	H	Ph	3.4% Rh/C	2.5	NaOAc	2-C ₃ OH/ H ₂ O	4.6	165

continues^a SC, single crystal; ND, not determined.^b Gas-phase reaction if temperature is indicated; experiments in EtOH were at room temperature, approximately 300 K.^c Saturated aldehyde divided by allylic alcohol; smaller numbers indicate greater selectivity for hydrogenation of C=O bond relative to that of C=C bond. This value does not reveal yield.^d Estimated from percentage allylic alcohol; percentages of saturated aldehyde and other products were not published, so relative amounts are uncertain and values are likely too large.^e ML, monolayer.^f Estimated from H/Pt data.^g Assumed value; only codes reported, not data.^h Citral (actually, a mixture of E and Z, likely E/Z ≈ 2).

TABLE 2.6 *continued*

	Substituents			Catalyst/ support	Avg. size (nm) ^a	Modifier(s)	Temp. or solvent ^b	C=O/C=C (surviving db) ^c	Ref.
	a	c	t						
38	H	H	Ph	3.4% Rh/C	7	NaOAc	2-C ₃ OH/ H ₂ O	1.4	165
39	H	H	H	5% Cu/ Al ₂ O ₃	ND	—	353 K	Very large	166
40	H	H	H	5% Cu/ Al ₂ O ₃	ND	Thiophene	353 K	1.17	166
41	H	H	CH ₃	5% Cu/ Al ₂ O ₃	ND	—	353 K	7.7	166
42	H	H	CH ₃	5% Cu/ Al ₂ O ₃	ND	Thiophene	353 K	0.95	166
43	CH ₃	H	CH ₃	5% Cu/ Al ₂ O ₃	ND	—	353 K	1.13	166
44	CH ₃	H	CH ₃	5% Cu/ Al ₂ O ₃	ND	Thiophene	353 K	0.22	166
45	H	CH ₃	CH ₃	5% Cu/ Al ₂ O ₃	ND	—	353 K	0.15	166
46	H	CH ₃	CH ₃	5% Cu/ Al ₂ O ₃	ND	Thiophene	353 K	0.025	166

^a SC, single crystal; ND, not determined.^b Gas-phase reaction if temperature is indicated; experiments in EtOH were at room temperature, approximately 300 K.^c Saturated aldehyde divided by allylic alcohol; smaller numbers indicate greater selectivity for hydrogenation of C=O bond relative to that of C=C bond. This value does not reveal yield.^d Estimated from percentage allylic alcohol; percentages of saturated aldehyde and other products were not published, so relative amounts are uncertain and values are likely too large.^e ML, monolayer.^f Estimated from H/Pt data.^g Assumed value; only codes reported, not data.^h Citral (actually, a mixture of *E* and *Z*, likely *E/Z* ≈ 2).

the ability of a metal to selectively catalyze the hydrogenation of the C=O bond over the C=C bond. For example, CO, CS₂, pyridine, and thiophene exhibit this effect (see Table 2.5, lines 17, 16, and 10–11; Table 2.6, lines 40, 42, 44, and 46). We must remember that these, as well as many of the metal

modifiers, are typical poisons for the hydrogenation of C=C bonds (see Section 2.1.1.1). How much these modifiers rearrange or block surface sites and how much they interact electronically with the carbonyl group of the aldehyde is a matter of speculation. Many theories seem to have been proposed. Taking a simplistic view, one might surmise that the planes contain favorable sites for hydrogenating C=O bonds and the edges and/or corners contain favorable sites for hydrogenating C=C bonds. These contain not the exclusive sites for each hydrogenation, but rather the most favorable sites. Therefore, modifiers that attach to edge and corner sites inhibit C=C bond hydrogenation more than C=O, whereas those which attach to plane sites inhibit the reverse, unless, of course, they enhance C=O adsorption, as may be the case in enantioselective hydrogenations of prochiral C=O bonds (Chapter 3).

Besides the results in Table 2.6, other evidence exists for planes favoring C=O and edges and corners favoring C=C hydrogenations. Data that we discuss in Chapter 3 show that modification for enantioselective hydrogenation of prochiral C=O bonds works best on large crystallites (a high fraction of planes) and results that we discussed earlier in this chapter suggest that edges and possibly corners excel in the hydrogenation of C=C bonds. Interestingly, if the two types of double bonds are far separated, as for example in two different molecules, cyclohexene and butanal, the C=C bond hydrogenates first.¹⁶⁸

2.2.2. KETONES

The keto carbonyl group can be hydrogenated fairly readily and many of the characteristics of aldehyde hydrogenations also apply here. Initially, the alcohol is produced, but overhydrogenation may result in hydrogenolysis of the C–O bond to form the alkane (Fig. 2.23). Acidic media facilitate hydrogenolysis whereas basic media or basic substituents inhibit hydrogenolysis.

Some information about how the carbonyl group adsorbs onto the catalyst surface has been determined and is summarized by Tanaka.¹⁶⁹ On the basis

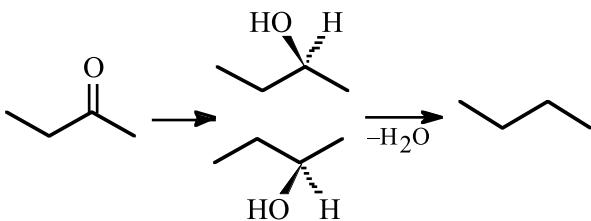


FIGURE 2.23

that hydrogenations of ketones over Ru, Os, Ir, and Pt proceed by the simple addition of two hydrogens (deuteriums), associative adsorption is postulated with two possibilities, A and B, shown in Fig. 2.24. However, spectral evidence suggests species such as π -bonded, (D), or oxygen-coordinated species (E), exist on these catalysts, whereas on Pd π -allyl (π -oxallyls) (C), may exist. Species like C are also postulated for Pt, whereas on Rh, species A, B, and C may lead to other species (for example, 1,2- and 1,6-diadsorbed), which account for exchange at other carbons.^{170,173}

Several metals catalyze hydrogenation and hydrogenolysis of the ketone C=O bond. Comparison of the various catalysts¹⁷¹ reveals that Pd is very good for hydrogenating aromatic ketones but relatively ineffective for aliphatic ketones; however, it is good when the goal is to minimize hydrogenolysis (except in acidic media); Pt gets deactivated easily, but deactivation is inhibited by small amounts of ferrous or stannous chlorides; Rh is used under mild conditions and its activity is increased by alloying with Sn;¹⁷² Ru is excellent and can be used with water; Ir is rarely used; Os is sluggish; Ni usually requires vigorous conditions; and copper chromite requires elevated temperatures and pressures, but Cr- or Mo-containing nickel and nickel boride are active catalysts.^{68,173}

The solvent is very important for the hydrogenation of ketones. One of the most important factors in the liquid-phase hydrogenation of ketones is whether the medium is acidic, neutral, or basic, and a great deal of work has gone into attempting to understand chemoselectivity and stereoselectivity based on combinations of the metal catalyst and the reaction medium.

2.2.2.1. Chemoselectivity

Sometimes hydrogenation of a keto group is in competition with a phenyl group. Some differences among the various catalysts are shown in Fig. 2.25.¹⁷⁴

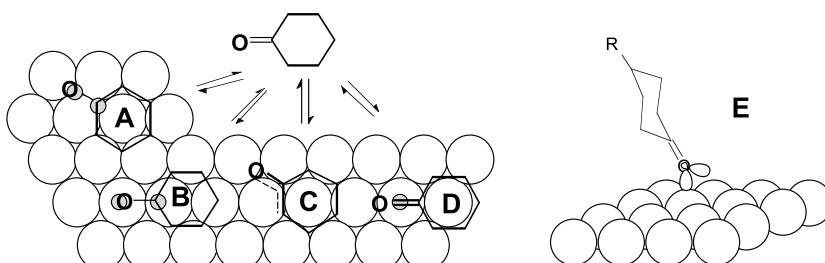


FIGURE 2.24 Possible modes of adsorption of cyclohexanone

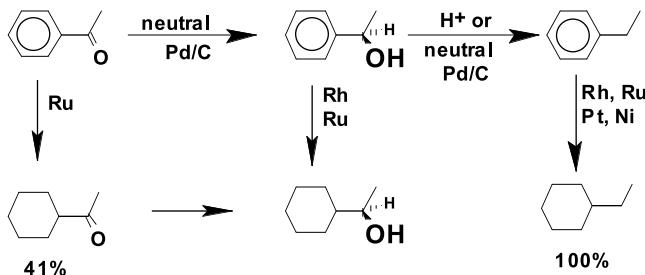


FIGURE 2.25 Some difference in selectivity among different catalysts.¹⁷³

However, sometimes Pd/C in ethanol catalyzes overhydrogenation and hydrogenolyzes off the OH group at 40 psig¹⁷⁵ as well as at 1 atm¹⁷⁶ and sometimes it will not.¹⁷⁷

Another competition is between the keto group and the C=C bond (Fig. 2.26). Generally the C=C bond hydrogenates faster than the C=O bond, especially over Pd, whereas the C=O bond hydrogenates faster over Pt and Ru; however, the structure of the unsaturated ketone plays an important role. For example, if the C=C bond is hindered, Pd may first catalyze hydrogenation of the C=O bond. Decreasing activities in the order Pt > Pd > Rh » Ru > Ni > Cu were found for the hydrogenation of 3-penten-2-one in methanol over various catalysts supported on SiO₂.¹⁷⁸

The Use of deuterium has revealed interesting mechanistic details. Over Rh/C, Pt/C, and Pd/C, the butanone resulting from the deuteration of methyl vinyl ketone contains substantially more deuterium at position 4 than at 3 (Table 2.7). This can generally be accounted for by the classic mechanism assuming the α -carbon (position 3) remains preferentially attached to the surface while the β -carbon (position 4) undergoes multiple exchange by repeated second-point attachment (Fig. 2.27). However, over Pd/C, even less deuterium

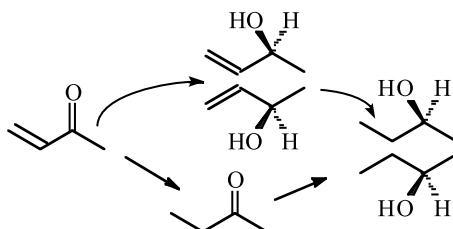


FIGURE 2.26

appears at position 3, whereas more appears at 4 (Table 2.7). This suggests some special mechanism operating over Pd. The suggestion has been made that a 1–4 hydrogen shift is occurring. That is, a deuterium displaces a hydrogen from carbon 4 onto the carbonyl group, which forms an enol upon desorption. The enol spontaneously converts to the keto form, putting the hydrogen on carbon 3 (path B in Fig. 2.27).¹⁷⁹

Sometimes two keto groups are present in the same molecule. In such cases, Pt usually catalyzes the hydrogenation of the least hindered keto group first, and it is possible to stop the reaction at this stage.

2.2.2.2. Stereoselectivity

Whereas general activities and selectivities for hydrogenations of ketones are similar to those of aldehydes, one big difference exists between the two. The hydrogenation of prochiral ketone carbonyls produces chiral carbons. Over symmetrical catalysts, racemic alcohols are formed; however, over unsymmetrical surfaces, enantioselectivity may occur. Enantioselective hydrogenations of ketones is an increasingly active research field and is covered in Chapter 3. Here we discuss that aspect of stereoselectivity associated with ring systems.

In a ring system, the resulting alcohol may be axial or equatorial, and much work has gone into examining the stereochemistry of the hydrogenation of sub-

TABLE 2.7 Locations of Deuteriums in Saturated Products from Deuteriumation of Terminal Alkenes over Different Catalysts^a

	Rh/C	Pt/C	Pd/C
	1.55 0.49	1.52 0.50	1.69 0.34
	1.33 0.65	1.38 0.62	1.56 0.38
	—	1.32 0.68	1.41 0.58

^a In the saturate, a statistical distribution would place 1.2 deuteriums on the β -carbon and 0.8 deuteriums on the α -carbon.

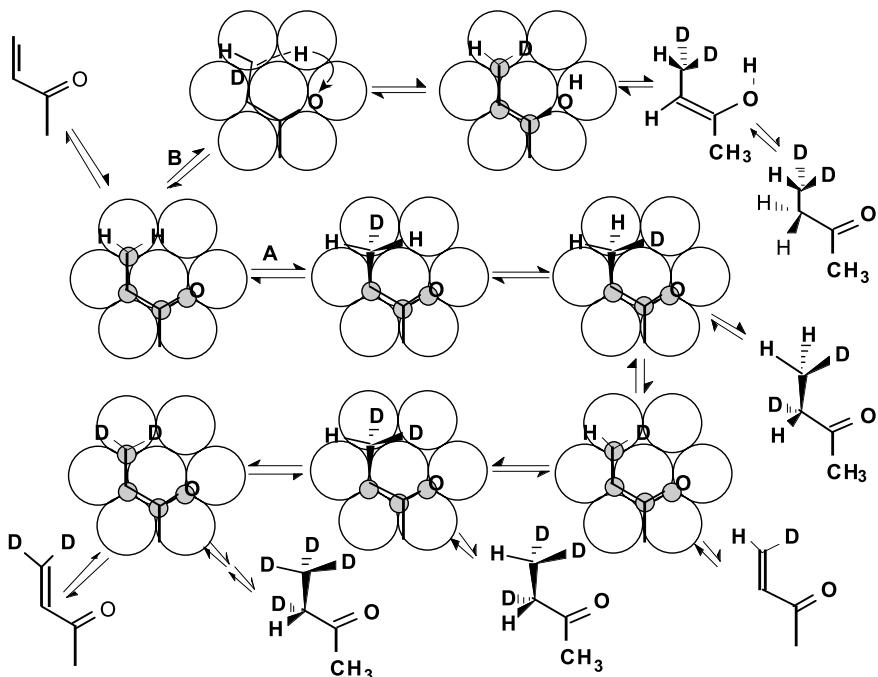
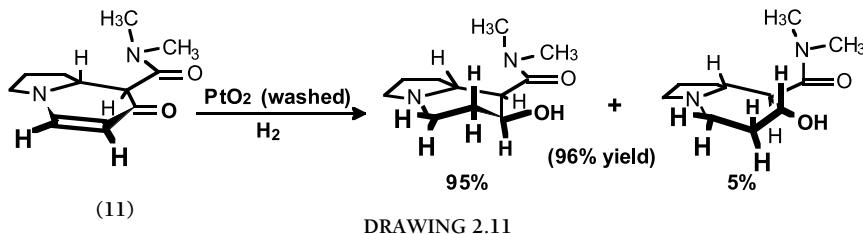


FIGURE 2.27 Two possible mechanisms to explain deuterium distributions resulting from deuteriumation and exchange of methyl vinyl ketone. Deuterium is assumed to move subsurface and to attack adsorbed carbons from threefold hollows. Path A: multiple exchange by repeated addition-rotation-abstraction at the β -carbon (classic mechanism); path B: 1-4 hydrogen shift followed by desorption as enol.

stituted cyclopentanones and cyclohexanones.¹⁸⁰ Interests in these structures stem from concerns about predicting product stereochemistry from hydrogenation of ketone-containing steroids, such as cholestenone and testosterone. The conditions under which the resulting hydroxyl group is axial or equatorial are instructive for a mechanistic elucidation but the results present a distinctly complicated mechanistic challenge. It is not surprising, therefore, that no unified mechanistic conclusion has been reached. A summary of the empirical rules are essentially as follows: In acidic media the axial OH is formed and in basic media the equatorial OH is formed. In neutral media, the equatorial OH is formed from nonhindered ketones, and the axial OH from hindered ketones. A recent application of some of these principles can be found in the hydrogenation of **11**,¹⁸¹ in which an earlier-discovered washing procedure¹⁸²



removed alkaline substances from PtO_2 and allowed the *cis* (axial) product to dominate followed by a conformational rearrangement to the equatorial position. When one is predicting the product outcome, clearly several steric considerations must be taken into account.¹⁸³

Most workers try to explain the final stereochemistry of the OH group on the basis of adsorption. That is, the mode of adsorption determines the resulting stereochemistry, assuming that the addition of hydrogen occurs *cis* from the surface up to the bottom of the adsorbed carbonyl group. Most investigators seem to assume that the carbonyl is protonated in acidic media and the mode of adsorption of this species is different from the unprotonated species (in neutral and basic media).

Certainly, one consideration must be the polar nature of the $\text{C}=\text{O}$ bond and the resulting metal–O bonds formed upon adsorption and during surface reaction. Although these latter bonds are not ionic, they are highly polarized on most metals. And this invites consideration of mechanisms involving hydrogen ions,¹⁷⁴ both hydride and proton and possibly a polarized hydrogen molecule. Such a mechanism has been proposed (Fig. 2.28)¹⁸⁴ in which the usual protonated carbonyl is adsorbed in the equatorial position such that the addition of a hydride ion from the surface puts it into an axial position. On the other hand, in basic media, the enolate anion is formed and also adsorbs such that the oxygen is in the equatorial position, but now the addition of a hydride ion to the α -carbon (adjacent to the carbonyl carbon) produces a carbanion at the carbonyl carbon with the molecule mono-adsorbed through its oxygen. Finally, it is proposed that a proton attacks the top of the molecule from the basic solution to produce the OH in the equatorial position. This mechanism differs from the frequently drawn mechanism⁶⁸ (Horiuti-Polanyi type) only in the designation of the kind of hydrogen, proton or hydride, added from the surface and in the topside attack of a proton from the medium. Usually, an unidentified hydrogen is depicted as adding at the appropriate time and place with the assumption being that the charges are absorbed or furnished by the metal catalyst. Additionally, there are complex interactions between the adsorbed molecule and the surface atoms as well as between groups within the adsorbed species.

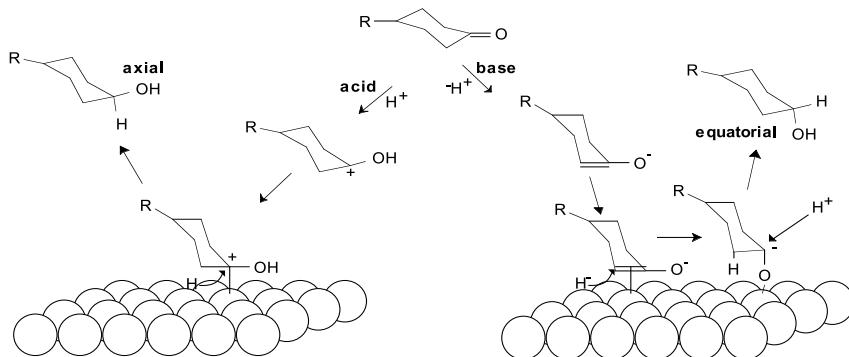


FIGURE 2.28 Showing proposed ionic mechanism to account for stereochemistry during hydrogenation of cyclic ketones. Surface attachments of adsorbed species are uncertain.

Let us examine this mechanism in basic media in Fig. 2.28. Presumably, the addition of a hydride to the adsorbed enolate anion results in the corresponding adsorption of one of the resulting negative charges by the surface (certainly the addition of a hydrogen atom might be preferred); however, the proposed addition of a proton from a basic medium seems unlikely. Nevertheless, this is an attempt to address the problem of how to get the OH equatorial after adding hydrogen to the adsorbed enolate. If the hydrogen adds from the surface, then the molecule must turn over; alternatively, a hydrogen must add on top as proposed in Fig. 2.24. In spite of these questions, such a proposal attempts to take into account the polarity of the C–O and metal–O bonds; it attempts to write the mechanism in a more standard organic form; and it stimulates mechanistic thinking. One of the interesting aspects of this mechanism is the *trans* addition of the two hydrogens. At least one other group proposes a similar addition mode to account for stereochemical results.¹⁸⁵ Such proposals encourage one to wonder whether the addition of hydrogen (in some form), from solvents or from other substrate molecules, to the topside of adsorbed substrates is reasonable and actually occurs. It certainly furnishes a universal explanation for apparent *trans* addition during liquid-phase hydrogenations.

2.2.3. ACIDS, ESTERS, LACTONES, AMIDES, IMIDES, AND ANHYDRIDES

Hydrogenation of these functional groups is difficult and a variety of catalysts and conditions have been developed to accomplish the reaction.^{186,187} Usually,

but not always, high temperatures and high pressures are required. An approximate order of ease of hydrogenation is anhydrides \geq imides \gg lactones > esters > acids > lactams > amides. But the ease of hydrogenation of each depends on structural factors as well as catalyst and conditions. Useful catalysts are Cr-based (Cu-CrO_2 ,^{188–192} Cu-Ba-CrO_3 ,^{193–197} Zn-CrO_2 ,^{192,196,197} Mg-CrO_2 ,¹⁹² Cd-CrO_2 ,¹⁹² Ru-based (RuO_2 ,¹⁹⁸ Ru/C ,¹⁹⁸ $\text{Ru-Sn/Al}_2\text{O}_3$,^{199,200} Re-based (ReO_7 ,^{201–203} Re-Co ,²⁰⁴ Re-Os ,²⁰⁵ Re-Sn ,²⁰⁶ $\text{Re-Ni-Ba/SiO}_2\text{-Al}_2\text{O}_3$,²⁰⁷) PtO_2 ,^{208,209} Pd/C ,^{210–212} ZrO_2 ,^{213,214} Cr/ZrO_2 ,^{213,215} ZnO ,²¹⁴ CeO_2 ,²¹⁴ and Ra-Ni .^{196,216–218} Many of the hydrogenations amount to adding hydrogen to a C=O bond and then hydrogenolyzing off the OH group. Although not a hard and fast rule, these hydrogenations–hydrogenolyses seem to be facilitated by strong acids, which suggests carbonyl oxygen protonation as a first step. On the other hand, the Cr-based catalysts seem not to require acid but usually require high pressures and temperatures.

2.3. HYDROGENATION OF NITROGEN-CONTAINING MULTIPLE BONDS AND REDUCTIVE AMINATION

Hydrogenations of multiple bonds containing nitrogen are relatively easily accomplished and have been extensively reviewed through approximately 1994.^{219,220} It must be remembered, though, that the product amines are frequently used to poison catalysts. This emphasizes the fact that these nitrogen compounds are relatively strongly adsorbed on most catalytic surfaces. Therefore, they reside on the surface sufficiently long enough to allow side reactions to occur. One of these reactions is the alkylation of nitrogen compounds, commonly called *reductive amination* or *reductive alkylation*. This reaction forms secondary and tertiary amines from the hydrogenation of aldehydes or ketones in the presence of amines (the product of hydrogenation of unsaturated nitrogen compounds). The nitrogen of the amine attacks the carbonyl carbon, and water elimination forms the ketimine, which is hydrogenated (Fig. 2.29).^{221–226} This happens also with primary imines, which are readily hydrogenated but can undergo self-alkylation as shown in Fig. 2.30.^{227,228} Since imines are intermediates in the hydrogenation of nitro compounds, nitriles, and oximes, reductive amination may be expected as a side reaction. Imines such as 12 may be hydrogenated with $\text{Pt/Al}_2\text{O}_3$.²²⁹ An interesting rearrangement and internal alkylation occurs during a 1,5-addition of hydrogen to 13.²³⁰

Catalytic hydrogenation of nitriles may result in several products: primary, secondary, and tertiary amines; imines; hydrocarbons; aldehydes; amides; and

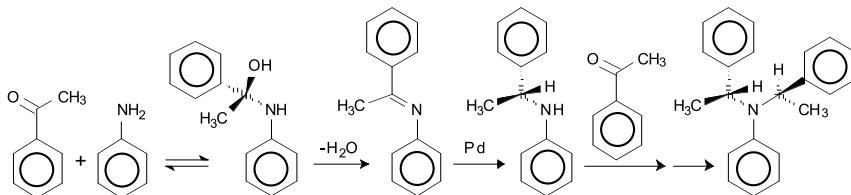


FIGURE 2.29 Reductive Amination

alcohols. The main product depends on the catalyst, substrate, and reaction conditions. Since primary amines are frequently sought, alkylation must be avoided.

Accomplishing this involves making the primary amine unreactive or removing it from solution once formed. High pressures of hydrogen increase the rate of hydrogenation of the intermediate imine and lower the probability of alkylation. Strong acids render the amine unreactive, sodium acetate or acetic anhydride²³¹ trap the amine as the amide, and ammonia adds to the intermediate imine (later to be hydrogenolyzed off) making it less reactive for alkylation. Some recent successful conditions leading mainly to the primary amine are 50–55 psig H_2 , room temperature, water solvent (although acid is beneficial for lowering secondary amine formation²³²), and relatively large amounts of PtO_2 catalyst (approximately 125 mg of PtO_2/mmol of CN).²³³ The solvent system consisting of NH_3 -saturated EtOH ^{234,235} is effective when Ra-Ni

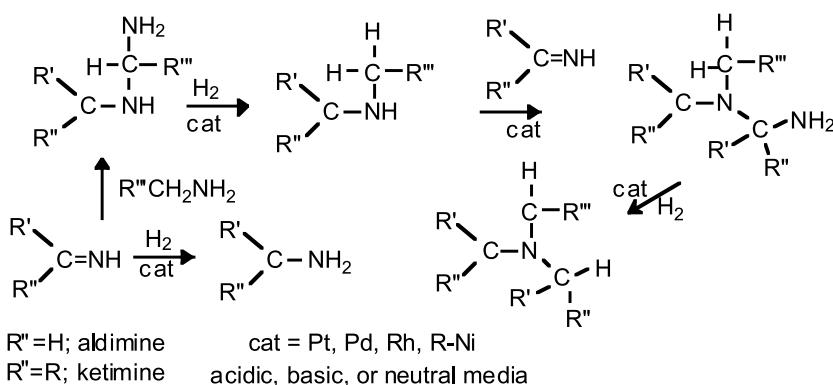
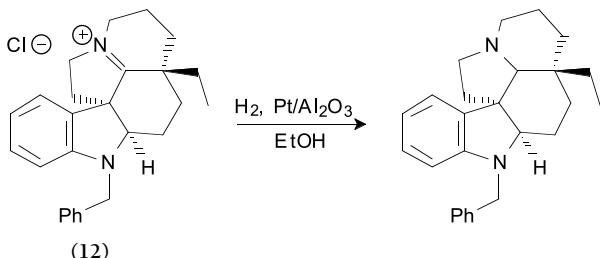


FIGURE 2.30 Hydrogenation and alkylation of imines

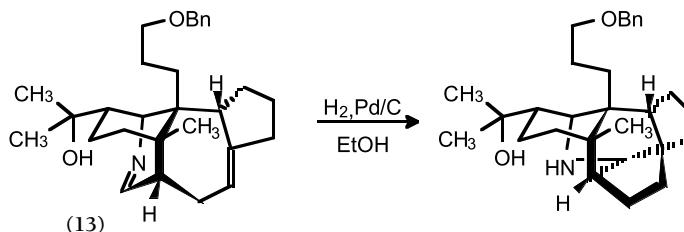


DRAWING 2.12

is used to accomplish the hydrogenation of nitriles, and basic supports lead to primary amines when supported nickel catalysts are used.²³⁶ The use of Ra-Ni can also produce an aldehyde when $\text{NaH}_2\text{PO}_2 \cdot \text{H}_2\text{O}$ is added in combination with a solvent system consisting of pyridine–HOAc– H_2O (2:1:1).²³⁷ An effective set of conditions is 35°C, 1 atm H_2 , 1 mmol nitrile, 25 ml 1% NH_3 in EtOH, and 400 mg 5% Rh/Al₂O₃.²³⁸ Over 5% Pd/C, DMF–benzene (1:1 v/v) has been effective.²³⁹

Hydrogenations of aromatic nitro compounds are important in industry. A nitro group can be easily introduced into a benzene ring and then hydrogenated to the amine. During the hydrogenation, a number of coupling and alkylation reactions are possible as depicted in Fig. 2.31.

Complete hydrogenation to the amine can be accomplished in several ways. Over 5% Pt/C in EtOAc at 25°C and 20 psig H_2 , an aliphatic nitro group has been hydrogenated in preference to C=C bonds, although an indole nitrogen in the starting compound may have poisoned the catalysts.²⁴⁰ PtO₂ in methanol or ethanol is frequently used to hydrogenate aromatic^{241–244} and aliphatic²⁴⁵ nitro groups. However, PtO₂ in HCl has catalyzed the hydrogenation of both a nitro group and a benzene ring.²⁴⁶ Hydrogen gas need not be used. Hydrogenations



DRAWING 2.13

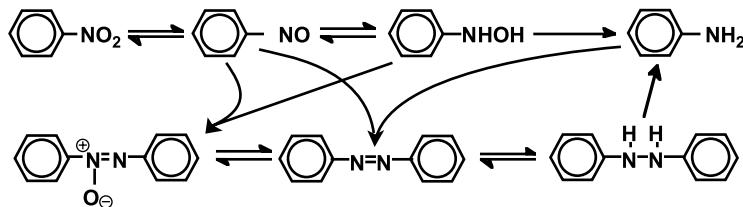


FIGURE 2.31 Reactions associated with hydrogenation of nitro groups.

of aromatic nitro groups have been accomplished over Pd/C using cyclohexene^{247,248} and ammonium formate^{237,249} in hydrogen transfer hydrogenations (see Section 2.4.1). Pd/C and hydrogen gas have been successfully used to hydrogenate aromatic nitro groups in a variety of solvent systems: ethanol,^{250–255} methanol,^{256–261} ethanol–chloroform,²⁶² methanol–DMF,²⁶³ DMF,²⁶⁴ ethyl acetate,²⁶⁵ and THF.^{266–269} Ra-Ni has also been used successfully for the hydrogenation of aromatic nitro groups.^{270–272}

Considerable work has gone into stopping the hydrogenation at different stages. Although stopping at the nitroso group is difficult by hydrogenation techniques, obtaining it by a reductive deoxygenation has been achieved²⁷³ (Table 2.8).

Stopping at the hydroxylamine stage can be accomplished for aromatic (but not aliphatic) nitro compounds by poisoning Pt catalysts with dimethylsulfoxide (DMSO) (Fig. 2.32).²⁷⁴ The authors believe that this difference is explained by the differences in adsorbability of the aromatic and aliphatic nitro compounds. Whereas DMSO poisons aliphatic nitro group hydrogenations, it does not poison aromatic nitro group hydrogenations because the aromatic competes favorably with DMSO for active sites. Stopping at the

TABLE 2.8 Reductive Deoxygenation of Nitro to Nitroso

$-\text{NO}_2 \xrightarrow[\text{573 K}]{\text{CH}_4}$		$-\text{NO}$
Catalyst	Conversion	Selectivity
Mn_3O_4	14.3	90
V_2O_5	1.88	96
MoO_3	1.08	98



FIGURE 2.32 DMSO modification of Pt catalysts to stop hydrogenation at hydroxylamine. Note: DMSO is not effective with Pd catalysts.

hydroxylamine stage can also be accomplished by hydrogen transfer (Section 2.4.1.) from phosphinic acid or sodium phosphinate.^{275,276}

However, one must remember that the accumulation of phenylhydroxylamines presents a serious danger because these compounds disproportionate with the liberation of much heat and may cause a runaway reaction, that is, an explosion (Fig. 2.33). This becomes especially dangerous if the reaction temperature gets close to 250°C, the autodecomposition temperature of phenylhydroxylamine. Some of these accidents have been reported.²⁷⁷

On the other hand, phenylhydroxylamines undergo some interesting reactions that are commercially useful. For example they rearrange (Fig. 2.34) and undergo condensations into products such as *p*-aminodiphenylamine^{278,279} and others that are useful as antioxidants, antiozonants, dyes, medicinals, and resins.

Hydrogenation of nitro groups may be stopped at the hydrazo stage with a proper catalyst and inhibitors. As shown in Fig. 2.31, the hydrazo compounds result from condensation of the nitroso and hydroxylamine and can be maximized or minimized (see the later discussion of nitroso group hydrogenation) depending on conditions. For example 2,2'-dichlorohydrazobenzene can be prepared in 90% yield (Fig. 2.35).²⁸⁰

Accumulation of hydroxylamine is dangerous

It disproportionates with liberation of lots of heat

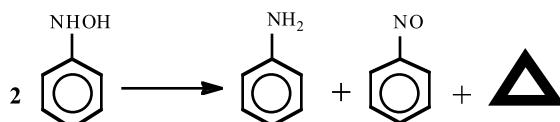
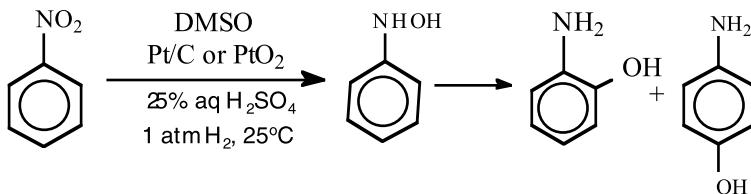


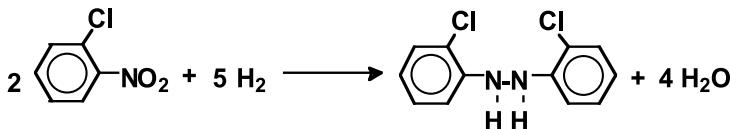
FIGURE 2.33



When HCl or HF is used, one gets ortho and para halogen-substituted anilines.

FIGURE 2.34 Rearrangements of phenylhydroxylamines.

One of the problems associated with hydrogenating halogenated nitroaromatics is dehalogenation. A fair amount of work has gone into establishing conditions for retaining the halogen in the ring while hydrogenating the nitro group and several reviews have been published.^{281,282} The extent of hydrodehalogenation (halogen hydrogenolysis) may depend on the halogen (F is most resistant, then Cl > Br > I), the overall structure, the catalyst support (basic is better than acidic for resisting dehalogenation), the catalytic metal (Pd is better than Pt and Rh for hydrodehalogenation), the amount of catalyst (hydrodehalogenation decreases as the amount of catalyst is decreased), and the reaction conditions. Several of these, pressure, temperature, agitation, and the amount of catalyst, have been related in part to hydrogen availability at the surface. Thus hydrodehalogenation relative to nitro group hydrogenation is favored by hydrogen-poor catalysts and increasing temperatures, whereas it is



Conditions:

Solvent: 12% aqueous NaOH

Catalyst: 5% Pd/C

Inhibitor: 2,3-dichloro-1,4-naphthoquinone

Temperature: 60°C

Pressure: 60 psig

Results:

90% yield of 2,2'-dichlorohydrazobenzene

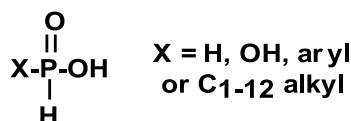
FIGURE 2.35 Conditions for formation of hydrazo compounds.

retarded by hydrogen-rich catalysts and increasing pressures. In general, Pt, with or without modifiers, is the best catalyst for minimizing dehalogenation while rapidly hydrogenating nitro groups. However, modifiers can play an important role. Bases, both inorganic and organic, inhibit hydrodehalogenation.^{283–285} Bases of various kinds are often used stoichiometrically to help accomplish catalytic dehydrohalogenation; yet, paradoxically, the same bases in smaller amounts can also be used to inhibit the loss of halogen during hydrogenation of halonitrobenzenes. Particularly effective modifiers are the phosphinic acids (Fig. 2.36),²⁸⁶ and cadmium acetate has been shown to have a pronounced suppression of hydrodechlorination.²⁸⁷ Catalyst particle size also plays a role. As shown in Fig. 2.38,²⁸⁷ hydrogenation of *p*-chloronitrobenzene over a series of differently dispersed 1% Pd/SiO₂ catalysts reveals that hydrodechlorination is favored on low dispersed catalysts (Pd -black, 0.05%D) relative to nitro group hydrogenation. Although the catalysts in the dispersion range of 50-94%D catalyze hydrogenation of the nitro group at approximately the same rate (Fig. 2.37), on the same catalysts hydrodechlorination passes through a minimum around 60%D (Fig. 2.38), which is approximately the maximum for edges. So one might conclude that edges and/or the atoms nearby are unfavorable sites for hydrodehalogenation whereas plane sites are more favorable.

o-Nitrotoluene can be converted into *o*-hydrazotoluene under conditions²⁸⁸ similar to those used for the conversion of *o*-choronitrobenzene. *o*-Hydrazotoluene is a valuable compound because it can be converted by the benzidine rearrangement to *o*-tolidine using acid catalysts. *o*-Tolidine has a worldwide market of 10 million pounds and is used in the organic dye industry for the production of azo dyes. Also, it is phosgenated to tolidine di-isocyanate, which is used to make high-performance, specialty polyurethanes.

Aromatic nitroso groups are as easily hydrogenated as nitro groups; however such groups attached to aliphatic moieties are not so readily hydrogenated.

Inhibition of dehalogenation by phosphinic acids



These are effective with both Pt and Pd catalysts

FIGURE 2.36 Catalyst modifier for inhibiting hydrodehalogenation during nitro hydrogenation.

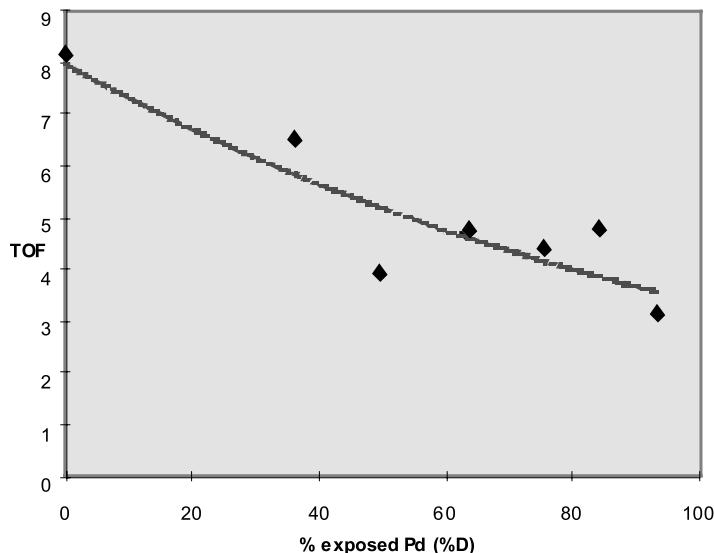


FIGURE 2.37 Decrease in rate of hydrogenation of p-chloronitrobenzene with decrease in particle size.

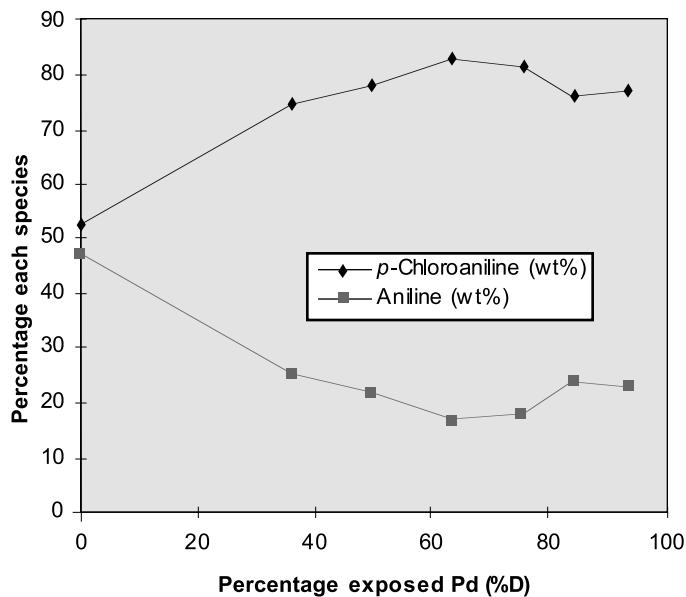


FIGURE 2.38 Effect of particle size on hydrodechlorination.

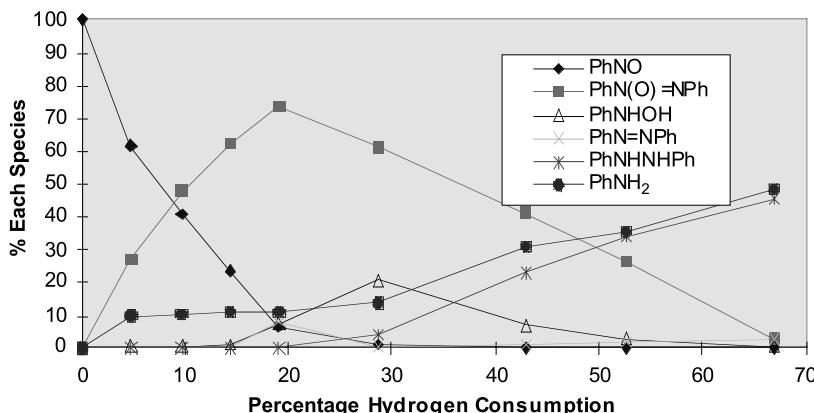


FIGURE 2.39 Product distribution during hydrogenation of nitrosobenzene over Pd black at ambient temperatures in methanol.

Nitroso groups are intermediates in the hydrogenation of nitro groups and their mechanisms are the same as in Fig. 2.31 without $-\text{NO}_2$.

Studies of the hydrogenation of aromatic nitroso compounds have rarely been published. One of the earliest studies is the Pd/C catalyzed hydrogenation of *p*-nitrosothymol to its corresponding amine (100%) in ethanol at 1 atm hydrogen.²⁸⁹ Useful antioxidants and gasoline stabilizers are made from diamines, which can be produced by hydrogenating their relatively easily formed nitroso derivatives.²⁹⁰ As a result, the hydrogenation of 4-nitroso-diphenylamine has been studied more heavily than others.^{291–293}

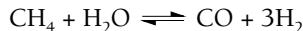
An example of the product distribution during hydrogenation is shown in Fig. 2.39. The main difference between hydrogenation of aromatic nitro and nitroso groups is that the nitroso group reacts rapidly with intermediate hydroxylamine to form side products (see Fig. 2.31), so their concentrations must be kept low to avoid this reaction.²⁹⁴

A mild structure sensitivity accompanies hydrogenation of nitrosobenzene over a series of dispersed 1% Pd/SiO₂.²⁹⁴ The lower dispersed catalysts (larger particle sizes) catalyze faster rates, suggesting that planes are more active than either edges or corners for catalyzing the hydrogenation of nitrosobenzene.

2.4. HYDROGEN SOURCES

In addition to hydrogen gas, other sources of hydrogen are available. In principle, hydrogen may be obtained from any molecule containing hydrogen

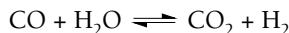
provided it can be decomposed. However, some sources are better than others and are more readily accessible than others. Among these are transfer hydrogenation (Section 2.4.1.) and its variant, membrane hydrogenation (Section 2.4.2.); steam reforming of methane and other hydrocarbons;²⁹⁵ carbon dioxide reforming of methane;²⁹⁶ and the water gas shift reaction.^{297–299} In organic chemistry the first two are more important than the latter three.



Steam reforming of methane



Carbon dioxide reforming of methane



Water gas shift reaction

2.4.1. HYDROGEN TRANSFER CATALYSIS

Hydrogen may be abstracted from a variety of donor molecules over different catalysts, usually Pd, and used to hydrogenate or hydrogenolyze acceptor molecules. The field was extensively reviewed in 1974³⁰⁰ and in 1996.³⁰¹ Brief discussions are included in other places.^{302,303} Essentially, donor molecules may be any organic or inorganic compound that can give up hydrogens under the reaction conditions. These include formic acid and its salts,^{304–308} phosphinic acid and its salts,²³⁷ hydrazine,³⁰⁹ substituted cyclohexenes,^{310–313} substituted cyclohexadienes,^{314–316} tetralin,³¹⁷ H₂O-CO,³¹⁸ alcohols,^{319,320} and triethylsilane.^{321,322} These so-called hydrogen transfer reactions can be useful when gaseous hydrogen must be avoided. Sometimes the hydrogen transfer method gives superior results in selected cases. However, the results are not always predictable.

For example, in the transfer hydrogenation of the dimethyl ester of the 1,2-dicarboxybicycloheptadiene shown in Table 2.9,³²³ the product composition does not appear to correlate with the structure of the hydrogen donor (HD). However, because of its unique structure, the reacting diene serves as a molecular probe for detecting hydrogen availability on the catalytic surface. Results of the top entry (results enclosed in squares) suggest that the higher ratio of the HD, cyclohexene, places more hydrogen on the surface than the lower ratio. This results in a decrease in 5 and an increase in endo-4 (Table 2.9). Rearranging the hydrogen donors in order of their apparent ability to furnish hydrogen to the surface produces the order shown in Fig. 2.40. Apparently, cyclohexene furnishes hydrogen at a medium level such that variations in its

TABLE 2.9 Transfer Hydrogenation of Dimethyl Ester of 1,2-Dicarboxybicycloheptadene

Donor (HD)	HD/3 molar ratio	time (h)	Conversion (%)	% %		Yield (%)
				5	7	
	5	37	>99	64	36	
	7	22	>99	88	12	56
	5	37	>99	98	2	
	7	22	>99	98	2	52
	5	22	50	>99	<1	90
	7	32	30	>99	<1	48
	66	22	>99	24–26	74–76	55
	6	17	>99	12	88	66
	6	29	>99	27	73	60
	5	22	>99	50	50	92

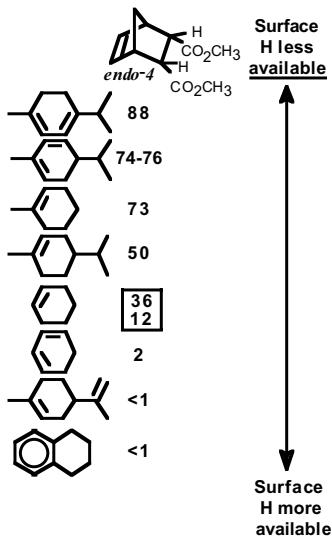


FIGURE 2.40 Order of ability of hydrogen donors to furnish hydrogen.

concentration influence the surface hydrogen concentration and therefore the relative rates of the pathways leading to the two products. Cyclohexadiene, on the other hand, furnishes much hydrogen to the surface, so the variations used by the investigators were not enough to change the relative rates of the two pathways. Likely, 1-methyl-4-isopropylcyclohexene would have exhibited the same behavior as cyclohexene had its concentration been increased similar to that of cyclohexene. Both limonene and tetralin produce so much hydrogen on the surface that the pathway leading to 5 is virtually the exclusive pathway. In contrast, 1-methyl-4-isopropyl-1,3-cyclohexadiene furnishes precious little hydrogen to the surface and the relative rates of the two pathways are reversed. Undoubtedly, differences in steric factors among the hydrogen donors as well as the number of available hydrogens in each molecule play roles in their relative abilities to furnish hydrogen to the surface. Analysis of the energy diagram shown in Fig. 2.41 reveals the likely reasons for this behavior. The diene may approach the surface in several ways but probably does so predominantly with the unsubstituted double bond toward the surface. Steric hindrance of the two carbomethoxy groups on the other double bond inhibit adsorption. On the other hand, once the disubstituted double bond does adsorb, it is strongly held by the anchoring effect of the carbomethoxy groups. Each diadsorbed species may then react according to its

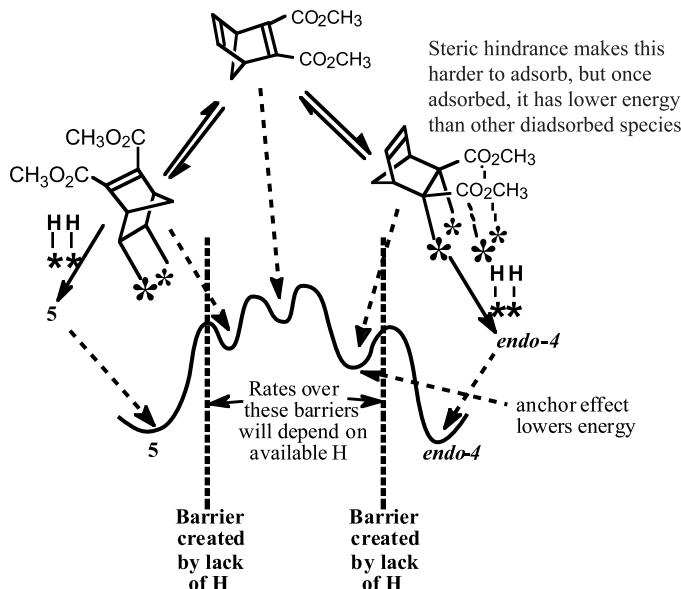


FIGURE 2.41

rate constant and the concentration of surface hydrogen. If surface hydrogen is sparse, the two diadsorbed species may desorb and readSORB many times and attain an equilibrium mixture that is richer in the anchored species leading to **endo-4** than in the one leading to **5** (Fig. 2.40). In that case, the energy barriers between diadsorbed species and products will control. That is, **endo-4** will dominate. In contrast, if hydrogen is plentiful, the energy barriers for adsorption will control and **5** will dominate.

Additional information about the nature of the interactions between hydrogen donor, surface, and hydrogen acceptor are revealed in another study³¹⁴ in which the prochiral molecules *N*-acetyl- α -amino cinnamic acid and methyl β -(4-methylphenyl)- α -phenylpropenoate were hydrogenated by hydrogen transfer from chiral hydrogen donors over a 10% Pd/C catalyst (Fig. 2.42). Only a racemic mixture of products resulted, which suggests that no strong interaction occurs between hydrogen donor and hydrogen acceptor. If such an interaction existed during hydrogen transfer, some enantioselectivity would be expected to occur. Of course, this does not prove there is no interaction between hydrogen donor and acceptor, but for this case, it is strong evidence.

2.4.2. MEMBRANE CATALYSIS

Growing interest in membrane catalysis has been stimulated by industry's dual desires to attain high selectivities and overcome thermodynamic constraints.

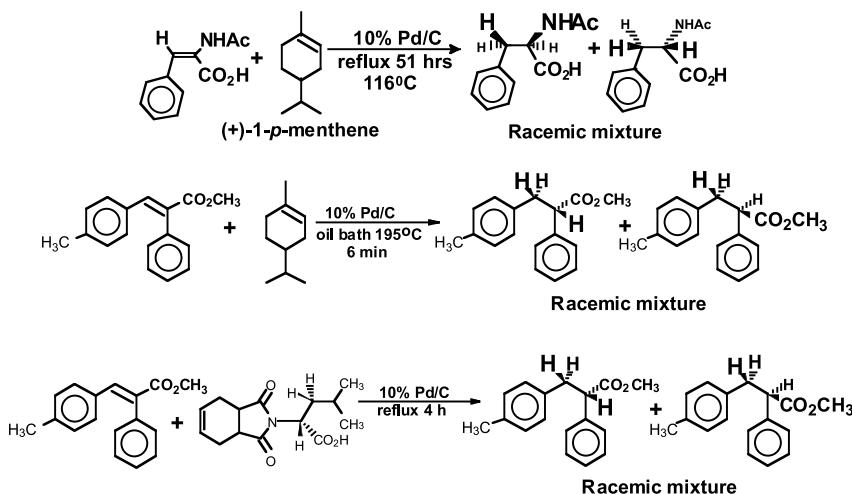


FIGURE 2.42 Hydrogen transfer hydrogenations using chiral hydrogen donors.

Membranes can achieve both of these. For example, a thin Pd membrane has the ability to selectively pass hydrogen atoms from one side to the other. On one side of the membrane, the hydrogen atoms may be formed from hydrogen molecules dissociating on the surface or from some organic or inorganic molecule adsorbing on the surface and losing its hydrogens to the metal. If a hydrogen donor is allowed to adsorb on one side of a Pd membrane and a hydrogen acceptor on the other side, the donor can lose hydrogen and the acceptor gain hydrogen. Thus dehydrogenations in excess of the thermodynamic equilibrium can be accomplished by removing the hydrogen from the vicinity of the dehydrogenated product so the rehydrogenation reaction cannot occur. Additionally, progress in construction has made available membranes that selectively pass small molecules to the exclusion of others; consequently, many new possibilities for the innovative use of membranes are available. Pioneering work in the field came from the group of Gryaznov, who worked mainly with Pd-based membranes.³²⁴ A 1995 review lists previous reviews and summarizes the advantages and disadvantages of membranes in catalysis and the critical needs and issues facing the field.³²⁵

Basically, three kinds of membranes are being studied: inorganic oxide membranes, polymer-based membranes, and metal and metal alloy membranes. Some combinations of these are also used, such as impregnating inorganic oxide membranes with catalytic materials. A key term in this field is *permselective membrane*, which is a thin material that can allow a certain component of a mixture, but not other components, to pass through (or permeate) from one side to the other.

Because hydrogen can easily be removed from a reaction stream, many dehydrogenations have been studied. These include dehydrogenation of methane to carbon,³²⁶ ethane to ethene,^{327,328} propane to propene,³²⁹ n-butane to butenes,³³⁰ isobutane to isobutene,^{331,332} cyclohexane to benzene,^{332–334} methylcyclohexane to toluene,³³⁵ n-heptane to toluene,³³⁶ methanol to formaldehyde,³³⁰ and ethanol to acetaldehyde.³³⁷

Hydrogenations have been accomplished with hydrogen sources from either dihydrogen or a hydrogen donor. Some studies using dihydrogen for hydrogenations include benzene to cyclohexane,³³⁸ acetylene to ethene,^{339,340} ethyl-10-undecen-1-oate,³⁴¹ and methyl linolate.³⁴¹ In the latter example, a novel poison-resistant catalyst is demonstrated by embedding Pt crystallites inside a permselective membrane such that hydrogen can diffuse to the catalyst and become activated but poisons cannot reach the catalyst. An example of coupling hydrogenation to a hydrogen donor is the use of the cyclohexane dehydrogenation to benzene on one side of a Pd membrane to furnish hydrogen for the hydrogenation of ethene to ethane on the other side.³³⁴

Examples of creating highly selective catalysts by adjusting the pore diameter to accommodate certain-size reactants or products are (1) creating channels narrow enough that molecules move single file, so once products are

formed, they are forced out the opposite end from that which they entered and cannot undergo further reaction (for example, half-hydrogenation of 2-hexyne,³⁴² and (2) creating a permselective cellulose acetate membrane that can pass methanol but not isobutene resulting from the disproportionation of methyl *tert*-butyl ether.³⁴³

Steam reforming of methane is an important industrial process for producing large quantities of hydrogen or synthesis gas. A similar reaction, the water gas shift reaction also produces hydrogen from water. Because permeselective membranes offer the possibility of separating pure hydrogen from these reaction mixtures, considerable work has gone into examining Pd-based membranes.^{331,344,345}

Besides offering possibilities for overcoming thermodynamic restrictions and accomplishing selective separations, permselective membranes offer a unique opportunity to examine differences, if any, from subsurface hydrogen and surface hydrogen. Mentioned in Chapter 1 (Section 1.4.1.) is the growing evidence that subsurface hydrogen reacts differently from surface hydrogen (hydrogen positioned on the top of surface metal atoms). Therefore, it is not surprising that several investigators have reported differences in reactivity between surface hydrogens resulting from dihydrogen adsorption on the same surface as the substrate and subsurface hydrogens resulting from hydrogen atoms permeating through a Pd or Pd-alloy membrane. Generally, it is agreed that permeating hydrogen is more active than surface hydrogen for hydrogenation.^{324,325,339} Also, the presence of subsurface hydrogen seems to be important for butene isomerization.³²⁴ Finally, subsurface oxygen rather than surface oxygen is the active species in the dehydrogenation of methanol to formaldehyde.³³⁰

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Enantioselective Hydrogenations

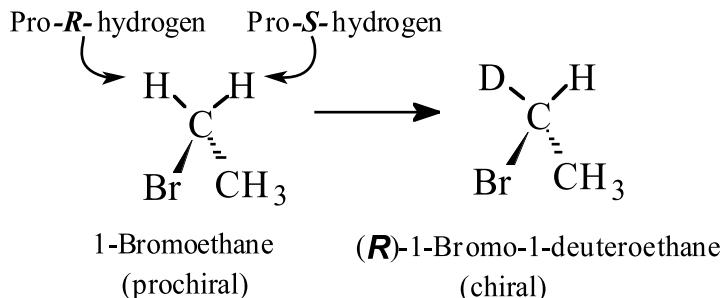
- 3.1. Basic Concepts
- 3.2. Considerations of Chiral Surfaces
- 3.3. Mechanisms of Enantioselectivity on Surfaces

References

3.1. BASIC CONCEPTS

As any good organic chemistry textbook documents, standard nomenclature exists for describing chiral compounds and their precursors. Chiral centers in organic compounds usually are found in sp^3 -hybridized atoms in columns IVA and VA of the periodic table, that is, those atoms containing a rare gas core of electrons plus xs^2xp^2 or xs^2xp^3 electrons, where x equals 2 or 3 (C, N, Si, and P). These are not the only kind of chiral entities, but these are of preparative concern for organic chemists. In fact, most syntheses are focused on creating a chiral center at sp^3 hybridized carbon.

To create a chiral center at an sp^3 -hybridized carbon requires a chiral environment to stereodirect the reaction. This chiral environment may exist as a chirally substituted sp^3 -hybridized carbon, on which appropriate substitution creates a new molecule with the same or inverted chirality at the former chiral center or as a chiral arrangement near a prochiral (prechiral) sp^2 carbon.



SCHEME 3.1

In the case of an sp^3 -hybridized carbon containing three different *substituents* (prochiral), the *substitution* of a fourth kind of substituent for one of the two identical substituents creates a new chiral center.

If two hydrogens and two different groups are bonded to an sp^3 carbon, the hydrogens are called *enantiotopic hydrogens*. For example, the two hydrogens in 1-bromoethane are enantiotopic hydrogens (Scheme 3.1). If one hydrogen in this molecule were to be replaced by deuterium, the carbon would become a sterogenic center. In Scheme 3.1 one of the hydrogens is substituted by deuterium and the (*R*)-1-bromo-1-deuteroethane is produced. Thus, this hydrogen is called *pro-R-hydrogen*, whereas the other is called *pro-S-hydrogen*.

In the case of an sp^2 -hybridized carbon containing three different substituents (prochiral), the *addition* of a fourth kind of substituent to form an sp^3 -hybridized carbon creates a new chiral center (Fig. 3.1).

Stereodirection of either the substitution or the addition requires a chiral environment. This chiral environment may be either in the same molecule

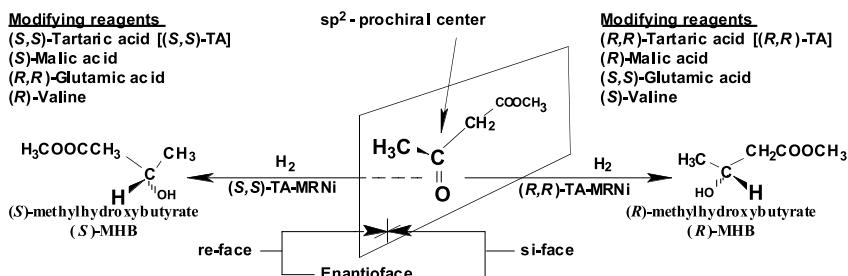


FIGURE 3.1 Formation of a chiral center from a prochiral center.

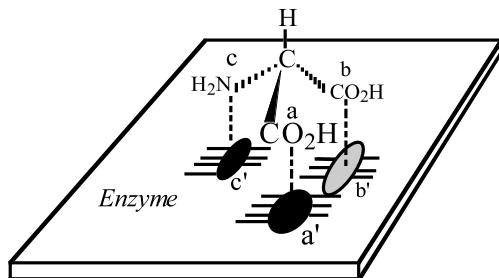
near the newly forming chiral center or in the reagent responsible for the substitution or addition. In the case of a catalytic reaction, however, the chiral environment is usually furnished by the catalyst; neither the prochiral substrate nor the reagent is chiral. So the challenge for the chemist and engineer is to create chiral catalysts with high enantioselectivities (the production of one enantiomer in larger amount than the other), but also these catalysts must have long lives and not present environmental problems.

Naturally occurring catalysts, enzymes, exist, and some of them are enantiospecific (produce only one enantiomer). But mimicking them is difficult because they usually contain a metal atom imbedded in a complex chiral protein structure into which the prochiral substrate and other reactants uniquely fit. Moreover, during the reaction the protein structure may change to accommodate incoming and outgoing species. How then, in the absence of such specific tools with which to start constructing catalysts, might one begin to create enantiospecific, or at least enantioselective, catalysts? What are the principles underlying the creation of chiral catalysts?

Many homogeneous chiral catalysts have been created. Basically these catalysts consist of a catalytically active metal-ligand arrangement of which one or more of the ligands exhibit chirality. Since they are small enough to dissolve in the reaction medium, they are called *homogeneous catalysts* as opposed to *heterogeneous catalysts*, which are larger and do not dissolve. Homogeneous catalysts have produced high enantioselectivities and several have been used in commercial processes. However, homogeneous catalysts have disadvantages, so heterogeneous catalysts exhibiting high enantioselectivities are eagerly desired by industry, especially heterogeneous metal catalysts, the surfaces of which catalyze much of the fine chemicals and specialty chemicals processes. The basics of chirality on surfaces stems from the principles of Ogston.¹

A. G. Ogston in 1948 explained the dilemma of how an enzyme can enantiospecifically produce a chiral product from a prochiral molecule such as citric acid or 2-aminomalonic acid. He pointed out two requirements: three-point contact at three active sites (a' , b' , and c') and catalytic dissimilarity between the two active sites (a' and b') associated with the pro-R and pro-S groups (a and b) of the prochiral molecule as shown in Fig. 3.2.

In principle, sites a' , b' , and c' need not be association sites as depicted by Ogston but could be steric sites that form obstructions such that the adsorbed molecule is chirally directed. Only one “active” site is actually required providing the remaining two sites (protuberances or cavities) are different from each other and from the active site that catalyzes the reaction. They could be identical providing they are not symmetrically oriented with respect to the active site (not an isosceles triangle). These are the basic concepts for a chiral environment on a surface and they lead to the three basic methods for creating chiral surfaces in heterogeneous catalysis.

FIGURE 3.2 The principle of Ogston.¹

3.2. CONSIDERATIONS OF CHIRAL SURFACES

Enantioselective catalytic surfaces may be conceived of being synthesized three basic ways (Fig. 3.3): (1) attach a catalyst to, or embed a catalyst in, a chiral matrix; (2) create a chiral arrangement of active sites on a catalytic surface; and (3) adsorb or attach chiral molecules onto a catalytic surface. We discuss each in turn.

3.2.1. ATTACH A CATALYST TO, OR EMBED A CATALYST IN, A CHIRAL MATRIX

These methods are the oldest and have led to some successes; however, there seem to be some limitations. For example, in the case of attaching metals to

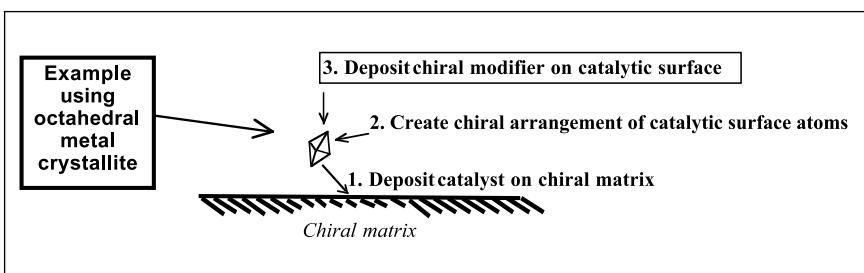


FIGURE 3.3 Three possible ways of creating heterogeneous enantioselective catalysts.

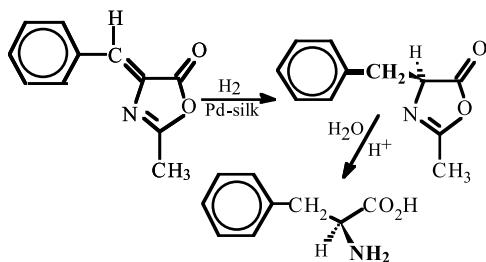
chiral matrices, it is possible to easily deposit nanometer-size metal particles on chiral matrices, but chiral induction appears to occur at the metal–support interface. The Ogston criteria only occur at the interface. Since the interface involves only a small percentage of the active catalytic sites, the competing nonchiral active sites lower enantioselectivities. The challenge with this method is either to increase the fraction of surface sites in contact with the chiral matrix by depositing extremely small metal particles or to decrease the fraction of nonchiral sites by poisoning them. Another challenge associated with this method is the instability of many naturally occurring chiral matrices. This problem surfaced with the creation of the enantioselective Pd-on-silk catalyst system.

3.2.1.1. Pd–Silk Catalyst

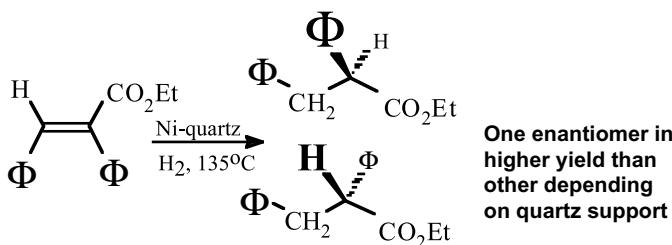
For the Pd–silk catalyst,² PdCl_2 was deposited on silk and reduced to Pd° ; moderate enantioselectivities were obtained for the hydrogenation of a $\text{C}=\text{C}$ bond (66% enantiomeric excess, ee, which is the difference between enantiomers divided by the sum of enantiomers), but the silk support presented two problems: it tended to deteriorate with time on stream and it varied from source to source, so enantioselectivities were not reproducible (Scheme 3.2). On the other hand, deterioration was not a problem with the *metal–quartz* catalysts.

3.2.1.2. Ni–, Cu–, Pd–, and Pt–Quartz Catalysts

Experiments with these catalysts, from an old study by Schwab and Rudolph,³ showed that enantioselectivity occurs at the metal–quartz interface during enantioselective dehydrations of racemic 2-butanol. Klabunovskii and colleagues expanded on this idea and prepared a chiral Ni–quartz catalyst that



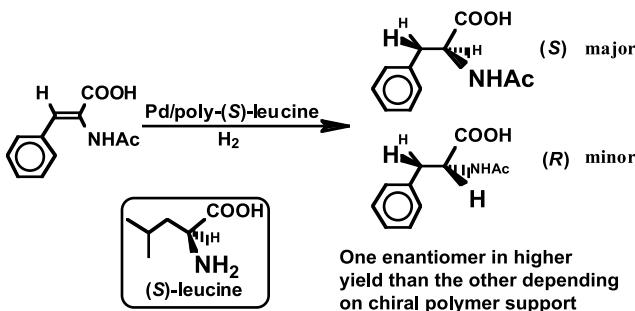
SCHMENE 3.2

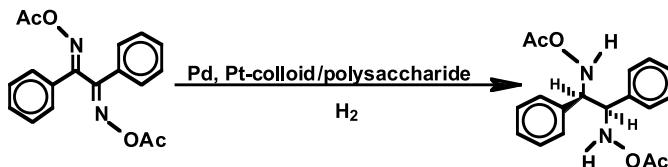


catalyzed the enantioselective hydrogenation of the prochiral C=C bond in α -phenyl cinnamic acid (Scheme 3.3).⁴

Likely, this idea will continue to be explored because new chiral matrices are created frequently. Examples of published possible stable chiral matrices are chiral microporous cross-linked polymers⁵ and nanoscale chiral helical columns created from various inorganic materials.⁶ However, the interface problem will still exist.

One way to overcome the problem of chirality existing only at the metal–matrix interface is to encase the metal particle inside the chiral matrix. In that case, all of the metal surface atoms should be close to a chiral center; however, this approach has some problems too. For example, access to the metal surface may be inhibited by the encasing matrix. In spite of this, several attempts have produced moderately successful catalysts by creating *metal–polymer* catalysts. Pd has been deposited on poly-(S)-leucine (Scheme 3.4) and Pd and Pt colloids have been encased in a polysaccharide to produce catalysts that enantioselectively hydrogenated prochiral C=C and C=N bonds (Scheme 3.5).⁷





SCHEME 3.5

A 1996 work deposited four different catalytic metals on a β -cyclodextrin-epichlorohydrin copolymer to prepare Pd(Pt, Rh, Ru)- β -cyclodextrin copolymer catalysts.⁸ These were used to catalyze the asymmetric hydrogenations of the C=C bonds of *trans*-2-methyl-2-pentenoic acid, and dimethyl itaconate.

3.2.2. CREATE A CHIRAL ARRANGEMENT OF ACTIVE SITES ON THE CATALYTIC SURFACE

An excellent enantioselective heterogeneous metal catalyst should be one in which the active metal sites are set in a chiral arrangement fulfilling the Ogston principles. Assuming no surface atom rearrangement, such a catalyst should furnish high enantioselectivities.

3.2.2.1. Ag(643)^S and Ag(643)^R

Such a possibility has been recognized by early workers,⁹ but in spite of this intriguing possibility, only recently has such a metal surface been created. Chiral kink sites were created on Ag single crystal surfaces to produce the enantiomeric surfaces Ag(643)^S and Ag(643)^R; however, no differences between (R)- and (S)-2-butanol were observed for either the temperature-programmed desorption from the clean surfaces or the dehydrogenation (to 2-butanone) from preoxidized surfaces.¹⁰ Unfortunately, Ag exhibits few catalytic properties, so only a limited array of test reactions is available to probe enantioselectivity over this metal. It would be good if this technique were applied to a more catalytically active metal such as Pt.

*trans*-2-Methyl-2-pentenoic acid dimethyl itaconate

DRAWING 3.1

Nevertheless, this fine set of careful experiments is instructive. Why do these chiral surfaces not differentiate between (*R*)- and (*S*)-2-butanol when the metal–quartz catalysts do? One reason may be that the mechanism of dehydrogenation is different on Ag than on Cu, Ni, Pd, or Pt. Whereas this may be true, it does not seem too probable in view of the rather simple mechanism. Besides, these Ag surfaces do not differentiate between the enantiomers even with respect to desorption properties. Is it possible that the chiral environment is different? Evidence suggests the chiral-determining environment in the metal–quartz cases occurs at the interfaces between the metal and the quartz. In these cases the Ogston principles must be met in that the alcohol adsorbs on the metal but it finds chiral steric hindrance when adjacent to the quartz support. On the other hand, Ag(643)^R exhibits chirality only near its steps. The steps contain kink sites (³M) and edge sites (²M) in chiral arrangements, but several plane sites (¹M) are not in chiral arrangements. Even though the kink and edge sites are in chiral arrangements with each other, they may not meet the Ogston criteria. They do only if the active site for dehydrogenation is adjacent to a chiral environment *and* if the adsorbed 2-butanol interacts with the chiral environment. As the authors point out, the ethyl group of secondary butanol is so small compared with the Ag atoms that it interacts with the edge sites adjacent to the kink sites approximately equally. That analysis assumes the oxygen of the butanol adsorbs on a kink atom. If, however, secondary butanol adsorption on Ag is structure-insensitive (adsorption occurs on any surface atom), little differentiation is likely to be observed.

3.2.2.2. Screw Dislocations

A naturally occurring chiral metal structure is a *screw dislocation* (Fig. 3.4),¹¹ which is a chiral arrangement observed in metal crystals but never resolved and tested for enantioselective heterogeneous catalysis. A possible method of making chiral arrangements like screw dislocations is by the glancing angle deposition technique, which can produce chiral sculptured thin films.¹²

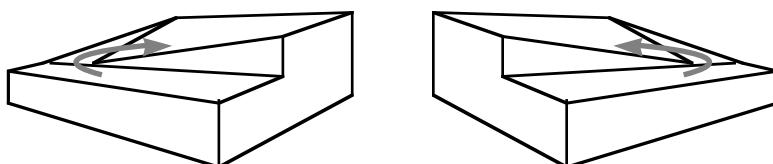


FIGURE 3.4

3.2.2.3. Asymmetric Leaching or Rearrangement of Surface Atoms

Besides natural structures, one can imagine how other chiral metal surfaces might be created. For example, **asymmetric leaching or rearrangement of surface atoms** might produce enantioselective metal catalysts (Fig. 3.5).⁹ Indeed, some investigators believe tartaric acid modified nickel involves leaching the nickel surface in a chiral arrangement.¹³ Likewise, deposition of an asymmetric triad of sites according to the principle of Ogston¹ would create a chiral surface (Fig. 3.5).

3.2.2.4. Imprint a Chiral Arrangement on a Catalytic Surface

There exists the possibility that one can **imprint a chiral arrangement on a catalytic surface**. Although chiral imprinting is now occurring on silica surfaces¹⁴ and in polymers,¹⁵ it has not been used to induce chirality in metal surfaces. This is difficult to explore.

3.2.2.4.1 Chiral Urea Adduct

A related possibility can be readily explored, that is, growing a metal surface on a chiral matrix followed by removing it from the matrix and using it as a catalyst. This has been accomplished by preparing the **chiral urea adduct** (helical) of (*R*)-(-)-2-octanol, impregnating it with Pd(OAc)₂, and reducing that to Pd° in H₂ (Fig. 3.6). This Pd° catalyzed the hydrogenations of α -methylcinnamic acid at 25°C under 16.7 psi hydrogen to produce the saturated acid of between 4.0 and 5.2% ee [(+)-2-methylhydrocinnamic acid dominated]. When the urea

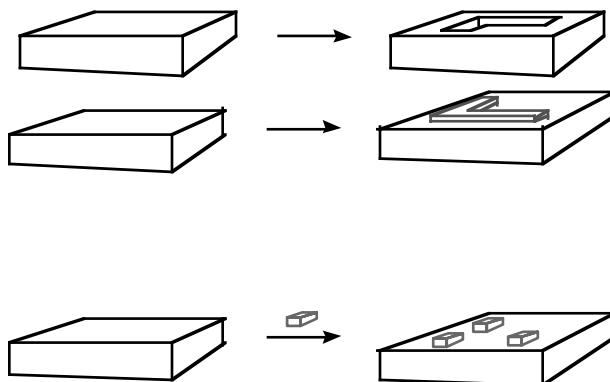


FIGURE 3.5

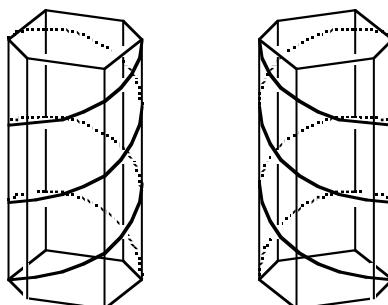


FIGURE 3.6 Chiral helical hexagonal structure of urea and thiourea adducts. A chiral guest generates one helical form. (Straight chain alkyl guests fit in the urea adduct channel; larger molecules such as *trans*-decalin fit in thiourea adduct channel.)

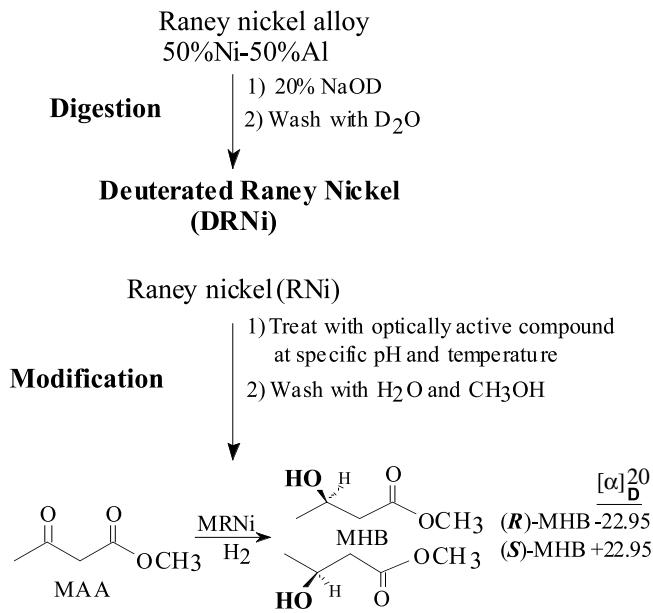
was dissolved, the remaining Pd crystallites catalyzed the same reaction to produce a saturate of between only 0.7 and 1.2% ee. Thus, the desupported Pd seemed to retain some enantioselectivity. Presumably, most of the enantioselectivity from the supported Pd occurred at the interface between the Pd and the chiral urea adduct; however, the results suggest that chirality was also imprinted on the formerly attached side of the desupported Pd particles. On the other hand, enantioselectivity may have occurred because the helical arrangement of the urea adduct support was transmitted to the exposed surface of the Pd but largely lost upon desupporting the Pd.

3.2.3. ADSORB OR ATTACH CHIRAL MOLECULES TO THE METAL SURFACE

This method has produced two catalysts with high enantioselectivities for hydrogenating prochiral ketones.

3.2.3.1. Modified Nickel

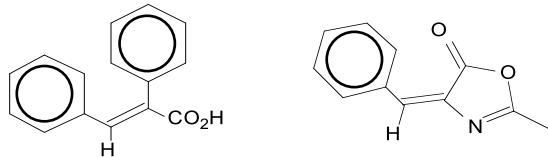
One catalyst, **modified Raney Ni, MRNi** (Scheme 3.6 and Fig. 3.1), is highly successful for the enantioselective hydrogenation of β -keto esters.¹⁶ Gradually, over the years, product ee's have increased due to various innovations^{17,18} and recently, after fine tuning reaction parameters and substrate structure, a 96% ee has been achieved from the hydrogenation of methyl 3-oxo-4-methylpentanoate.¹⁹ Unfortunately, modified Ni catalysts give relatively low enantioselectivities for C=C bond hydrogenations; the highest reported ee's are 17% from (E)- α -phenylcinnamic acid²⁰ and 50% from 2-methyl-4-benzaloxazo-



SCHEME 3.6

line.²¹ As a result of its long existence, modified Ni catalysts have been used in many studies and mechanistic proposals have been advanced.²²

A common theme is the existence of modified (enantioselective) sites and unmodified (racemic) sites. For the case of the tartaric acid modified Ni, it is postulated that the tartaric acid is adsorbed on the surface and stereodirects (through hydrogen bonding) adsorption of the incoming β -ketoesters.^{18,19} Support for this comes from an isotope effect from deuterium labeling.²³ Increased enantioselectivities resulting from co-modification with NaBr is believed to result from poisoning the racemic sites.²⁴ A similar technique in

(E)- α -Phenylcinnamic acid 2-Methyl-4-benzaloxazoline

DRAWING 3.2

which one enantiomer of a racemic catalyst is poisoned has been advanced for use with homogeneous catalysts.²⁵ Likewise, increased enantioselectivities from insonation during catalyst preparation is attributed to eliminating racemic sites.²⁶ In contrast to the enantioselective–racemic site mechanism, a different two-site mechanism has been proposed in which hydrogen dissociates on one site on the Ni surface and migrates to another site consisting of an adsorbed tartrate– β -ketoester complex.²⁷

3.2.3.2. Cinchona Alkaloid Modified Pt, Pd, and Ir Catalysts

The other highly successful catalyst systems are **cinchona alkaloid modified Pt, Pd, and Ir catalysts**. They have high enantioselectivities for hydrogenating α -keto acids and esters. A cinchonidine–Pt system was first prepared by Lipkin and Stewart (Fig. 3.7),²⁸ and modifications of it have been heavily studied by several groups with detailed mechanisms proposed and debated. Essentially, two mechanisms have been proposed. Wells's group originally proposed ordered adsorption of cinchona alkaloid molecules on a surface plane in such a way that chiral cavities remain exposed.²⁹ This idea is like the Ogston concept mentioned earlier. Incoming prochiral keto groups were proposed to be stereo-directed to adsorb on either their *si* or *re* face, with hydrogen adding from the surface. However, the authors revised this mechanism³⁰ to agree more with the other mechanism, a 1:1 interaction between pyruvate (the usual α -keto ester studied) and adsorbed cinchona alkaloid, originally proposed by Blaser's and Baiker's groups,³¹ with variations by Augustine and associates³² and Margitfalvi and colleagues.³³ Blackmond and associates have conducted some exhaustive kinetic studies on this system and found that enantioselectivities increase initially up to about 10% hydrogenation in a “reaction-driven equilibration” of the surface environment.³⁴ Mathematical models have added further insight.³⁵ So

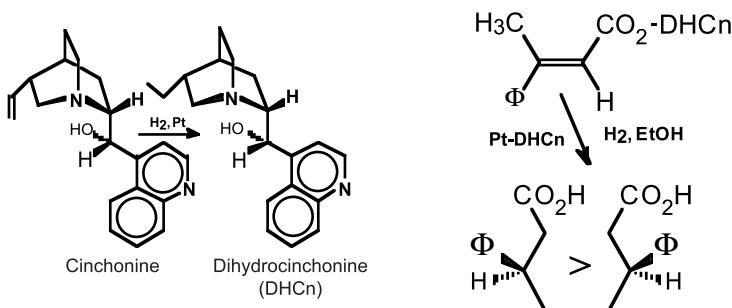


FIGURE 3.7

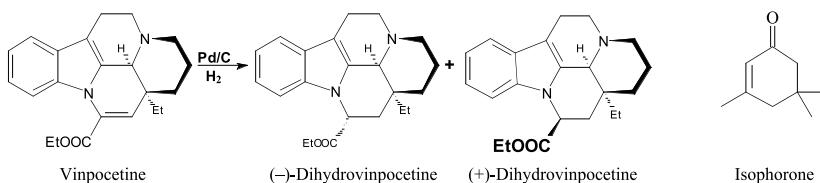
this type of modification may involve subsequent surface rearrangements to form the chiral active sites. Whether the recently discovered ultrasonic pre-treatment by Bartók's group gains its increased enantioselectivities by this type of modification or by increasing the modifier density is not yet clear.³⁶ Until recently, this catalyst system has exhibited only poor enantioselectivities for hydrogenation of prochiral C=C bonds. However, Nitta and Kobiro have reported an ee of 72% from the hydrogenation of (*E*)- α -phenylcinnamic acid over a cinchona-modified Pd/TiO₂ catalyst system in which the solvent, pressure, and temperature are optimized.³⁷ This is the current record ee reported for any enantioselective heterogeneous hydrogenation of a prochiral C=C bond.

3.2.3.2.1. New Modifiers Resulting from Mimicking and Modifying the Cinchona Alkaloid System

New modifiers have traditionally been discovered by the trial-and-error method. Many naturally occurring chiral compounds (the chiral pool³⁸) have been screened as possible modifiers. Thus, the hydrogenation product of the synthetic drug vinpocetine was discovered to be a moderately effective modifier of Pt and Pd for the enantioselective hydrogenation of ethyl pyruvate and isophorone.³⁹ Likewise, ephedrine, emetine, strychnine, brucine, sparteine, various amino acids and hydroxy acids, have been identified as chiral modifiers of heterogeneous catalysts.³⁸

Recently, with the aid of computational techniques, enough understanding of the mechanism of chiral induction at surfaces has been developed that new chiral modifiers have been synthesized.^{40,41} Their success at chiral induction confirms the theoretical understanding upon which they were created.

Basically, the cinchona alkaloid structure (Drawing 3.4) was examined and determined to contain three important features that make it a good chiral-inducing modifier for metal surfaces. First, the flat quinoline ring system is believed to anchor the molecule to a flat metal plane through π -bonding (a naphthyl group was found to be just as effective, but phenyl and pyridyl were not); second, the chiral region encompassing the carbon between the quinoline and quinuclidine



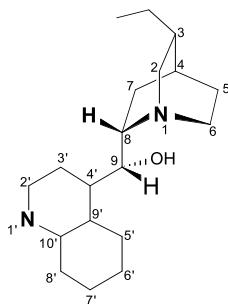
DRAWING 3.3

ring systems (C-9) as well as the adjacent carbon on the quinulclidine ring (C-8) stereodirects the chirality of the product (inverting their configurations inverts the chirality of the product); and third, the tertiary nitrogen on the quinulclidine ring associates with the keto oxygen of the α -keto ester (alkylation of that nitrogen eliminates enantioselectivity).

Using these basic features, new modifiers were constructed that retain the basic elements of the cinchona alkaloid structure 1 in Fig. 3.8.^{40,41} Several of them (3, 5, 6, 7, and 8) produced enantioselectivities of the same order as ee's produced by the cinchona alkaloid family. Interestingly, 2 combines with ethylpyruvate, undergoing reductive alkylation in the presence of hydrogen and the catalyst to form the secondary amine 3, which is the true modifier.⁴⁰ In hindsight, it can be seen that several of the naturally occurring modifiers discovered by trial and error contain some of the essential basic features of the cinchona alkaloid family. For example, dihydrovinpocetine, strychnine, and brucine^{38,39} contain an extended flat aromatic ring system capable of anchoring these molecules to a flat metal surface, and they contain a tertiary nitrogen capable of complexing a keto group.

3.2.3.3. Other Modified Catalyst Systems

Instead of the absorption of chiral modifiers on metal surfaces, a new method using a slightly different approach attaches chiral moieties directly to metal surfaces through chemical bonds. Chiral silyl ethers have been attached to Pd surface atoms; these new catalysts have the form $(Pd)_s \equiv Si-O-R^{(R \text{ or } S)}$.⁴² Their synthesis arose from studies of the effects of siliconation on the catalytic activities and selectivities of dispersed, supported Pd and Pt.⁴³⁻⁴⁷ The results from



Dihydrocinchonidine

DRAWING 3.4

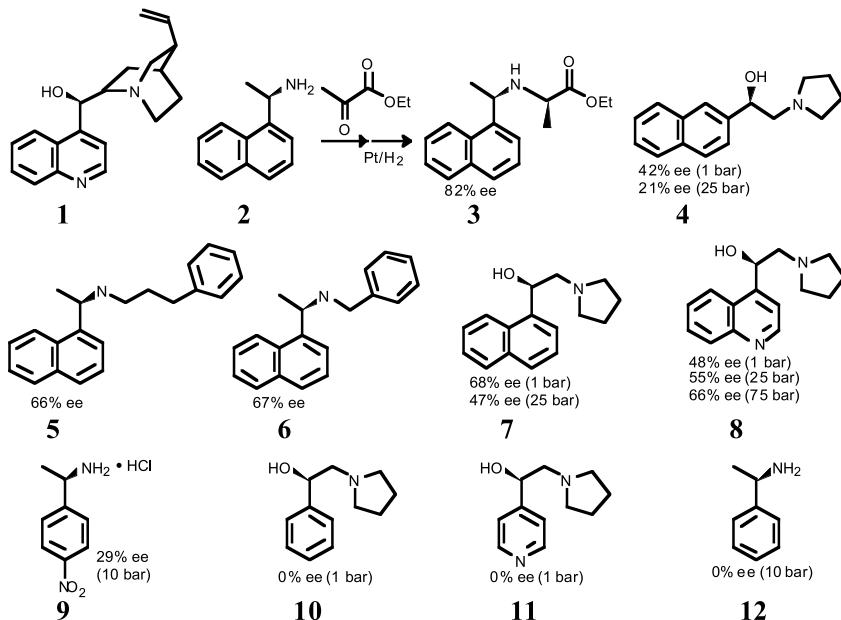


FIGURE 3.8

these and other studies^{48,49} suggest that stepwise hydrogenolyses of trialkylsilanes occur over Pd and Pt. This process pointed to a possible route for attaching chiral species to metal surfaces by incorporating a chiral moiety in the silyl fragment. Indeed, chiral alkoxytrimethylsilanes do undergo partial hydrogenolysis on Pd and form residues which impart enantioselectivities to the catalytic surfaces. (Fig. 3.9) A catalyst on which boreoxytrimethylsilane had been hydrogenolyzed catalyzed the hydrogenation of α -methylcinnamic acid in 10–12% enantiomeric excess. Chiral induction by this new catalyst may not occur through polar interactions between the prochiral substrate and the modifier but rather through the steric requirements imposed by the attached modifier. In fact, the modifier appears to have an optimal surface concentration (ee's pass through a maximum as a function of modifier surface concentration), which suggests its surface density is important.

3.3. MECHANISMS OF ENANTIOSELECTIVITY ON SURFACES

Three factors seem to be important for enantioselectivity to occur on surfaces: the steric factor, the polar factor, and the mobility factor. Each of these

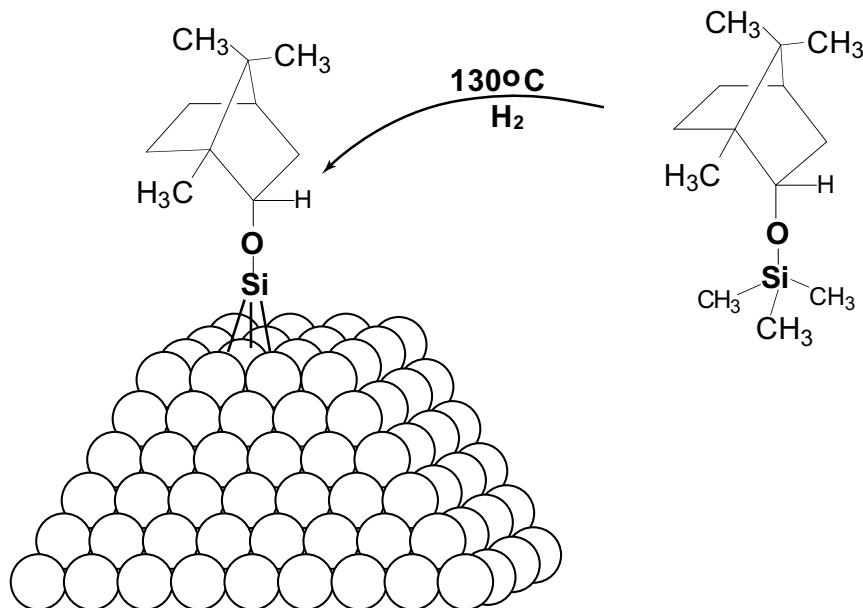


FIGURE 3.9 Depiction of modification of Pd crystallite with (S)-borneoxytrimethylsilane.

factors affects the chiral environment in ways that determine its magnitude and stability.

The steric factor results from physical interactions between atoms. From this factor comes the basic chirality. For the cases of solid metal catalysts, chirality may come from the support, the arrangement of active sites on the metal surface (Ogston concept¹), or from an adsorbed or attached chiral entity.

The polar factor addresses how the modifier interacts with the prochiral substrate. This usually happens through some strong interaction between a polar group near a chiral center on the modifier and a polar group on the prochiral substrate. For the cinchona alkaloid modifiers and their mimickers, a tertiary nitrogen stereodirects the incoming substrate, which interacts through hydrogen bonding with its carbonyl group. For tartaric acid modifier, it is the OH group that interacts through hydrogen bonding with the incoming carbonyl group, and for amino acid modifiers, the amino group interacts with the carbonyl group of the incoming substrate. This results in an isotope effect.²³

The mobility factor acknowledges the fact that organic molecules seem to move about on surfaces. For example, Blackmond and Augustine and associates have identified an induction period in the cinchona alkaloid modified

platinum system during which the chirally active site forms.⁵⁰ This induction period has been confirmed by Blaser's group,⁵¹ but Baiker's group has argued that it results from impurities.⁵² Enantioselectivity increases during the first 10% of the reaction and remains constant thereafter. This formation is a function of conversion and appears to signal a rearrangement of the surface into the optimal chiral environment. Since chirality is coming from the modifier, this suggests migration of the modifier into optimum positions under the influence of the reaction, perhaps the product. The mobility factor also accounts for the anchoring effect of strongly adsorbing parts of the modifier molecules. In the case of the cinchona alkaloid type modifiers, the anchoring appears to come from the naphthyl-type systems, which are believed to strongly adsorb on the metal planes. Likewise, in the cases of tartaric acid and the amino acids, the anchoring is thought to be accomplished through the carboxyl groups. Whereas these anchoring groups distinguish successful modifiers, other anchoring groups have been identified in substrate molecules, and these anchoring groups may have a profound influence on the ability of prochiral molecules to attain significant chiral induction.

A molecule like *trans*-2-methyl-2-pentenoic acid contains a low number of directing or *anchoring groups*.^{53,54} *Trans*-2-Methyl-2-pentenoic acid contains only one anchoring group (carboxyl); α -methylcinnamic acid contains two (carboxyl and phenyl); and (*E*)- α -phenylcinnamic acid contains three (carboxyl and two phenyls). The effect of these groups is to increase enantioselectivities, presumably because they tend to anchor the molecules to the surface and slow the rates of isomerization and flipping processes. This effect has also been called the *phenyl effect*⁵³ and more generally the *haptophilic effect*.⁵⁴ Virtually, all prochiral C=C bonded compounds yielding high ee's over enantioselective heterogeneous catalysts contain at least one of these and typically three (two phenyls and one carboxyl) as in the case of (*E*)- α -phenylcinnamic acid^{20,37}. Whether high enantioselectivities can be attained from prochiral C=C bonds not containing such anchoring groups has yet to be determined.

Although polar effects are influential in homogeneous catalysis, the apparent effect of anchoring groups on enantioselectivities over heterogeneous catalysts is one mechanistic difference between heterogeneous and homogeneous catalysis. Another difference is that heterogeneous catalysts have surfaces over which organic molecules and hydrogen may migrate. Moreover, these surfaces have edges and corners that almost certainly exhibit different catalytic activities and selectivities, and as the particle size becomes small a metal–nonmetal transition occurs.⁵⁵ The complexity of the metal surface raises formidable barriers to understanding heterogeneous catalysis, so it is understandable that many mechanistic ideas have been adopted from the better understood mechanisms of homogeneous catalysis. These are beneficial but tend to focus on one metal atom (for example a corner atom or an adatom³²) as the active site

responsible for everything, including hydrogen dissociation, modifier adsorption, and substrate adsorption. Whereas a single metal atom may be the active site in some cases, more likely a grouping of several atoms is involved. These groups of atoms have been variously called *clusters*,⁵⁶ *multiplets*,⁵⁷ and most recently *ensembles*.⁵⁸

In contrast, some theories treat the metal surface as some vague entity. For example, the most recent model for enantioselective hydrogenation on a modified nickel surface focuses strictly on polar interactions between an adsorbed modifier and a substrate on an unidentified nickel surface.¹⁹ Not quite so vague are attempts to model surfaces and organic molecules adsorbed on them. A recent approach along these lines is based on polar interactions between the modifier and the substrate. In that example, computer modeling by Baiker's group produced "best fit" relations between the cinchona alkaloid modifier and the substrate superimposed on a flat (111) surface.⁵⁹ Here, however, good evidence suggests that such a plane surface may be involved in modifier adsorption.⁴⁰

Finally, even the location of hydrogen on metal surfaces is influenced by homogeneous catalysis. Typically, hydrogen atoms are pictured as sitting on top of surface atoms. Recent evidence, however, suggests that the hydrogens involved in heterogeneous catalysis may be sitting in sublayer sites just below the surface atoms.⁶⁰ Thus, the complexities of the surfaces of metal catalysts and their differences from homogeneous catalysts are just beginning to be understood.

Several mechanisms for enantioselectivity on metal surfaces have already been proposed. Basically, they consist of two premises: stereodirection from *polar interactions* between modifier and substrate and stereodirection from *steric interactions* between modifier and substrate. The polar interaction mechanism enjoys greatest support. In the modified nickel system, Klabunovskii and colleagues¹⁶ and Tai and associates¹⁷ use polar effects to explain enantioselectivity. In the Pt–cinchona alkaloid system Blaser and Jalett³¹ propose polar effects. For the same system, Wells and associates first proposed a steric effect (chiral holes),²⁹ and then, after further studies, proposed a polar effect.³⁰ Augustine and co-workers³² propose polar interactions for the same system, and Margitfalvi and colleagues³³ proposes a shielding effect (steric hindrance) resulting from polar interactions. Usually, the modifier and substrate are shown in a complex that represents the best fit, sometimes suggested by computations, and this complex is superimposed on a (111) surface. Augustine attaches both the modifier and the substrate to an adatom or corner atom and considers polar interactions within that constraint.

Another important effect is that of poisons on enantioselectivity. Izumi¹⁶ uses the rationale of poisoning of racemic sites to account for increased enantioselectivity from NaBr co-modifier, and Baiker⁶¹ discusses auxiliaries

as co-modifiers. These co-modifiers, or selective poisons, have profound effects on enantioselectivities and must be taken into account in any comprehensive mechanism. Poisons have been found to increase enantioselectivities in the modified nickel system.^{23,24,62,63}

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Hydrogenolysis

- 4.1. Breaking C–O Bonds
- 4.2. Breaking C–N Bonds
- 4.3. Hydrogenolysis of C–S Bonds
- 4.4. Hydrogenolysis of C–Se Bonds
- 4.5. Hydrogenolysis of C–Halogen Bonds
- 4.6. Hydrogenolysis of C–Si Bonds
- 4.7. Hydrogenolysis of C–C Bonds
- 4.8. Hydrogenolysis of N–O Bonds
- 4.9. Hydrogenolysis of N–N Bonds
- 4.10. Hydrogenolysis of Si–O Bonds

References

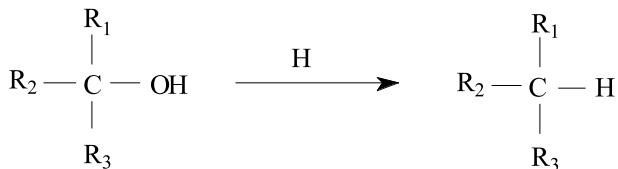
C–X

Reactions are called *hydrogenolysis* if hydrogen is added across a σ -bond. *Hydrogenolyses* of the more polarized bonds are easier than hydrogenolysis of nonpolarized bonds. For example, the carbon–heteroatom (heteroatoms are mostly O, N, S, or halogens) bonds are polarized and cleave more easily than the carbon–carbon bond.

4.1. BREAKING C–O BONDS

The most important C–O bond breaking reaction is the hydrogenolysis of the carbon–oxygen σ -bond. During the hydrogenolysis of alcohols, the OH group is substituted by a hydrogen atom; therefore, the hydrogenolysis is referred to sometimes as *deoxygenation* or reduction to *alkanes* (Scheme 4.1).

The deoxygenation of cyclic ethers means the cleavage of both C–O bonds and leads to alkenes or alkanes depending on the hydrogenating activity of the catalyst (Scheme 4.2).



SCHEME 4.1

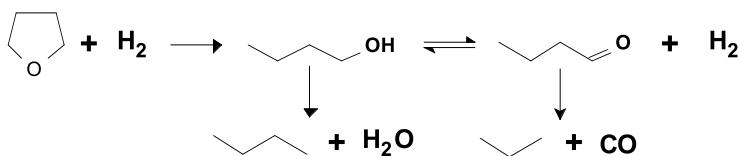


SCHEME 4.2

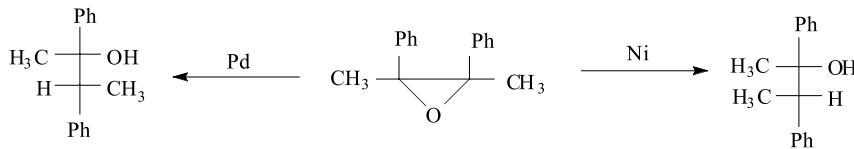
4.1.1. HYDROGENOLYSIS OF C–O BONDS

The hydrogenolysis of a normal C–O bond in alcohols or in alkyl ethers is usually difficult to accomplish and requires favorable structural features in the substrate to take place easily. Facile hydrogenolysis of the C–O bond occurs, however, if the C–O bond is reactive enough, especially in the case of benzyl groups. Usually the molecules that are active in hydrogenolysis contain carbon atoms, which are able to produce stable carbenium ions, connected to a good leaving group.

However, normal alcohols and ethers can also be hydrogenolyzed if the catalyst can activate the C–O bond. It was found that THF undergoes hydrogenolysis to 1-butanol, which undergoes hydrogenolysis (hydrodeoxygenation) to butane (Scheme 4.3) and the turnover frequency of the titania-supported catalyst was much higher than that of the silica-supported one. It was assumed that the reaction occurs at the interface between the platinum and the support.¹ The high catalytic activity of the titania-supported catalysts was attributed to the



SCHEME 4.3



presence of surface oxygen vacancies. The first step is the adsorption of the alcohol on the oxygen vacancy. In the second step, the adsorbed species are hydrogenolized by atomic hydrogen, which is supplied by platinum via hydrogen spillover, or direct hydrogenation takes place when the surface species are close to the platinum atoms.²

4.1.1.1. Stereochemistry of C–O Hydrogenolysis

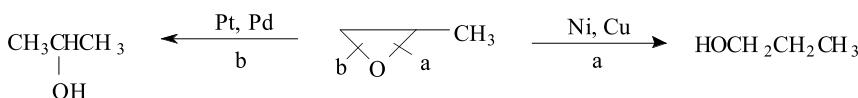
The hydrogenolysis of the C–O bond proceeds mainly with inversion of the configuration of the carbon atom over a Pd catalyst but with retention of the configuration on Ni (Scheme 4.4).^{3–6}

Pd and Ni also have different regioselectivities in the case of unsymmetrically substituted epoxides (Scheme 4.5).³

The metals are also different in the transformation of the *cis*- and *trans*-2,3-dimethyloxiranes. The *cis*-2,3-dimethyloxirane is transformed at a much higher rate than the *trans* isomer on Pt and Pd catalysts, whereas on Ni the two isomers are converted at almost the same rate.⁷

4.1.1.2. Mechanism of C–O Hydrogenolysis

Basically, the cleavage of the C–O bond takes place through two mechanisms. The first mechanism (the hydrogenolytic cleavage) is a hydrogen-assisted bond-cleavage reaction, whereas the second mechanism is an ionic insertion of the metal into the C–O bond. The characteristic features of the two mechanisms are summarized in Table 4.1.



SCHEME 4.5

TABLE 4.1 Characteristic Features of the Mechanisms of C–O Hydrogenolysis

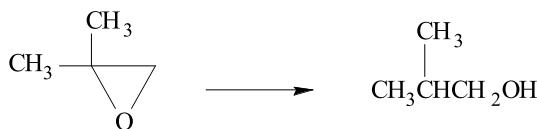
Hydrogenolytic cleavage	Insertion
Cleavage b in Scheme 4.4	Cleavage a in Scheme 4.4
Inversion of configuration	Retention of configuration
The <i>cis</i> isomer reacts faster than <i>trans</i>	Both <i>cis</i> and <i>trans</i> react with similar rates
Occurs on Pt and Pd	Occurs on Ni and Cu

These reactions need good leaving groups to take place easily. Better leaving groups undergo faster hydrogenolytic cleavage. Compounds without good leaving groups react slowly. Hydrogenolytic cleavage, especially its stereochemistry, is characteristic of an S_N2 -type reaction, whereas ionic insertion is similar to an S_N1 reaction. Hydrogenolytic cleavage probably needs surface H^- ions, which can react with the electrophilic carbon atom in the molecule.

During the insertion mechanism, the metal is inserted into the carbon–oxygen bond. The insertion is promoted by a strong metal–oxygen interaction. It is thought that unreduced metal ions may play an important role in the insertion mechanism (electrophilic catalysis). The type of the catalyst, the method of preparation, and the additives can influence the concentration and stability of these ions.

If a molecule contains carbon atoms that can stabilize the positive charge (e.g., a tertiary carbon) the cleavage may also exhibit S_N1 character on Pd and Pt catalysts. In accordance with this, hydrogenolysis of 1,1-dimethyloxirane occurred at the more hindered C–O bond over Pt (Scheme 4.6).³

Electrophilic catalysis may play an important role in the case of the similar benzylic carbon, too. For an O-benzyl system, it was found in a 1997 experiment that palladium oxide is a much more effective catalyst than palladium metal when the catalyst has been prereduced with chemical reducing agents.⁸ This finding shows very clearly that the electrophilic character of the unreduced metal ions plays an important role in the hydrogenolysis of the benzyl C–O bonds. Additional support for this mechanism is the fact that a small amount of butylamine can inhibit the hydrogenolysis of the benzyl C–O bond.



SCHEME 4.6

4.1.1.3. Oxygen Bonded to Tetrahedral Carbon Atoms

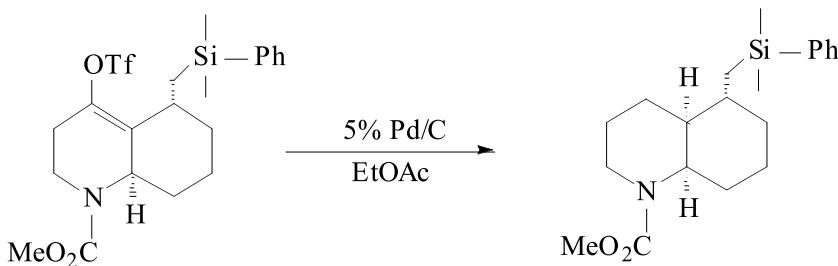
The bonds between an oxygen and an sp^3 carbon atom in alcohols, ethers, or esters are quite resistant to hydrogenolysis. Elevated temperatures and pressures are required to induce C–O bond cleavage and the high temperature can cause the cleavage of the C–C bonds, too.

R₃C–O In the case of a tertiary carbon atom, the reduction to alkane is more facile. Acid-catalyzed hydrogenolyses of tertiary alcohols were performed on Pt and Pd catalysts at 1 atm of hydrogen^{9,10} and tertiary alcohols and esters and secondary tosylates were hydrogenolyzed over Pt in AcOH.¹¹ These transformations were ascribed to alkene formation before reduction. Primary alcohols were dehydrogenated to aldehydes and then subsequently decarbonylated, secondary alcohols were dehydrogenated to ketones, and tertiary alcohols were deoxygenated using Raney Ni (Ra-Ni) in refluxing toluene.^{12,13} For substrates that were deoxygenated rapidly, alkenes were the major products, however, with longer reaction times, more alkanes were observed.

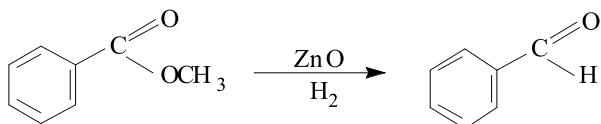
4.1.1.4. Oxygen Bonded to Trigonal Carbon Atoms

C=C–OR Vinyl ethers and vinyl esters are not employed extensively in organic transformations. During the synthesis of phlegmarine, however, the stereogenic center at C-10 was to be introduced stereoselectively by catalytic hydrogenation–hydrogenolysis of the vinyl triflate (Scheme 4.7).

Initial attempts to remove the vinyl triflate involved mild catalytic hydrogencations over Pt/C or PtO₂, since these two catalysts are known to be effective in olefin hydrogencations while minimizing double bond migration. Under these mild conditions, hydrogenation of an aromatic ring would not be anticipated. The crude product from these hydrogencations, using Li₂CO₃ to remove acid, showed some hydrogenation of the phenyl group, which must be attributed to

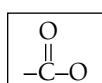


SCHEME 4.7



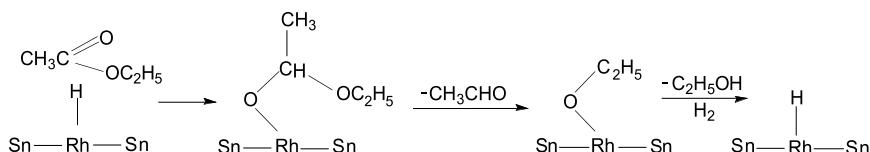
SCHEME 4.8

activation of the phenyl ring by the Si atom. Consequently, a Pd/C catalyst was selected to prevent the undesired phenyl group hydrogenation. The hydrogenation–hydrogenolysis was then accomplished quantitatively in ethyl acetate using 5% Pd/C in the presence of Li_2CO_3 as an acid scavenger.¹⁴

 Hydrogenolyses of carboxylic acids and esters to the corresponding aldehydes seems very attractive due to their simplicity. Copper chromites are the most widely used catalysts.¹⁵ Raney copper and zinc oxide–chromium oxide have also been used for this process.^{16–18} The hydrogenolysis of methyl benzoate to benzaldehyde was studied on various metal oxides at 300–350°C. ZnO , ZrO_2 and CeO_2 presented high activities and selectivities (Scheme 4.8).

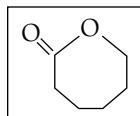
It was found that acidic or basic properties of metal oxides are not directly connected to their hydrogenolytic power, but redox properties seem to play a more important role.¹⁹

Nevertheless, hydrogenolyses of esters are difficult to achieve. High temperatures and pressures are required and the resulting drastic conditions can lead to hydrogenolysis of the product alcohol itself. It was found that bimetallic catalysts, Rn–Sn, Ni–Sn, and Ru–Sn, prepared via an organometallic route, can be very selective for the hydrogenolysis of ethyl acetate to ethanol.^{20,21} This is an elegant method for the hydrogenolysis of fatty esters to alcohols. In the hydrogenation of ethyl acetate, Rh/SiO_2 gives CH_4 , C_2H_6 , CO , and CO_2 , corresponding to unselective C–C and C–O bond cleavage. The addition of Sn via the organometallic route leads to drastic changes. The new Rh–Sn catalyst exhibits a very high chemoselectivity. Kinetic data lead to the proposal of the reaction mechanism involving a single Rh atom (Scheme 4.9).



SCHEME 4.9

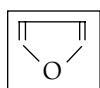
It is possible that the Sn atoms participate by complexation but there is no direct evidence in favor of this hypothesis.²²



Lactones can be hydrogenolyzed on copper chromite catalysts.²³ Diol formation is favored at lower temperatures, whereas higher temperatures give cyclic ethers. This process is not widely used, however, because of experimental difficulties.



Phenols are frequently used compounds in organic chemistry. Deoxygenation without hydrogenation of the aromatic ring is rarely observed during catalytic hydrogenation of phenols. There are, however, several catalytic methods available for the reductive removal of phenolic hydroxyl groups. Reductive transformation of O-aryl-p-toluenesulfonates can be achieved by Ra-Ni.²⁴ One of the most efficient and widely used procedures of synthetic importance is the catalytic hydrogenolysis of O-aryl-N,N-dialkylisoureas by Pd/C.²⁵ Deoxygenation of the N,N-diethylisourea derivative of 2,2-dimethyl-7-hydroxy-4-chromanone produces valuable compounds that could not be directly prepared. The catalytic hydrogenolyses were performed over Pd/C under hydrogen atmosphere at room temperature in ethanol and gave 2,2-dimethyl-4-chromanone in good yield (Scheme 4.10).²⁶

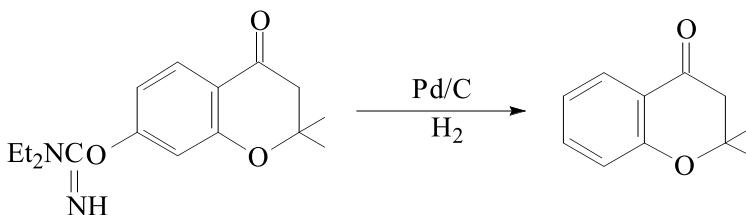


It has been found that furans undergo hydrogenolyses under very mild conditions. Such conditions are too mild to hydrogenolyze oxolanes (saturated furans). As concerns regioselectivity, the furan C–O bond rupture takes place in the sterically less hindered position, similar to the reaction in the oxolanes. The oxacycloalkene intermediate of an intramolecular Diels-Alder furan reaction was hydrogenolized over Pd/BaSO₄.²⁷

4.1.1.5. Oxygen Bonded to Activated Tetrahedral Carbon Atoms



Acetals Removing the acetal protecting group is easily achieved by acid-catalyzed hydrolysis, although catalytic hydrogenolysis is better for acid-sensitive compounds. The oxygen connected to the



SCHEME 4.10

carbon atom in acetals activates the C–O bond for hydrogenolysis. Such was the case when a Pd^{II}O-catalyzed hydrogenolysis under 50 psi hydrogen at 25°C for 2 days was employed for some acid-sensitive compounds.²⁸ Similarly, hydrogenolysis of the C–O bond in a nitroso acetal was performed over Ra-Ni in MeOH under 260 psi hydrogen pressure.²⁹

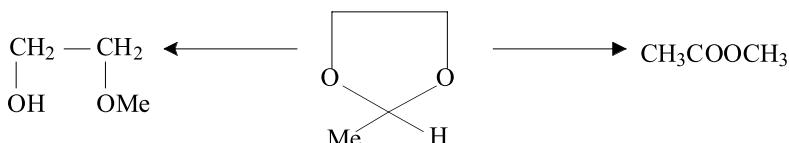
Dioxacycloalkanes In the case of 1,3-dioxacycloalkanes, there are two possibilities for the rupture of the C–O bond. Esters or diol monoethers can be prepared depending on the regioselectivity of the bond rupture (Scheme 4.11).

On Pt, Pd, Ni, and Rh the regioselectivity depends on the conditions. Mainly ester is formed at low hydrogen pressures, whereas mainly diol monoether is formed at higher pressures.^{30,31} Selectivity is structure-sensitive; more ester is formed on highly dispersed catalysts.

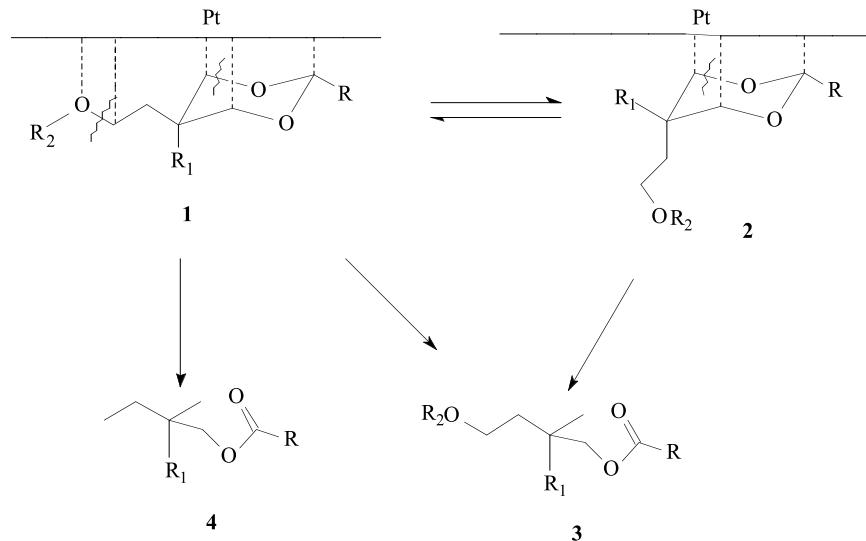
The study of the transformation of 5-alkoxyalkyl-5-alkyl-1,3-dioxanes provided the first experimental evidence that the conformation of the reactant molecule plays a determining role regarding the direction of the catalytic reaction. The reason for the differing reaction directions clearly indicates that the conformers adsorb in different ways.³² The 5-alkoxyethyl isomers can exist in their chair conformations (1 and 2 in Scheme 4.12). The main reaction of the adsorbed surface species is the formation of an ester (3) by the rupture of the C–O bond in the ring. In one of the two isomers (1) the R₂-O group can also be adsorbed and this adsorption leads to a smaller ester molecule (4).

In contrast to this, one of the two 5-alkoxymethyl isomers (5 in Scheme 4.13) exists as a twist-boat conformer. The adsorbed twist-boat conformer reacts much faster than the corresponding chair form (6) and leads to the hydrogenolysis product 7 (Scheme 4.13).

Dioxacycloalkanes are cyclic acetals that are used frequently as protective groups. Substituted derivatives have been synthesized to achieve easy removal. Simplest of all, the 4-phenyl-1,3-dioxolane has not been used commonly because cleavage needs electrolytic conditions. A mild hydrogenolysis method was developed in 1997 to make this protective group more popular (Scheme 4.14).³³

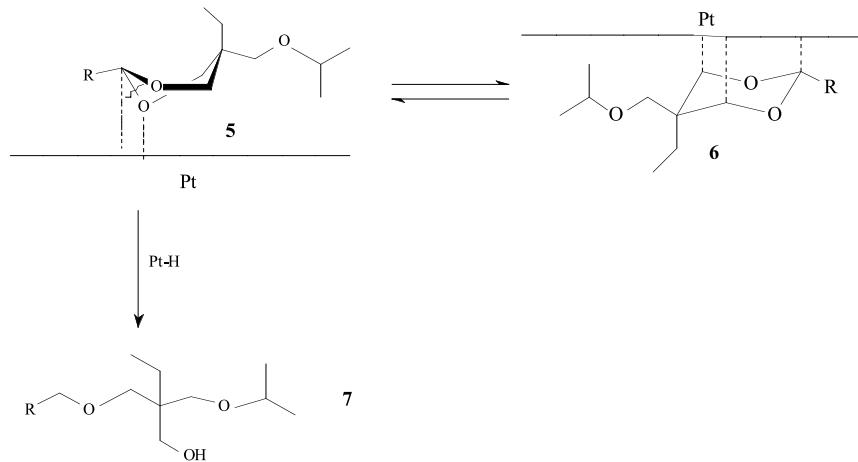


SCHEME 4.11

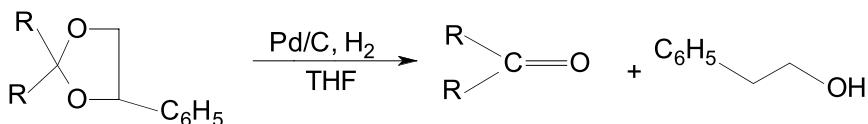


SCHEME 4.12

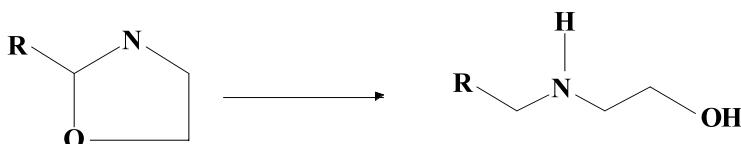
CN–C–OC Azaacetals Oxazolidines are formed from ethanolamines and aldehydes or ketones. The C–O bond in oxazolidines can be cleaved selectively by catalytic hydrogenolysis (Scheme 4.15).



SCHEME 4.13



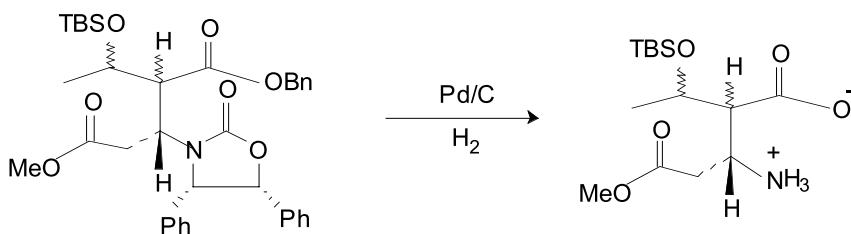
SCHEME 4.14



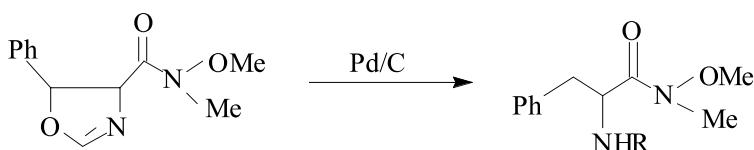
SCHEME 4.15

The benzyl ester protecting group and oxazolidinone ring were hydrogenolyzed on 5% Pd/C in MeOH for 16 hours (Scheme 4.16).³⁴

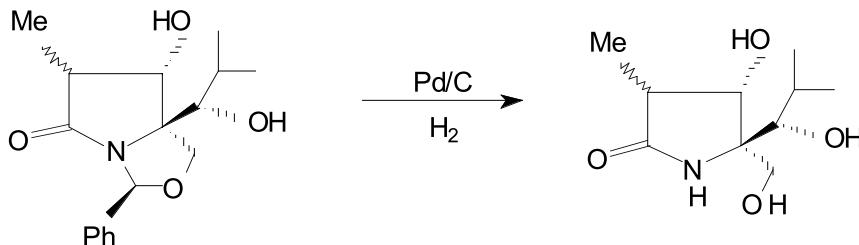
The palladium-catalyzed opening of an oxazolidine ring followed by the hydrogenolysis of a benzylic OH group was performed over 5% Pd/C in ethanol at 140 atm H₂ in 45 hours (Scheme 4.17).³⁵



SCHEME 4.16



SCHEME 4.17

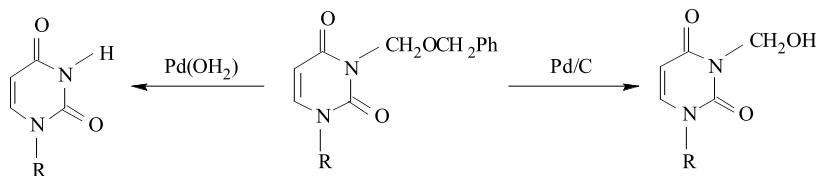


SCHEME 4.18

The C–O bond in a phenyl substituted oxazole ring was hydrogenolyzed on Pd/C in AcOEt,³⁶ in CH₂Cl₂–MeOH,³⁷ and in EtOH.³⁸ In the presence of a small amount of HClO₄, the hydrogenolysis of the benzylic OH group also occurred. Both the *O*-benzyl and *N*-benzyl bonds in an oxazole ring were cleaved in a hydrogen atmosphere using Pd/C in MeOH–HCl at room temperature (Scheme 4.18).³⁹

PhCH₂–O–CH₂–N A nitrogen-containing compound protected by a benzylloxymethyl protecting group has two reactive bonds, the bond between the benzylic carbon and the oxygen and the activated C–N bond of the azaacetal. The regioselectivity of the hydrogenolysis depends on the catalyst used. Although, the C–O bond was ruptured and a hydroxymethyl derivative was obtained as the major product using Pd/C as a catalyst, deprotected lactone was obtained quantitatively by the rupture of the C–N bond when hydrogenolysis was performed with Pd(OH)₂ in MeOH (Scheme 4.19).⁴⁰

Benzyl and Allyl Carbon Atoms Hydrogenolysis of a carbon–heteroatom bond is extremely fast if the heteroatom is connected to allylic or benzylic carbon atoms. The benzylic compounds are used very frequently in organic chemistry as protecting groups. Because of its great importance the benzylic compounds are discussed separately in the next section.



SCHEME 4.19

$\boxed{\text{C}=\text{C}-\text{CH}_2-\text{OR}}$ **Allyl Compounds** Hydrogenolysis of the allylic C–O bond occurs much more readily than hydrogenolysis of the normal C–O bond in a corresponding saturated compound. The olefinic bond, however, also hydrogenates readily and the outcome of the hydrogenation is determined by the relative rates of the two competitive reactions. The saturated molecule very often is stable under the same conditions that permit facile hydrogenolysis of the allylic function. This means that the successful hydrogenolysis of an allylic compound needs conditions under which hydrogenolysis is faster than hydrogenation.⁴¹

An allyl ether-protecting group was removed by dissolving it in methanol–ethyl acetate, adding Pd/C and *p*-toluenesulfonic acid, and refluxing for 90 minutes.⁴² A similar procedure was used for deallylation during the synthesis of (–)-hikizimycin.⁴³ Deallylation was also performed over 10% Pd/C in ethanol–acetic acid–water mixture for 48 hours at 75°C.⁴⁴ α,β -Unsaturated carbonyl compounds can be hydrogenated–hydrogenolyzed to hydrocarbons over platinum oxide catalyst.⁴⁵

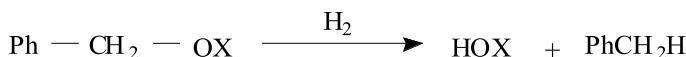
In some cases it is necessary to hydrogenate allylic compounds to saturated molecules without hydrogenolysis. It was found that nickel boride is a good catalyst for this purpose.⁴⁶

4.1.1.6. Hydrogenolysis of Benzyl–Oxygen Bonds

Benzyl groups are among the most useful protecting groups for O-, N- and S-containing compounds in synthetic organic chemistry, primarily because of their ease of formation, their relative stability, and the efficiency of cleavage under mild conditions. Because of its great synthetic importance, the removal of the benzyl group (Bn) has a special name, namely *debenzylolation* (Scheme 4.20).

Palladium is widely used for debenzylation. It has high activity for hydrogenolysis with low activity for saturating aromatic rings. Platinum and ruthenium saturate aromatic rings with minimal hydrogenolysis. Rhodium is useful in the hydrogenolysis of certain complex benzyl alcohols, especially when dehydrohalogenation is to be avoided, but with simpler molecules, ring saturation is likely to take precedence over hydrogenolysis.

The structure of the substrate influences the rates of hydrogenolyses. Over Pd, the rates of hydrogenolysis of benzyl derivatives increase in the order OH < OR << OAr < OCOR, according to their leaving group ability. Therefore, ben-



SCHEME 4.20

zyl esters, which contain the best leaving group in this series, can be hydrolyzed at the highest reaction rate (characteristic for the S_N reactions).

4.1.1.6.1. Hydrogenolysis of Benzyl Alcohols

PhC–OH Hydrogenolyses of benzyl alcohol derivatives (Scheme 4.21) proceed at reasonable rates even at room temperature. The reaction is usually carried out in ethanol. Since the hydroxyl is a poor leaving group, a catalytic amount of a strong acid is usually added to produce a protonated alcohol ($R-OH_2^+$) making water the leaving group. Because the water is a very good leaving group, acidic media increase the rates of hydrogenolyses of benzyl alcohols.

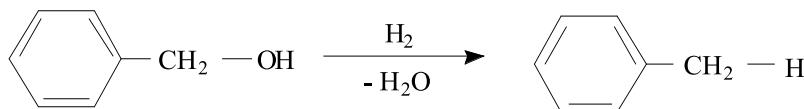
Pd is the most widely used catalyst for the cleavage of benzylic C–O bonds, and 10% Pd/C is the most popular form of Pd for hydrogenolysis of benzyl alcohols. This catalyst usually contains residual acids, which increase reaction rates.

For example, 10% Pd/C in CH_2Cl_2 with catalytic amounts of *p*-TsOH was used for 56 hours to reduce benzyl alcohol.⁴⁷ Likewise, the catalytic hydrogenolysis of an epimeric mixture of another benzyl alcohol was performed in dry ethanol using 10% Pd/C and two drops of $HClO_4$ for 3 hours at room temperature and atmospheric pressure.⁴⁸

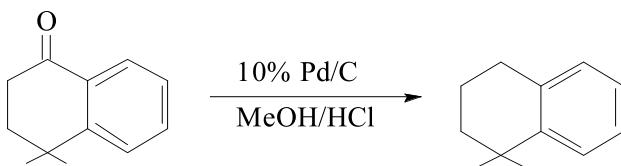
PhC=O Hydrogenation of a C=O double bond followed by catalytic hydrogenolysis of the resulting OH group is an alternative method for the conversion of aromatic aldehydes and ketones to alkanes. Pd/C and PtO_2 are the most often used catalysts.^{49–51} In this way, dimethyltetralone was hydrogenated–hydrogenolyzed under 60 psi H_2 for 5 hours in MeOH–HCl with 10% Pd/C (Scheme 4.22).⁵²

The [1₄], [1₅],⁵³ and [1₇]-orthocyclophane-1,3-diones⁵⁴ were hydrogenated–hydrogenolyzed to the corresponding orthocyclophanes by stirring with 10% Pd/C under H_2 (35–40 psi) in a mixture of EtOH–HCl for 3 days (Scheme 4.23).

In contrast, the Pd-catalyzed hydrogenation of the [1₆]-orthocyclophane-1,3-dione was attempted repeatedly for 7 days, over a wide range of H_2 pressures (35–45 psi) and temperatures (25–40°C), to produce a similar reduction



SCHEME 4.21



SCHEME 4.22

product. However, it was not possible to extract the expected product from the reaction mixture, and only a trace of the starting material was recovered.⁵⁵

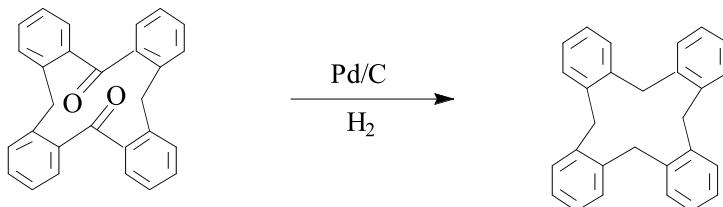
During the synthesis of 2-pyridones, hydrogenation–hydrogenolysis of the ketone intermediate was performed on different catalysts (Scheme 4.24).^{56,57}

The ketone was reduced in acetic anhydride with 10% Pd/C and two drops of trifluoroacetic acid at 1 atm H₂ for 36 hours. The triple bond was fully hydrogenated, the ketone group removed (hydrogenated–hydrogenolyzed), and the benzyl–oxygen bonds hydrogenolyzed. On the other hand, in ethanol, Ra–Ni fully hydrogenated both the triple bond and the ketone but did not hydrogenolyze the resulting alcohol nor the benzyl–oxygen bonds. These latter were hydrogenolyzed in ethanol THF over 10% Pd/CaCO₃ without hydrogenolysis of the benzylic OH group.

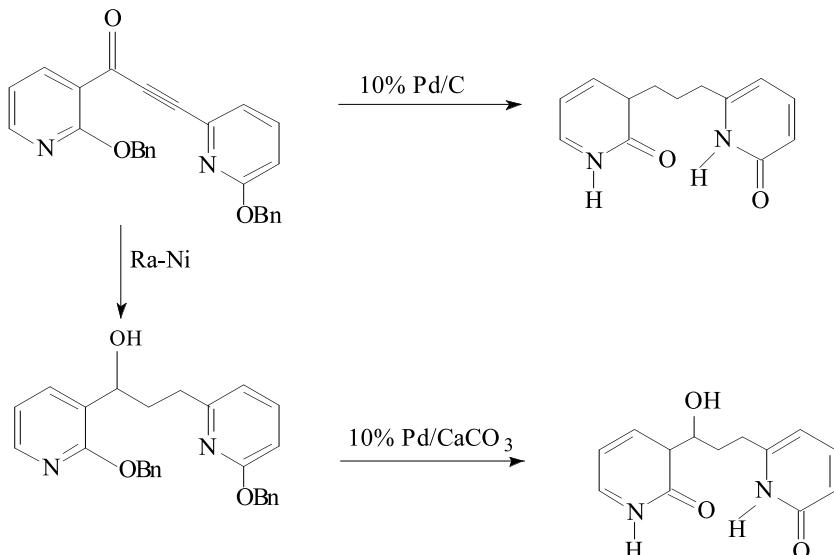
During the hydrogenation of benzophenone to benzhydrol, the undesired side-product, diphenylmethane, is obtained by hydrogenolysis of the C–O bond (Scheme 4.25).

No suppression in hydrogenolysis of the C–O bond was observed over either bimetallic catalysts or TiO₂-supported catalysts, indicating involvement of different types of sites than C–C bond hydrogenolysis.⁵⁸

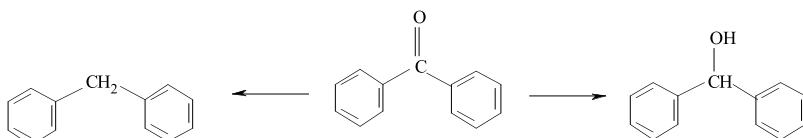
In some cases an indirect method, tosylation of a benzyl alcohol followed by catalytic hydrogenolysis of the resulting tosylate, has been used to remove benzylic OH groups (Scheme 4.26).



SCHEME 4.23



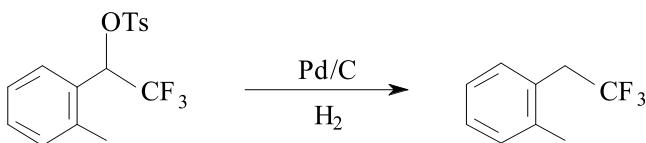
SCHEME 4.24



SCHEME 4.25

Such a hydrogenolysis over 10% Pd/C in ethanol at room temperature and atmospheric pressure gave the desired product in 83% yield.⁵⁹

In the catalytic hydrogenation of benzaldehyde to benzyl alcohol, it is very important to prevent the hydrogenolysis of the product. Nickel^{60–63} and copper



SCHEME 4.26

chromite⁶⁴ are suitable catalysts for the hydrogenation of benzaldehyde without hydrogenolysis.

4.1.1.6.2. Hydrogenolysis of Benzyl Ethers

PhC—O Benzyl ethers are among the most popular O-protecting groups in synthetic organic chemistry, primarily because of their ease of formation and removal. The removal of benzyl ether-protecting groups (Scheme 4.27) are most often carried out over palladium catalysts (Pd/C or Pd(OH)₂/C) in ethanol or acetic acid along with small amounts of strong acids. The acid protonates the oxygen and makes it a better leaving group.

The disadvantages of the general method using supported palladium and hydrogen are a lack of selectivity and overreduction. Where selectivity is not an important requirement, Pd/C is a widely used catalyst for the hydrogenolysis of the C—O bond in benzyl ethers.

Examples In a typical experiment, a benzyl ether in absolute methanol was added to a tube containing Pd/C and a stir bar. Three drops of concentrated HCl were added and the mixture was stirred under a gentle flow of hydrogen for 5 minutes. The tube was sealed and pressurized with hydrogen (40 psi) and stirring was continued for 6 hours. During these circumstances, the benzyl group was completely removed.⁶⁵

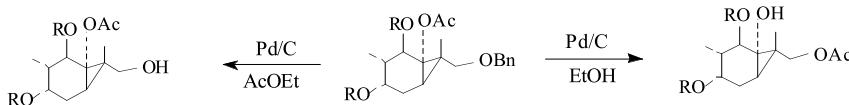
Boc-O-benzyl-L-homoserine (Boc = *t*-butoxycarbonyl) was transformed to L-proline methyl ester, and the benzyl ether was removed by hydrogenolysis. The compound was dissolved in 50% acetic acid in methanol and the reaction mixture was degassed by bubbling nitrogen for 5 minutes; then 10% Pd/C was added. The system was evacuated for 5 minutes and then pressured to 45 psi of hydrogen for 48 hours at room temperature.⁶⁶

During the synthesis of tellimagrandin, debenzylation was accomplished over 10% Pd/C in dry THF. The mixture was purged six times with hydrogen and stirred at room temperature under 1 atm of hydrogen for 48 hours and finally purged with argon.⁶⁷

Deprotection of a primary benzyl ether was carried out by hydrogenolysis over 10% Pd/C in ethanol. Hydrogenolysis of its acetate derivative in polar-protic solvents like ethanol gave a 61% yield of the undesired product result-



SCHEME 4.27



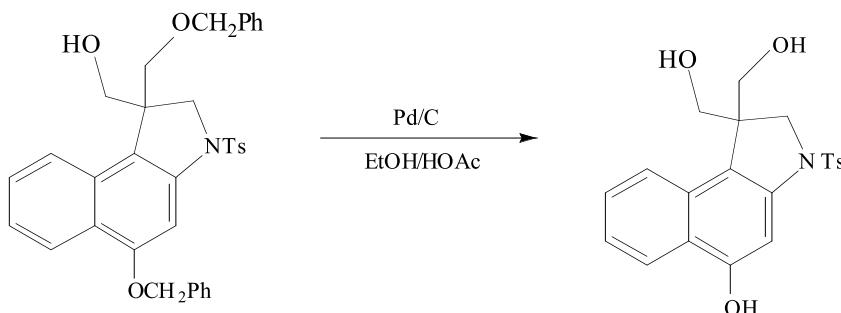
SCHEME 4.28

ing from acetyl transfer. Carrying out the same sequence in ethyl acetate afforded up to 33% of the desired product along with an equal amount of the undesired primary acetate (Scheme 4.28).⁶⁸

Benzyl protecting groups were removed over 10% Pd/C in EtOH containing 5% acetic acid at 23°C for 24 hours under hydrogen. Procedures for hydrogenolysis conducted in the absence of the deliberately added acid catalyst proved slow and capricious and often hydrogenolysis halted before completion, whereas under modest pressures of hydrogen (50 psi, EtOH, 24 hours) or for prolonged reaction periods (48 hours) hydrogen treatment resulted in detectable hydrogenation of the central aromatic ring of the substrate (Scheme 4.29).⁶⁹

Other examples of debenzylation of benzyl ethers on the frequently used Pd/C catalysts are summarized in Table 4.2.

Palladium hydroxide on carbon is also widely used for removing benzyl ether-protecting groups. The Pearlman catalyst, Pd(OH)₂ (moisture content 50%), contains 20% Pd (dry weight basis). It is a neutral, nonpyrophoric catalyst that has been used as a hydrogenation catalyst for a variety of functional groups.^{121–122} Degussa-type wet Pd(OH)₂/C (20% Pd) is a very useful reagent for debenzylation. Examples of debenzylation on Pd(OH)₂/C catalysts are summarized in Table 4.3.



SCHEME 4.29

TABLE 4.2 Benzyl Ether Hydrogenolysis on Pd/C Catalysts

Catalyst	Solvent	Pressure	Time	Temperature	Citation
10% Pd/C	MeOH		18 h		70
10% Pd/C	MeOH		1 h		71
10% Pd/C	MeOH		24 h		72
10% Pd/C	MeOH	1 atm	4 d		73
10% Pd/C	MeOH		2 h	Room	74
10% Pd/C	MeOH	50 psi			75
5% Pd/C	MeOH		3 h		76
20% Pd/C	MeOH	50 psi	24 h		77
20% Pd/C	MeOH–HCl	50 psi	24 h		77
10% Pd/C	MeOH–H ₂ O	1 atm	3 h	Room	78
10% Pd/C	MeOH–HCl	3 bar	2 d		79
10% Pd/C	MeOH–HCl	50 psi	6 h		80
10% Pd/C	EtOH		4 h	Room	81
10% Pd/C	EtOH			20°C	82
10% Pd/C	EtOH				83,84
10% Pd/C	EtOH	1 atm	4 h	25°C	85
10% Pd/C	EtOH		4 h	Room	86
10% Pd/C	EtOH		16 h	Room	44
10% Pd/C	EtOH		20 h	Room	87
10% Pd/C	EtOH	3.3 atm	2 d	Room	88
10% Pd/C	EtOH	40 psi	Overnight		89
10% Pd/C	EtOH	1 atm	Overnight		90
10% Pd/C	EtOH–NaHCO ₃				84
5% Pd/C	EtOH		3 h		91
5% Pd/C	EtOH	1 atm			92
20% Pd/C	EtOH	55 psi	15 h	25°C	93
10% Pd/C	95% EtOH	1 atm	Overnight	Room	94
10% Pd/C	EtOH–HCl	1.3 bar	Overnight	50°C	95
10% Pd/C	EtOH–MeOH	1 atm	1.5 h		96
10% Pd/C	EtOH–HCO ₂ H	4 atm	5 h		97
10% Pd/C	MeOH–AcOH	750 psi	20 h		98
10% Pd/C	EtOH–NaHCO ₃				84
10% Pd/C	EtOH–THF–HCO ₂ H	60 psi	36 h		99
10% Pd/C	AcOEt	4 atm	19 h	20°C	100

continues

TABLE 4.2 *continued*

Catalyst	Solvent	Pressure	Time	Temperature	Citation
10% Pd/C	AcOEt		1 h	20°C	101
10% Pd/C	AcOEt				102,103
10% Pd/C	AcOEt	1 atm		Room	104
10% Pd/C	AcOEt		6 h		105
10% Pd/C	AcOEt			Overnight	106
10% Pd/C	AcOEt		3 h	Room	107
10% Pd/C	AcOEt		48 h	25°C	108
10% Pd/C	AcOEt	1000 psi		80°C	109
10% Pd/C	AcOEt	1 atm	24 h		110
10% Pd/C	AcOEt–HCl		0.5 h	Room	111
10% Pd/C	AcOEt–MeOH	35 psi	5 h		112
10% Pd/C	THF			20°C	82
10% Pd/C	THF		30 min		113
10% Pd/C	THF		2 h		114
10% Pd/C	THF/HCl	1 atm	3 h		115
10% Pd/C	CHCl ₃ –MeOH				
10% Pd/C	Acetone	1 atm	3 h	20°C	100
10% Pd/C	Cyclohexane	15 atm	6.5 h	Room	118
10% Pd/C	2-Propanol				119
PdO	AcOH				120

Pd/CaCO₃ is also used for the hydrogenolysis of benzyl–oxygen bonds.¹⁵² Hydrogenation and hydrogenolysis of an unsaturated benzyl ether over 5% Pt/C and Pd(OH)₂ gave the saturated and deprotected product.¹⁵³ In contrast, transfer hydrogenolysis with 1,4-cyclohexadiene or ammonium formate failed to provide the product cleanly, rapidly, or dependably.

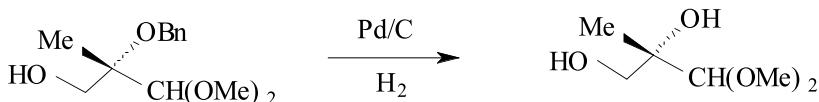
Selective removal of the benzyl ether-protecting group without hydrogenolysis of the ketal C–O bonds was performed on Ra–Ni in EtOH.^{154,155} A solution of benzyloxy acetal in MeOH with 5% Pd/C was stirred at room temperature with a H₂ pressure from a balloon until the reaction was complete (Scheme 4.30).¹⁵⁶

Cyclic phosphonate analogues of hexopyranoses were debenzylated in MeOH–H₂O on Pd/C. The system was purged with H₂, and the reaction was run under 1 atm of H₂ while being stirred vigorously. The reaction was complete after 12 hours. On the other hand, when sodium iodide in acetonitrile

TABLE 4.3 Benzyl Ether Hydrogenolysis on Pd(OH)₂/C Catalyst

Catalyst	Solvent	Pressure	Time	Temperature	Citation
20% Pd(OH) ₂ /C	MeOH	1 atm	4 h		123
20% Pd(OH) ₂ /C	MeOH		2 h	22°C	124,125
20% Pd(OH) ₂ /C	MeOH	1 atm	3–6 h		126
Pearlman's catalyst	MeOH	1 atm	30 min	60°C	127
20% Pd(OH) ₂ /C	MeOH	50 psi	3 h		128
20% Pd(OH) ₂ /C	MeOH		1 h	40°C	129
20% Pd(OH) ₂ /C	AcOEt	34 psi	36 h		130
Pd(OH) ₂ /C	MeOH	1 atm	2 h		131
Pd(OH) ₂ /C	MeOH				132
Pd(OH) ₂ /C	MeOH	50–65 psi	24–40 h		133
Pearlman's catalyst	MeOH	1 atm	24 h		134
Pd(OH) ₂ /C	MeOH	30 min		60°C	135
Pd(OH) ₂	MeOH		2 h		136
Pd(OH) ₂ /C	THF–MeOH	1 atm			137
Pd(OH) ₂	MeOH–AcOEt–H ₂ O				138
Pearlman's catalyst	AcOEt	1 atm	4 h		139
20% Pd(OH) ₂ /C	EtOH				140,141
Pd(OH) ₂	EtOH		2 h		136
Pd(OH) ₂ /C	MeOH–H ₂ O		48 h	25°C	142
Pd(OH) ₂ /C	EtOH–AcOEt		5 h		143
20% Pd(OH) ₂ /C	AcOEt				144
10% Pd(OH) ₂ /C	AcOEt		1.5 h		145
10% Pd(OH) ₂ /C	AcOEt	1 atm	0.5 h	25°C	146
10% Pd(OH) ₂ /C	AcOEt		2 h		147
Pd(OH) ₂ /C (10% Pd)	AcOEt–MeOH		16 h	Room	147
Pd(OH) ₂	AcOEt		1 h		136
10% Pd(OH) ₂ /C	MeOH		3 h		148
10% Pd(OH) ₂ /C	MeOH	1 atm	10 h	25°C	149
Pearlman's catalyst	MeOH	1 atm			150
5% Pd(OH) ₂ /C	AcOEt	1 atm	12 h		151

was used to produce the demethylated compound, debenzylation of the demethylated derivative was very slow and gave only a mixture of partially debenzylated products. This was true even when the reaction proceeded over the course of 5–8 days at 4 atm pressure (Scheme 4.31).



SCHEME 4.30

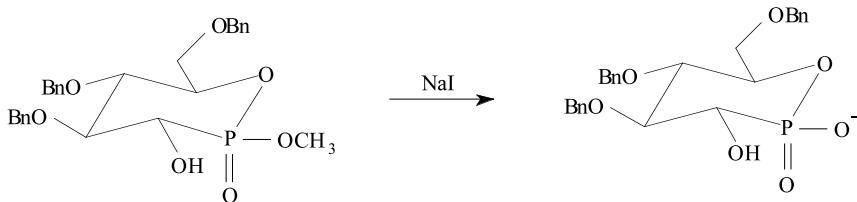
The use of additional catalyst or varying reaction temperatures (20–40°C), varying solvents (0–25% H₂O in MeOH, 0–25% H₂O in EtOH), varying concentrations of reactants, and different catalyst types (10% Pd/C, Degussa-type 10% Pd/C, PtO₂) improved neither the rate nor the yield significantly.¹⁵⁷ Apparently, the adsorption of the oxygen atom onto the metal surface is essential for hydrogenolysis of the C–O bond, but the negative charge on the demethylated oxygen makes its adsorption so strong that the required adsorption of any benzylic oxygen is hindered and debenzylation is prevented.

Benzyl-deoxyguanosine was dissolved in a mixture of EtOH–H₂O–NH₃ and hydrogenated over 20% Pd/C at 25°C for 48 hours (Scheme 4.32).¹⁵⁸

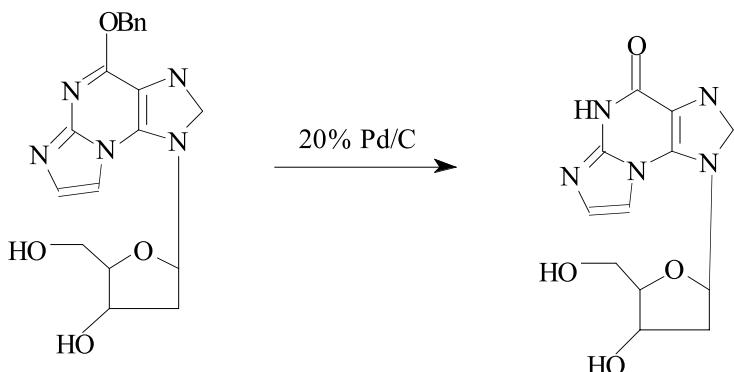
PhC–O–C–O **Benzyl Acetals** Acyclic acetals are used for the protection of OH groups. The most common ones are derived from formaldehyde. The benzyl acetal of formaldehyde is known as the benzyl oxymethyl (BOM) protecting group. The hydrogenolysis of the benzylic C–O bond in a benzyloxymethyl protecting group leads to a hemiacetal that is unstable; CH₂O is liberated and the OH group deprotected (Scheme 4.33).

Benzyl acetal protecting groups were hydrogenolyzed over Pd/C,¹⁵⁹ over 20% Pd(OH)₂/C in AcOEt for 2 hours,¹⁶⁰ and over 10% Pd/C in AcOEt in the presence of NaHCO₃ for 30 minutes.¹⁶¹

Benzyl groups were removed from an acetyl-glucopyranoside over 5% Pd/C in EtOH–AcOH (5:1) under 50 psi H₂ at room temperature.¹⁶² Hydrogenolysis of a hexapyranoside was made in EtOH–AcOH over 10% Pd/C under 55 psi hydrogen at room temperature for 21 days. The reaction time was shortened to 2 days by heating to 50°C.¹⁶³ Benzyl-2,6-dideoxy-β-D-glucopyranoside was



SCHEME 4.31



SCHEME 4.32

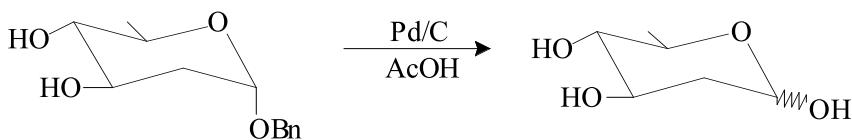


SCHEME 4.33

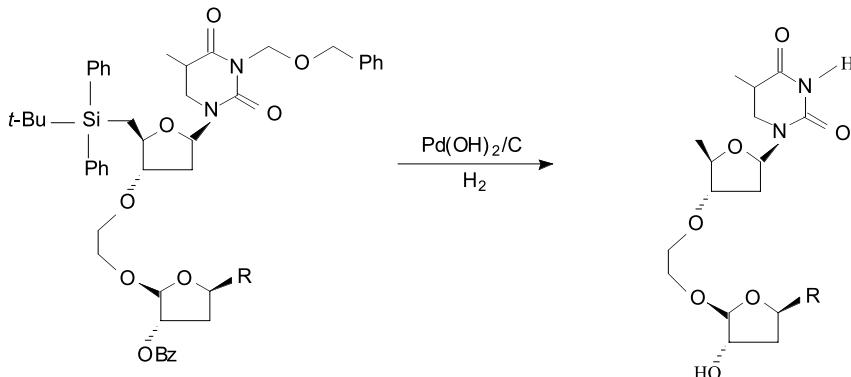
hydrogenolyzed in 60% aqueous AcOH over 10% Pd/C under atmospheric pressure for 12 hours (Scheme 4.34).¹⁶⁴

Both benzyl ether, benzyloxymethyl and *t*-butyldiphenylsilyl protecting groups were removed on Pd(OH)₂/C in methanol–acetone (Scheme 4.35).¹⁶⁵

Cyclic Acetals Benzyl ethers are obtained from benzylidene acetals on Ni but the product ethers are cleaved about as readily as the acetals.¹⁶⁶ The hydrogenolysis of a *p*-bromobenzylidene derivative was achieved on 10% Pd/C in AcOEt and NaHCO₃.¹⁵⁴



SCHEME 4.34

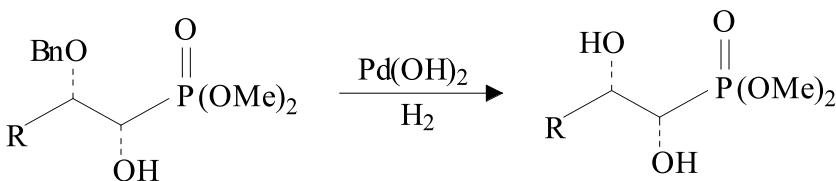


SCHEME 4.35

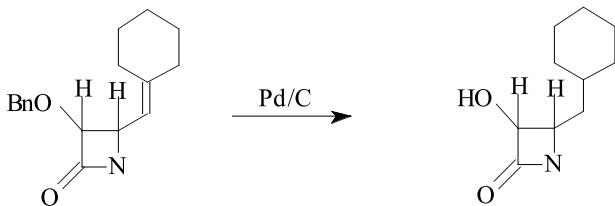
Hydrogenolysis of a benzyl ether C–O bond in a phosphoric acid dimethyl ester was done in MeOH in the presence of $\text{Pd}(\text{OH})_2$ at room temperature under atmospheric hydrogen pressure for 12 hours (Scheme 4.36).^{167,168}

During the total synthesis of the gilvocarcins, a careful choice of reaction conditions was necessary for final removal of the four benzyl protecting groups by hydrogenolysis. The use of 10% Pd/C in THF led to overreduction resulting in partial saturation of the tetracyclic moiety. This problem was circumvented by employing Ra-Ni in EtOH as an overreduction-free protocol, which, however, required long reaction times (84 h). The use of a mixed solvent system (MeOH–THF, 4:1) and 10% Pd/C under 1 atm H_2 at room temperature allowed clean hydrogenolysis in 5 hours to give (–)-gilvocarcin in 90% yield.¹⁶⁹

During the synthesis of siderophores, the simultaneous removal of the benzyl, *p*-nitrobenzyl, and *t*-butoxicarbonyl protecting groups was accomplished under acidic hydrogenolysis conditions (H_2 , 10% Pd/C in DMF–HCl– H_2O).^{170,171}



SCHEME 4.36



SCHEME 4.37

Hydrogenolysis of a triphenylmethyl protecting group was carried out over 10% Pd/C in dry CH_2Cl_2 at 25°C under 4 atm hydrogen pressure for 4 days.¹⁷²

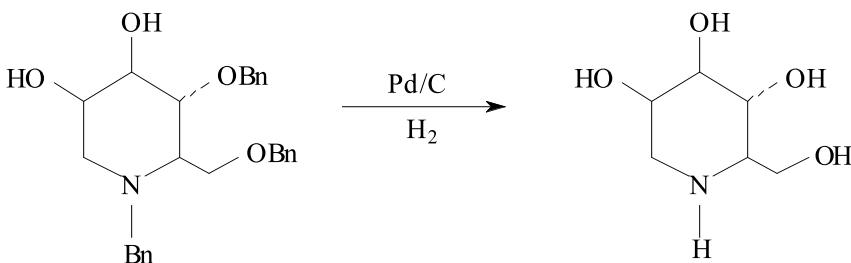
During the stereoselective synthesis of azetidin-2-ones the reaction with 1 atm hydrogen over 10% Pd/C hydrogenated the double bond and hydrogenolyzed the benzyl group (Scheme 4.37).¹⁷³

For removing both the O -benzyl and N -benzyl protecting groups, 10% Pd/C and 1.8 ml HCl was added to a solution of the starting compound in 2 ml EtOH and the mixture was stirred under hydrogen for 14 hours (Scheme 4.38).¹⁷⁴

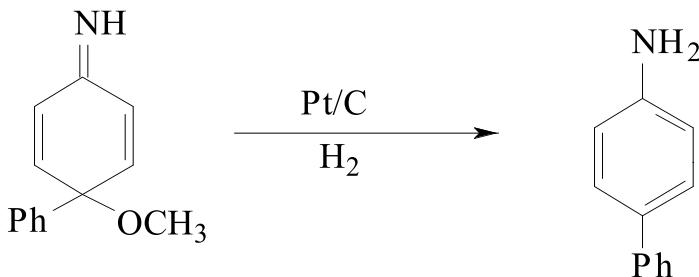
The hydrogenation of a quinol ether imine derivative on Pt/C led to the hydrogenolysis of the C–O bond (Scheme 4.39).¹⁷⁵

In some cases the hydrogenation of the double bond in an unsaturated benzyl ether is necessary without debenzylation. To hydrogenate the carbon–carbon double bond 5% Pd/C in AcOEt was used for 1.5 hours (Scheme 4.40).¹³⁶ The benzyl ether-protecting group was removed over $\text{Pd}(\text{OH})_2$ in AcOEt for 1 hour.

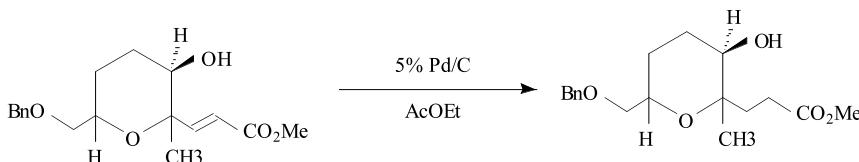
PhC–O–N Both benzyl–oxygen and nitrogen–oxygen bonds undergo hydrogenolysis readily in the presence of a benzyloxy–nitrogen bond but it appears that the benzyl–oxygen bond can be made to cleave selec-



SCHEME 4.38



SCHEME 4.39

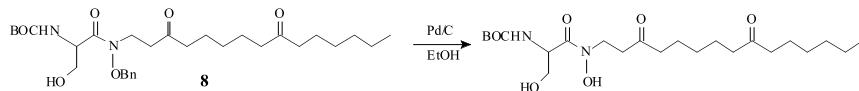


SCHEME 4.40

tively. For hydrogenolysis of a benzyl–oxygen bond in an *N*-benzyloxy compound, Pd/C (10%) was added to a solution of this compound in MeOH. The reaction flask was purged three times with nitrogen, and hydrogen was introduced at 1 atm. The mixture was stirred for 20 minutes. After that the flask was evacuated and filled with nitrogen several times.¹⁷⁶

The *O*⁴-benzyl derivative of norneoenactin (8) was hydrogenolyzed over 10% Pd/C in EtOH at room temperature for 105 min (Scheme 4.41).¹⁷⁷

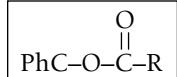
Treatment of the *O,O*-dibenzyl derivative of norneoenactin with 10% Pd/C in MeOH under hydrogen atmosphere resulted in the rapid deprotection (within 1 h) of the starting material. However, reduction of the benzyl ether functionality, without the concomitant hydrogenolysis of the N–O bond, required fine tuning of the conditions. When the hydrogenolysis was carried out using 20–25 mol % of 10% Pd/C at 20 or 30 mM concentrations for 22–31 hours, a



SCHEME 4.41

mixture of two inseparable products was obtained. One was believed to be the desired debenzylated product and the other the deoxygenated product resulting from hydrogenolysis of the N–O bond. Catalytic hydrogenolysis with 10% Pd/C (30 mol %) in dioxane over 3 days provided a mixture of the desired debenzylated and monobenzylated products as well as the starting material. Finally, carrying out the reaction with 30 mol % of 10% Pd/C at 6–8.6 mM concentrations for 11–16 hours provided the pure debenzylated product in 80% yield.¹⁷⁷

4.1.1.6.3. Hydrogenolysis of Benzyl Esters

 Benzyl esters of carboxylic acids are frequently used in organic synthesis for the protection of carboxyl groups. The C–O bond in benzyl esters can be cleaved more easily than the corresponding benzyl ether bond. The hydrogenolysis of an ester leads to carboxylic acid and toluene. Examples of debenzylation of benzyl esters of carboxylic acids on Pd/C catalysts are summarized in Table 4.4.

For certain hindered benzyl esters, tertiary amines are used as promoters. Such hydrogenolyses have been performed over 10% Pd/C in the presence of triethylamine in acetone at room temperature and 30 psi for 18 hours,²⁰¹ or in *t*-BuOH at atmospheric pressure for 1.5 hours.²⁰²

Both the benzyl ester and benzyl ether groups are hydrogenolyzed on Pd(OH)₂/C,²⁰³ over Pd black in THF–H₂O–AcOH (16:4:1) under 1 atm H₂ at 25°C for 8 hours,²⁰⁴ on Pd/C in THF–HClO₄,²⁰⁵ or over 10% Pd/C in MeOH.²⁰⁶

Concomitant hydrogenolysis of a benzyl ester and hydrogenation of a diene were performed in one step over PtO₂ in AcOEt.²⁰⁷ In contrast, 10% Pd(OH)₂/C in AcOEt or EtOH at room temperature for 1 hour under hydrogen was used for the hydrogenolysis of a benzyl group without the saturation of a cyclic carbon–carbon double bond.²⁰⁸

During the preparation of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, the benzyl ester protecting group was removed by catalytic hydrogenolysis (Scheme 4.42).

Careful control of reaction conditions was necessary to get as few by-products as possible. Employing palladium catalysts and CH₂Cl₂ or MeOH as solvents or higher pressures of hydrogen led to the same external overhydrogenolysis. Finally, it was found that consistent yields and purities of the desired product were achieved when the hydrogenolysis was terminated at 0.9 equiv of hydrogen consumption. Therefore, Pearlman's catalyst was used in AcOEt at room temperature and ordinary hydrogen pressure until 0.93 equiv of hydrogen were consumed.²⁰⁹

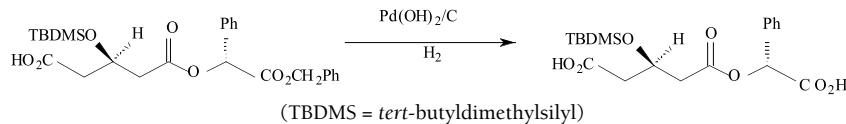
Removal of the 4-chlorobenzyl protecting group of a protected cryptand was performed under “buffered conditions”²¹⁰ in the presence of sodium ace-

TABLE 4.4 Benzyl Ester Hydrogenolysis on Pd/C Catalysts

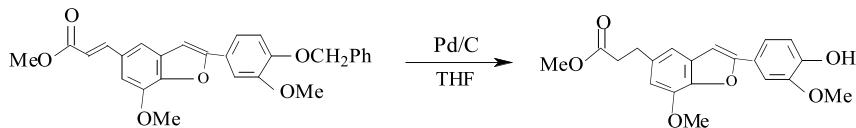
Catalyst	Solvent	Pressure	Time	Temperature	Citation
10% Pd/C	MeOH	1 atm	2.5 h	Room	178
10% Pd/C	MeOH		12 h	25°C	179
10% Pd/C	MeOH		0.5 h		180
10% Pd/C	MeOH–AcOH	40 psi	3 h		181
10% Pd/C	MeOH–HCl	50 psi	2 h		182,183
5% Pd/C	MeOH–NaHCO ₃	1 atm	1 h		184
5% Pd/C	MeOH	1 atm	5 h		185
5% Pd/C	MeOH–AcOEt	1 atm	36 h	Room	186
5% Pd/C	EtOH		24 h		187
5% Pd/C	MeOH		14 h		188
10% Pd/C	MeOH	50 psi		1°C	189
10% Pd/C	EtOH	1 atm			190
10% Pd/C	EtOH	3 atm	5 h		191
10% Pd/C	EtOH	1 atm	4 h	25°C	192
10% Pd/C	EtOH	1 atm	24 h	Room	193
10% Pd/C	EtOH		1 h	Room	194
10% Pd/C	EtOH		0.5 h		195
10% Pd/C	AcOEt		12 h	25°C	179
10% Pd/C	AcOEt		2 h	21°C	196
10% Pd/C	AcOEt		2 h	20°C	197
10% Pd/C	AcOEt		4–6 d		198,199
10% Pd/C	THF–H ₂ O				200

tate. A suspension of the protected compound, sodium acetate and 10% Pd/C in *t*-BuOH–H₂O was stirred slowly under 4 atm hydrogen for 2 hours in a Parr apparatus.²¹¹

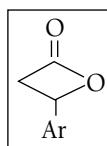
A solution of an α , β -unsaturated ester and 5% Pd/C in THF was stirred under H₂ for 10 hours to remove the benzyl group and saturate the C=C bond (Scheme 4.43).²¹²



SCHEME 4.42

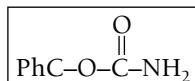


SCHEME 4.43

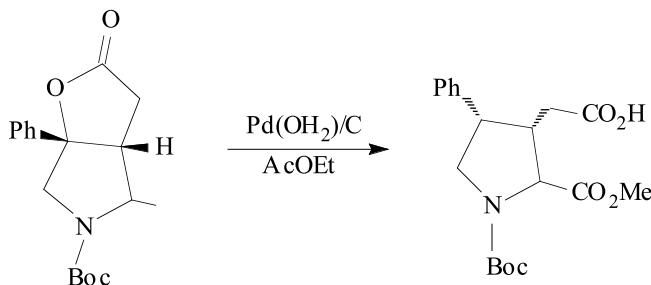


Lactones (cyclic esters) are usually stable toward hydrogenolysis. However, the aromatic lactones contain benzylic C–O bonds and can be hydrogenolyzed. As an example, the hydrogenolysis of an aromatic lactone was performed over Ra-Ni in THF under 4 atm H₂ pressure at 50°C for 30 hours.²¹³

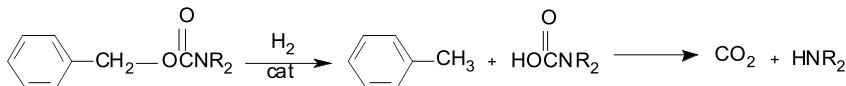
The hydrogenolysis proceeds usually with inversion on Pd. This ability of Pd was used for stereospecific hydrogenation of a lactone during the synthesis of a phenyl kainoid on 10% Pd(OH₂)/C in AcOEt at 40°C (Scheme 4.44).²¹⁴



Benzyl esters of carbamic acid (carbamates) also have benzylic C–O bonds that can be easily cleaved by hydrogenolysis. Carbamates can be prepared easily by the acylation of primary and secondary amino groups. So these amino groups can be protected by acylation. Carbamates enjoy a favorite position in amino protection during peptide synthesis owing to the fact that very little racemization occurs in the coupling step when the amino group is changed into a carbamate.²¹⁵ The best representatives are benzyl and *t*-butyl carbamates, which undergo deblocking by hydrogenolysis. Because the benzyl group can be removed easily by hydrogenolysis under mild conditions, mainly benzyl carbamates are used for the protection of amino groups. Benzyl carbamates can be considered as a benzylloxycarbonyl (otherwise known as carbobenzyloxy, Cbz or Z) protecting group for amino groups. During the hydrogenation of the protected amines



SCHEME 4.44

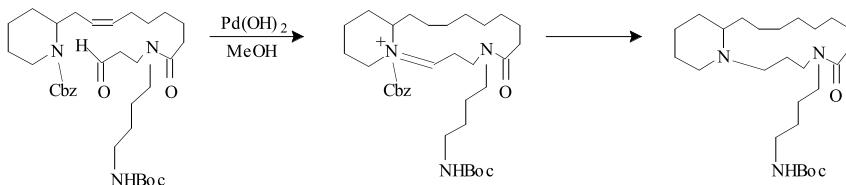


SCHEME 4.45

the benzylic C–O bond hydrogenolyzes easily and the resulting carbamic acid is decarboxylated spontaneously and CO_2 is liberated (Scheme 4.45). The extent of hydrogenolysis can be followed by measuring the amount of CO_2 . Electron withdrawing substituents in the aromatic ring may accelerate the cleavage of the C–O bond.

Examples For the catalytic hydrogenolysis of the N-Cbz group, the protected peptide was stirred with 10% Pd/C in EtOH containing 1% AcOH under 1 atm of H_2 for 16 hours at room temperature²¹⁶ or on 10% Pd/C in EtOH at atmospheric pressure and room temperature for 2 hours.²¹⁷ During the synthesis of a phosphinate inhibitor, the hydrogenolysis of the Cbz protecting groups provided the free amine. In this case, 5% Pd/C (0.04 mol/mol) was used in MeOH in hydrogen atmosphere for 11 hours.²¹⁸ In a similar way the Cbz group was removed quantitatively by catalytic hydrogenolysis from a β -lactam in methanol in the presence of 5% Pd/C in H_2 for 2 hours.²¹⁹ During the synthesis of a deglucoleicoplanin-derived tetrapeptide, a Cbz group was removed under hydrogenolysis conditions (1 atm hydrogen, 5% Pd/C), which were well tolerated by the rest of the molecule.²²⁰ Also, hydrogenolysis of the Cbz group has been performed with 10% Pd/C in AcOEt at room temperature and atmospheric pressure for 30 minutes²²¹ or over 5% Pd/C in EtOH.²²²

Deprotection of the amine and the hydrogenation of the alkene were performed on $\text{Pd}(\text{OH})_2$ and hydrogen atmosphere in MeOH under high dilution, leading to in situ formation of the transient iminium ion, which was further hydrogenated (Scheme 4.46).²²³



SCHEME 4.46



SCHEME 4.47

In the synthesis of the antibiotic *L*-azatyrosine, the simultaneous removal of the carbobenzyloxy and diphenylethylene protecting groups presented a problem (Scheme 4.47).

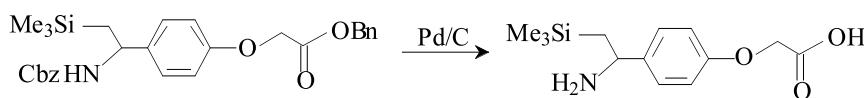
Hydrogenation over Pearlman's catalyst (24 h) yielded a variable mixture of the azatyrosine and an intermediate. Extended hydrogenation yielded overhydrogenolyzed products. The problem was solved by the following procedure: The starting compound was hydrogenolized in 2-propanol–THF (1:1) over 30% $\text{Pd}(\text{OH})_2/\text{C}$ at 50 psi for 18 hours. The mixture was filtered and evaporated, and the residue was dissolved in HCl. This mixture was then evaporated and redissolved in water and hydrogenated at 50 psi hydrogen over 5% Pd/C for 30 minutes.²²⁴ The same groups were also removed from a fully protected peptide over 5% Pd/C in CH_2Cl_2 –MeOH under 60 psi H_2 for 24 hours at room temperature.²²⁵

O-Bn, *O*-Bz and *N*-Cbz bonds were hydrogenolyzed in EtOH– H_2O –THF over 10% Pd/C.²²⁶ *O*-Bn and *N*-Cbz protecting groups were removed over 10% Pd/C in MeOH–AcOH (3:1) at 0°C and 50 psi overnight (Scheme 4.48).⁷⁴

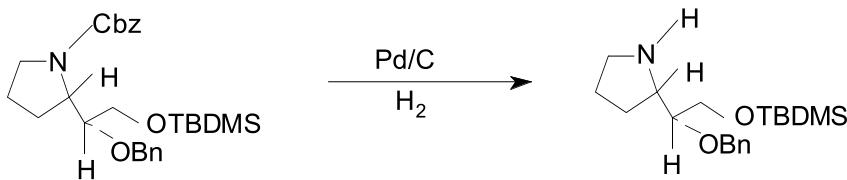
The *N*-benzyloxycarbonyl group was selectively removed in the presence of an *O*-benzyl group on 10% Pd/C (0.45 mol Pd/mol) in MeOH at 1 atm H_2 for 5 minutes (Scheme 4.49).²²⁷

Benzyl esters of phosphoric acid have been employed also with success in organic synthesis. Usually palladium catalysts are used to remove the benzyl protecting group (Scheme 4.50).

Examples Reaction mixtures include 10% Pd/C in THF–water at 50 psi H_2 in a Parr hydrogenation apparatus for 1 hour,²²⁸ 5% Pd/C in EtOH²²⁹ at



SCHEME 4.48



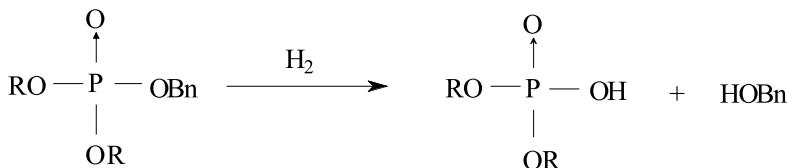
SCHEME 4.49

room temperature and 14.7 psi H_2 for 7 hours,²³⁰ 5% Pd/C in EtOH and 1N NaHCO_3 ,²³¹ and 10% Pd/C in EtOH at 50 psi H_2 and room temperature for 14 hours.²³²

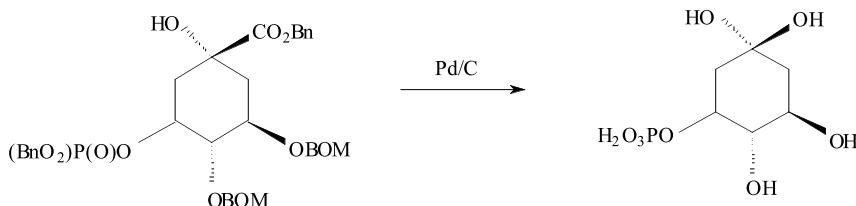
In the case of acid-sensitive compounds, bases were used to neutralize the liberated acid and prevent the acid-catalyzed degradation. The catalytic hydrogenolysis of a benzyl phosphate was conducted in the presence of a stoichiometric amount of cyclohexylamine. To the degassed solution of the compound in a mixture of methylene chloride and methanol under nitrogen was added successively Pd/C and cyclohexylamine. Hydrogen was bubbled into the solution for 15 minutes, and then a positive hydrogen pressure was maintained. The reaction was stopped when the benzyl phosphate could no longer be detected.²³³ In the same manner, during preparation of glucose 1-phosphate, NaHCO_3 was used to neutralize the liberated phosphoric acid.²³⁰

In a series of comparison experiments, both a benzyl and a phenyl group were removed from phosphate esters of dihydroxyacetone phosphate. Removal of the phenyl group was accomplished in 24 hours at room temperature by hydrogenolysis at 50 psi hydrogen using PtO_2 in EtOH. During the initial 3 hours, hydrogen uptake was very fast. To ensure completion of the reaction, small aliquots were analyzed by nuclear magnetic resonance (NMR). The benzyl group was removed over Pd/C at the same conditions for 4 hours.²³⁴

Both the benzyl esters of carboxyl and phosphoric acid groups and benzylloxymethyl protecting groups were removed in a one-step deprotection on 10% Pd/C in THF–water at 50 psi H_2 for 12 hours (Scheme 4.51).²³⁵



SCHEME 4.50



SCHEME 4.51

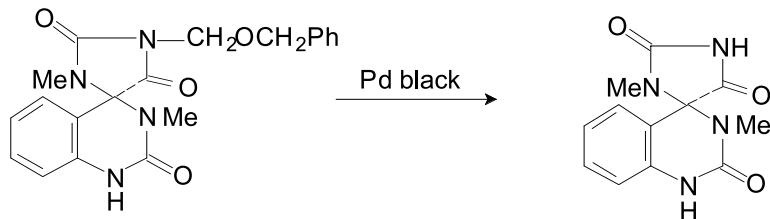
An N-benzyloxymethyl protecting group was removed on Pd black in EtOH at 45 psi H₂ for 15 hours (Scheme 4.52).²³⁶

4.1.1.6.4. Transfer Hydrogenolysis of Benzylic Compounds (See also Section 2.1.4.1)

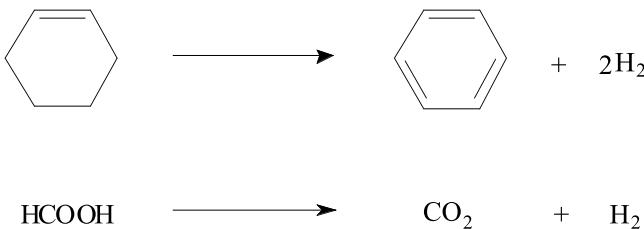
During hydrogenolysis, the hydrogen source is usually hydrogen gas, but in some cases hydrogen donor molecules are used as hydrogen sources.^{237–239} This is called *transfer hydrogenolysis*, which is usually designated as *transfer hydrogenation*. Catalytic transfer hydrogenolysis is preferred by many investigators over traditional catalytic hydrogenolysis because of its simplicity, efficiency, selectivity, and mild character.

One advantage of this method is that no special apparatus for handling gaseous hydrogen is required. But in some cases, this technique has other advantages, too. Rapid and selective removal of protecting groups under moderate conditions is a necessary step in organic synthesis, especially in the case of sensitive compounds. Catalytic transfer hydrogenolysis can often fulfil these requirements.

A number of hydrogen donors such as cyclohexene, 1,4-cyclohexadiene, and formic acid have been successfully used in the presence of different heterogeneous Pd catalysts (Scheme 4.53).



SCHEME 4.52



SCHEME 4.53

Formic acid is a widely used hydrogen donor.²⁴⁰ However, since the active species in formic acid is the formate anion, it has been demonstrated that formate salts are superior to formic acid. Ammonium formate is used frequently as a hydrogen donor.^{241–243}

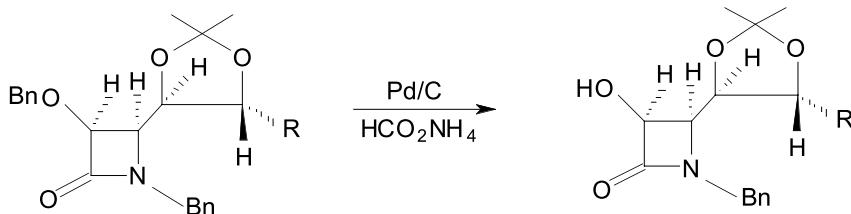
Transfer hydrogenolysis of benzyl acetate was studied on Pd/C at room temperature using different formate salts.²⁴⁴ Hydrogen-donating abilities were found to depend on the counterion: K⁺ > NH₄⁺ > Na⁺ > Li⁺ > H⁺. Formate ion is the active species in this reaction. Adsorption of the formate ion on the Pd metal surface leads to dissociative chemisorption resulting in the formation of PdH⁻ and CO₂. The kinetic isotope effect proves that the dissociative chemisorption of formate is the *rate-limiting step*. The adsorption and the surface reaction of benzyl acetate occurs very rapidly.

Benzyl Ethers Deprotection of the benzyl ether groups in carbohydrate chemistry are carried out usually by transfer hydrogenolysis. Pd/C catalyst and formic acid as the hydrogen donor²⁴⁵ or Pd(OH)₂/C and cyclohexene²⁴⁶ often have been used for deprotection of the O-benzyl groups. In one example, 10% Pd/C was added to the solution of a benzyl ether in a mixture of HCO₂H and MeOH under argon and the mixture was stirred for 4 hours.²⁴⁷

Usually the benzyl ether is dissolved in EtOH and cyclohexene, and 20% Pd(OH)₂/C is added (1:10 catalyst–substrate by weight) and stirred under reflux for the required period (thin layer chromatography monitoring).²⁴⁶ Without cyclohexene, the benzyl ether was usually recovered, signifying that the EtOH solvent is not a good hydrogen donor under these conditions.

Ammonium formate and Pd/C in boiling MeOH were used to remove benzyl ether groups in 1 hour.^{248,249} Transfer catalytic hydrogenolysis using 10% Pd/C and 25% ammonium formate–THF (1:30) at 25°C was run for 2 hours to remove a benzyl ether group.²⁵⁰ Benzyloxynaphthyl ether was hydrogenolyzed on 10% Pt/C and ammonium formate by refluxing in MeOH for 5 minutes or in THF for 30 min.²⁵¹

O-Benzylidene and O-benzyl groups were removed from an allylglucopyranoside by dissolving the compound in ethanol and cyclohexene and then adding



SCHEME 4.54

PdO and refluxing for 16 hours. The acylglucopyranoside was hydrogenolyzed on 5% Pd/C in EtOH–AcOH at 50 psi H₂ and room temperature.²⁵²

It was found that O-benzyl ethers can be selectively cleaved in the presence of other types of O-protecting groups by catalytic transfer hydrogenolysis using 10% Pd/C and ammonium formate as the hydrogen donor and the deprotection with ammonium formate was faster than formic acid under identical reaction conditions.^{253,254} For example, O-benzyl ethers can be selectively cleaved but the benzylidene acetal groups remained unaffected under these conditions whereas the benzylidene group was completely (HCO₂H)²⁴⁵ or partly (cyclohexene)²⁴⁶ removed if formic acid or cyclohexene were used as hydrogen donors. It was also possible to conduct the hydrogenolysis of the OBN group in preference to the NBn group (Scheme 4.54).²⁵⁵

Selective removal of the benzyl ether-protecting group in compound 9 (Fig. 4.1) was made through both transfer hydrogenolysis and the conventional catalytic hydrogenolysis.

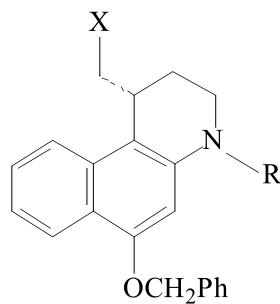
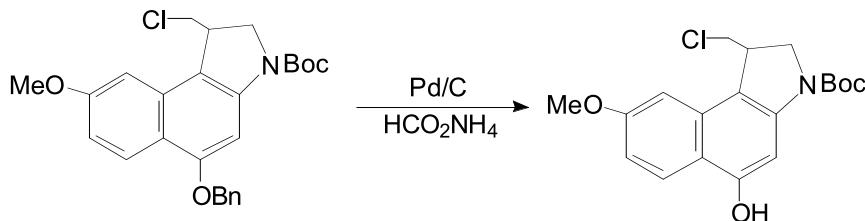


FIGURE 4.1



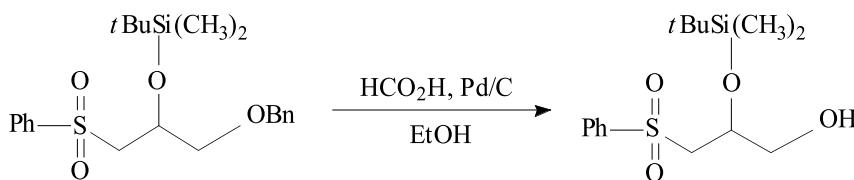
SCHEME 4.55

If X=OH, the compound was added to a suspension of 10% Pd/C in THF, and the suspension was carefully degassed, and saturated with argon. A 25% aqueous solution of HCO_2NH_4 was added and the mixture was stirred for 7 hours at 25°C. However, if X=Cl, the conventional hydrogenolysis (10% Pd/C, THF, 25°C, 2 hours, 1 atm H_2) was accomplished without competitive hydrogenolysis of the chloride and in higher conversion than comparable attempts to use transfer hydrogenolysis.²⁵⁶ In an earlier article by the authors, three methods were used. Hydroxyl-containing compounds were hydrogenolyzed by conventional hydrogenolysis using 5% Pd/C in THF, Cl-containing compounds were hydrogenolyzed by transfer hydrogenolysis with HCO_2NH_4 in THF (1:10), and S-containing compounds were hydrogenolyzed over 10% Pd/C at 1 atm H_2 in THF.²⁵⁷

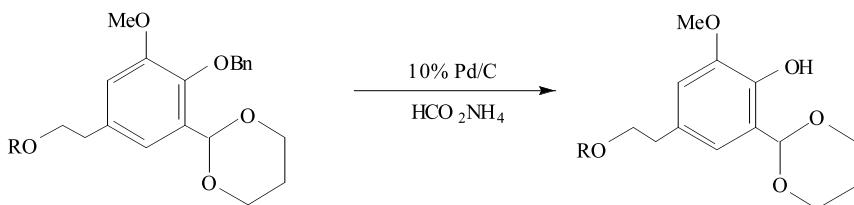
Selective hydrogenolysis of the benzyl ether group was performed in the presence of an N-Boc protecting group. In this case, 10 Pd/C (0.45 mol/mol) and HCO_2NH_4 (6.5 mol/mol) was warmed at reflux in acetone for 30 minutes (Scheme 4.55).²⁵⁸

The benzyl group was removed selectively from a silyl ether of the following compound by 10% Pd/C and formic acid in EtOH (Scheme 4.56).²⁵⁹

Hydrogenolysis of the benzyl group in a dioxane-containing compound under catalytic hydrogen-transfer conditions (10% Pd/C in MeOH and HCO_2NH_4 for 10 minutes at room temperature) proceeded without affecting the dioxane moiety (Scheme 4.57).^{169,260}



SCHEME 4.56



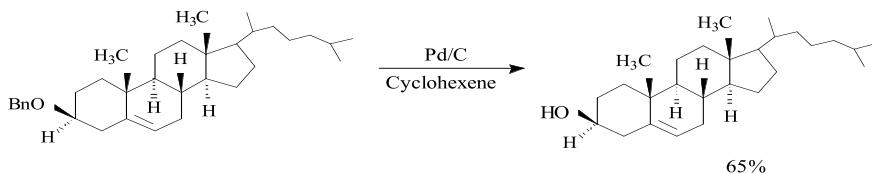
SCHEME 4.57

Pd/C-catalyzed transfer hydrogenolysis using cyclohexene as the hydrogen donor and boiling benzene as the solvent was found to deprotect readily alkyl benzyl ethers whereas aryl benzyl ethers are stable under these conditions. Hydrogenolysis of 2-benzyloxy naphthalene is not significantly promoted either by using large amounts of the catalyst or by changing the solvent to ethanol or methanol and longer periods of refluxing. In the case of cholesterol, debenzylation is faster than the hydrogenation of the double bond (Scheme 4.58).²⁶¹

THF was also used as solvent. The mixture of 10% Pd/C and cyclohexene in THF was refluxed under nitrogen for 36 hours, evaporated, and this was repeated two times under the same conditions until there were no benzyl groups present, as determined by NMR.²⁶²

Many organic reactions can be conducted very rapidly under microwave irradiation. Microwave-induced organic reaction enhancement chemistry techniques were used for the rapid formation of an α -benzyloxy- β -lactam (10 in Fig. 4.2) and the hydrogenolysis of its benzyloxy group on a few-gram scale in 1–5 minutes with HCO_2NH_4 and Pd/C in ethylene glycol as the reaction medium in a domestic microwave oven.²⁴³

Carbamates Both O-Bn and N-Cbz protecting groups have been removed by transfer hydrogenolysis (Scheme 4.59).



SCHEME 4.58

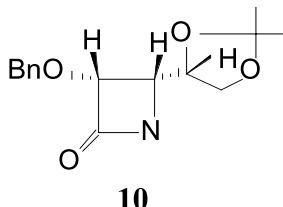
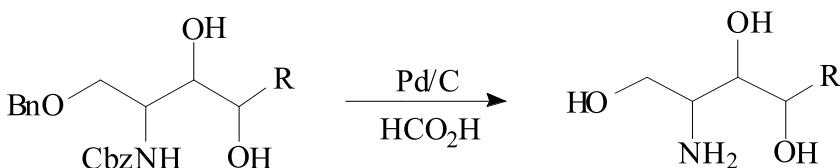


FIGURE 4.2

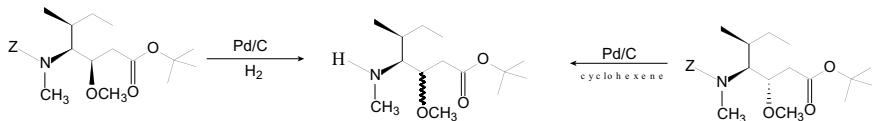


SCHEME 4.59

A mixture of diol, EtOH, HCO_2H and 10% Pd/C were stirred at room temperature for 40 hours.²⁶³ The N-Cbz bond was hydrogenolyzed on 10% Pd/C and HCO_2NH_4 in MeOH³ or with 10% Pd/C (0.1 mol Pd/mol) and HCO_2H (10 mol/mol) in MeOH.²⁶⁵

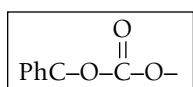
Two amino acid stereoisomers protected by benzyloxycarbonyl groups were deprotected in different ways. One isomer was hydrogenolyzed on 5% Pd/C (0.05 mol Pd/mol) in AcOEt–MeOH for 16 hours at ambient pressure and temperature. The other isomer was dissolved in MeOH, and cyclohexene (10 mol/mol) was added under nitrogen followed by 5% Pd/C (0.18 mol Pd/mol). The temperature was immediately raised to reflux, and stirring was continued for 7 minutes (Scheme 4.60).²⁶⁶

Cyclohexene as hydrogen donor is not practical for removing benzyl-type protecting groups in peptide synthesis because it must be run in boiling solvent and certain commonly used *tert*-butyl-derived protecting groups undergo



SCHEME 4.60

undesirable decomposition at the temperature of boiling MeOH, EtOH, or THF. Therefore, the removal of the benzylic protecting groups under moderate reaction conditions is often a necessary step in the area of peptide chemistry. To overcome this problem, 1,4-cyclohexadiene is a much more effective hydrogen donor and is used to carry out catalytic transfer hydrogenolysis at room temperature in the presence of 10% Pd/C.²⁶⁷ Under these conditions, the removal of the ether-protecting group from tyrosine and the removal of the N-benzyloxycarbonyl and benzyl ester protecting groups were complete within 2 hours. The more efficient Pd-black catalyst was required for the hydrogenolysis of the ether groups in serine and threonine.²⁶⁷ Alcohols protected by the benzyloxycarbonyl group are reduced smoothly on Pd/C catalyst using phosphonic acid as hydrogen donor.²⁶⁸



Benzyl Esters Pd/C catalyst and cyclohexene was used in boiling benzene to deprotect aliphatic benzyl esters whereas benzyl benzoates are resistant under these conditions.²⁵⁹ Selective deprotection of a benzyl ester was accomplished without hydrogenation of a carbon–carbon double bond by transfer hydrogenolysis using 1,4-cyclohexadiene and 10% Pd/C in MeOH.²⁰⁴ The benzyl ester protecting group was removed from polysiloxanes by transfer hydrogenolysis. A solution of polysiloxane in THF–EtOH containing 10% Pd/C was degassed, 10–15 equiv of cyclohexene per benzyl ester group were added, and the reaction mixture was refluxed for 4 days under N₂ atmosphere.²⁶⁹ Deprotection of a dibenzyl ester through catalytic transfer hydrogenolysis (HCO₂NH₄, 10% Pd/C, THF–CH₃OH–H₂O at 22°C) provided the diacid quantitatively.²⁷⁰

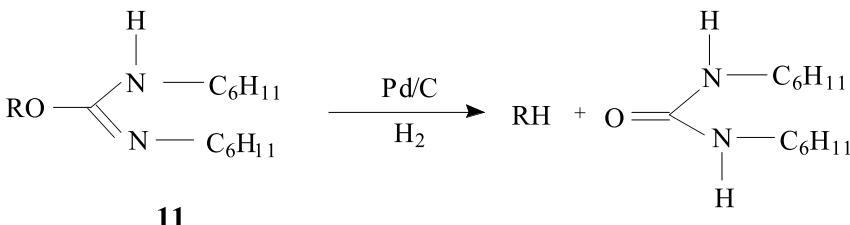
The α-carbonyl function of a lactam was removed by transfer hydrogenolysis. Its benzyl ester was dissolved in MeOH under argon; ammonium formate and 5% Pd/C were added; and the reaction mixture was stirred for 1.5 hours.^{271,272}

In spite of the successful application of catalytic transfer hydrogenolysis in the case of benzylic compounds, this method is not suitable for the cleavage of the allylic C–O bonds.

4.1.1.7. Compounds Containing Activated Oxygen

All of the compounds in the previous sections containing C–O bonds to be hydrogenolyzed easily were activated at the carbon atom. However, O-alkyl-N,N'-dicyclohexylisoureas (11), which can be prepared by the reaction of alcohols with dicyclohexylcarbodiimide, can also be hydrogenolyzed but they are activated on the oxygen atom (Scheme 4.61).²⁷³

Acyclic alcohols can be deoxygenated easily by this two-step reaction sequence (first, reaction of the alcohols with dicyclohexylcarbodiimide, then



SCHEME 4.61

the previously described hydrogenolysis). The hydrogenolysis needs usually 2–30 hours. Tertiary alcohols are the most reactive compounds, whereas cycloalkanols react extremely slowly.

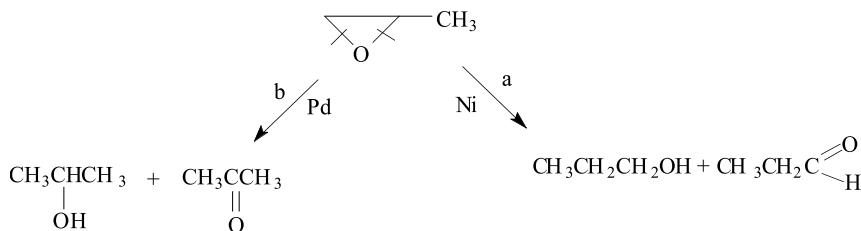
4.1.1.8. Ring Opening of C–O Containing Cyclic Compounds

The cyclic ethers can be classified into two groups. The three- and four-membered oxiranes and oxetanes are reactive enough to transform even at room temperature whereas the higher five- and six-membered rings, oxolanes and oxanes, undergo transformation only at higher temperatures. In the cases of the oxiranes and oxetanes, the strain energy of the rings facilitates the cleavage of the C–O bond, whereas in the larger rings, the strain energy is not important. In spite of this, cleavage of the C–O bond is easier in cyclic ethers than in acyclic ones. It is probable that the surface species formed at the adsorption of the oxacycloalkane rings is more favorable for hydrogenolysis than species formed by the adsorption of acyclic ethers.

4.1.1.8.1. Hydrogenolysis of Oxiranes

In the cases of oxiranes, the formation of alcohols and oxo compounds (ketones and aldehydes) are the result of primary processes.^{3,274–286} Hydrogenation of oxo compounds does not occur on surfaces covered with oxirane. The adsorption of oxiranes on metal surfaces is irreversible; during adsorption, ring-opening takes place also. As the temperature is raised, the proportions of the oxo compounds increase.

On Pt and Pd, cleavage of the C–O bond results from a hydrogenolytic cleavage, whereas on Ni and Cu, an insertion mechanism occurs. The regioselectivity of the two mechanism is different. The less sterically hindered bond (b) is cleaved on Pt and Pd, whereas the more hindered bond (a) is cleaved on Ni and Cu (Scheme 4.62).



SCHEME 4.62

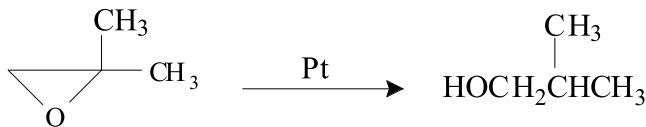
In the case of the oxiranes, the insertion is promoted by the strain of the three-membered ring. Insertion of the metal atom produces a surface-adsorbed four-membered metallaoxacyclobutane, and this process decreases the ring strain.

The insertion is also promoted by methyl substitution. In the case of 1,1-dimethyloxiranes, the sterically hindered bond is broken on a Pt catalyst too (Scheme 4.63).

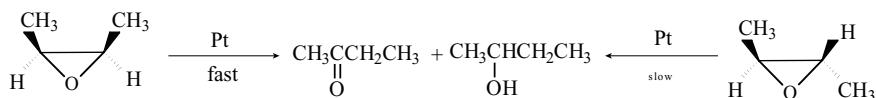
The *cis*-2,3-dimethyloxirane is transformed at a much higher rate than the *trans* isomer on Pt and Pd catalysts, whereas on Ni the two isomers are converted at almost the same rate (Scheme 4.64).⁷

During the total synthesis of taxol the oxirane C–O bond was selectively ruptured on 10% Pd/C in EtOH for 1.25 hours at –5°C (Scheme 4.65).²⁸⁷

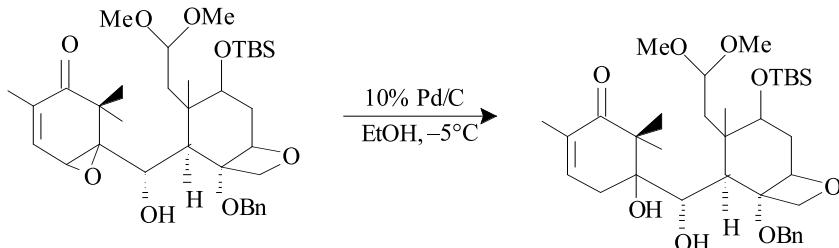
The selective cleavage shows clearly that the oxirane C–O bond at the allylic carbon atom can be cleaved easier than the benzylic one and the oxetane ring.



SCHEME 4.63



SCHEME 4.64



SCHEME 4.65

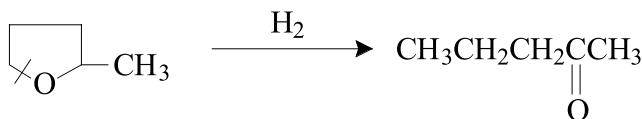
4.1.1.8.2. Hydrogenolysis of Other Oxacycloalkanes

Of the higher oxacycloalkanes, the four-membered oxetanes are similar to oxiranes whereas the higher rings are different. The Pt, Pd, and Ni catalysts cleave the oxolanes and oxanes in the sterically less hindered position (hydrogenolytic cleavage) (Scheme 4.66), whereas Cu is inactive toward these higher rings.

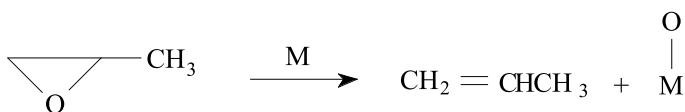
Adsorption of oxolanes and oxanes does not necessarily cause the opening of the ring. Hydrogenolysis of the C–O bond needs the simultaneous adsorption of oxygen and the vicinal carbon atom. This ring-opening reaction, however, differs from the “regular” hydrogenolysis, because the ring opening of cyclic C–O bonds is much easier than hydrogenolysis of the C–O bond in open chain ethers. It is likely that the cyclic geometry makes easier the simultaneous adsorption of oxygen and carbon atoms. Neither on Pt nor on Ni is any difference observed between the rates of transformation of the isomers among the dimethyl derivatives of oxolanes or oxanes.

4.1.2. DEOXYGENATION OF OXACYCLOALKANES

Usually, various quantities of alkane are found during the hydrogenolyses of oxacycloalkanes. This is especially so for the oxiranes on platinum metals in the presence of hydrogen. These alkanes presumably form from alkenes, which are formed from deoxygenation (Scheme 4.67).



SCHEME 4.66



SCHEME 4.67

Deoxygenation can oxidize the metal surfaces. It was found that the partially oxidized Cu surface was the most active in the isomerization of methyloxirane to propanal.²⁸⁸ The same is true for Ni. Therefore, it is very likely that the metal ions produced by the oxidation of copper or nickel surfaces during deoxygenation play an important role in isomerization to aldehyde.

In the case of Pt and Pd, the surface oxidation can also take place, but the resulting metal ions can be easily reduced in the presence of hydrogen. According to this fact, the observed difference in the regioselectivity of the rupture of the oxirane ring on Ni and Cu or Pt and Pd can be explained on the basis of the different stability of the metal ions in a hydrogen atmosphere.²⁸⁹

In the case of methyloxirane, however, on Pt and Pd catalysts the extent of the rupture of the sterically hindered bond is indicative of the electrophilic character of the catalyst. Unsupported or silica-supported ion-exchanged catalysts cleave the sterically less hindered bond, whereas on the impregnated catalysts, the rupture of the more hindered C–O bond is dominant.²⁹⁰ It is likely that Pt or Pd surface metal ions are responsible for the rupture of the sterically more hindered bond and residual chlorine from the catalyst preparation can stabilize these ions in the hydrogen atmosphere.

The appearance of large amounts of aldehydes in the reaction mixtures is indicative of the presence of stronger acidic sites on the catalyst surfaces. For this reason, a large amount of aldehyde can usually be detected on Pt/Al₂O₃ and Pd/Al₂O₃ catalysts. The acidic character of Pt/C catalyst could also be detected by this method.^{290,291}

4.2. BREAKING C–N BONDS

The most important C–N bond breaking reaction is the hydrogenolysis of the carbon–nitrogen σ-bond.

4.2.1. HYDROGENOLYSIS OF C–N BONDS

Hydrogenolytic cleavage of the C–N bond takes place more easily than that of the C–C bond but with more difficulty than that of the C–O bond. Activation

of the C–N bond in an amine is more difficult than the analogous process in an alcohol. The hydrogenolytic debenzylation of *N*-benzyl derivatives, however, has great importance in synthetic organic chemistry.

4.2.1.1. Hydrogenolysis of Benzyl–Nitrogen Bonds

Palladium catalysts, mostly palladium on carbon and Pearlman's catalyst, are used for the hydrogenolysis of the benzyl–nitrogen bond. However, in some cases, platinum, nickel, and copper chromite catalysts have also been used.

The benzyl–nitrogen bond is not so easily cleaved as the benzyl–oxygen bond, unless the *O*-benzyl group is sterically hindered. This difference in activity allows the selective removal of the *O*-benzyl function in a molecule containing both *N*-benzyl and *O*-benzyl protecting groups. The selectivity can be reversed if the amine is protected by the Cbz group. If a small amount of amine (e.g., butylamine) is added, then the selective removal of *N*-benzyl amines can be achieved.²⁹²

It was found in the case of *O*-benzyl systems that palladium oxide is much more effective than palladium metal. No such effect was observed with the *N*-benzyl system.⁸ It is possible that the *N*-compounds can poison the electrophile metal ions, and the hydrogenolysis of the *N*-benzyl bond can take place only by the hydrogenolytic cleavage instead of the insertion mechanism. This is supported by the experimental finding that the product amine can inhibit the catalyst, and this can be minimized by buffering at a pH less than 4.

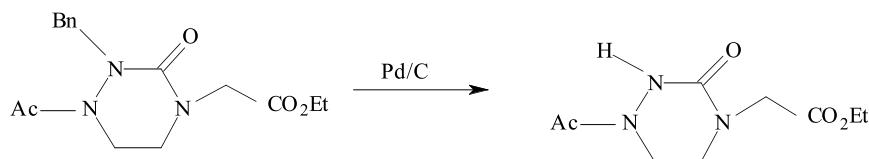
N–CPh An *N*-benzyl group was removed in MeOH using 10% Pd/C (0.1 mol Pd/mol). The mixture was stirred at room temperature under H₂ at 1 atm for 24 hours. After filtration over Celite, the same amount of Pd/C was added, and hydrogenolysis was continued for 24 hours.²⁹³ Catalytic hydrogenolysis of *N*-benzyl derivatives under acidic conditions (in MeOH–HCl) at 50 psi for 24 hours afforded the crystalline hydrochloride salt.²⁹⁴ The conversion of an *N*-benzyl tetracyclic ketone into an *N*-methyl ketone was achieved by methylation with methyl trifluoromethane sulfonate followed by catalytic debenzylation using Pd/C.²⁹⁵ During the total synthesis of strychnine, the benzyl–nitrogen bond was hydrogenolyzed on 10% Pd/C in MeOH under 1 atm hydrogen at room temperature for 2 hours.²⁹³ The 10% Pd/C and wet AcOH were added to the argon-flushed solution of *N*-benzylindoloazepine. The vessel was degassed and saturated with hydrogen, and the reaction progress was monitored by TLC.²⁹⁷ Other examples can be found in Table 4.5.

An *N*-benzyl protecting group was removed on 5% Pd/C (0.2 mol Pd/mol compound) in MeOH at room temperature for 19.5 hours (Scheme 4.68).³⁰⁹

In some cases the hydrogenolysis of the *N*-benzyl bond may be followed by an intramolecular *N*-acylation step (Scheme 4.69).³¹⁰

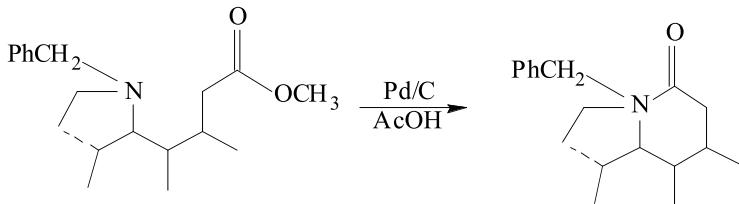
TABLE 4.5 Hydrogenolysis of N-Benzyl Compounds on Pd Catalysts

Catalyst	Solvent	Pressure	Time	Temperature	Citation
10% Pd/C	AcOH	1 atm	4.5 h		298
10% Pd/C	AcOH		2 h	25°C	299
10% Pd/C	AcOH	3 atm	41 h	50°C	300
10% Pd/C	AcOEt	50 psi	4 h		301
Pd/C	AcOEt				302
10% Pd/C	MeOH	40 psi	16 h		303
5% Pd/C	EtOH	3 atm	4 h	60°C	304
Pd/C	EtOH		1 h	23°C	305
5% Pd/BaSO ₄	MeOH	45 psi			306
5% Pd/C	MeOH/HCl				307
20% Pd(OH) ₂ /C	EtOH/HCl		6 h		308



Sulfuric acid in ethanol and Pd(OH)₂/C was used for removing the benzyl group from compound 12, whereas Pd/C was used in the case of compound 13 (Fig. 4.3).³¹¹

Removal of the N-benzyl protecting group from a pyrrolidine derivative was performed by 20% Pd(OH)₂/C (0.1 mol Pd/mol) in MeOH at 1 atm H₂ for 3 hours^{312,313} or by Pd/C in MeOH–HCl (Scheme 4.70).³¹⁴



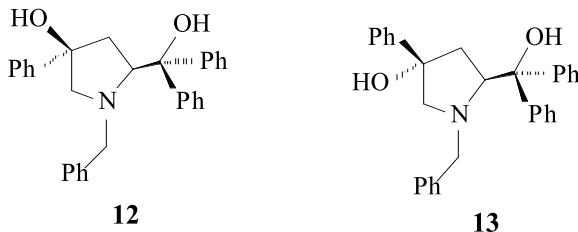
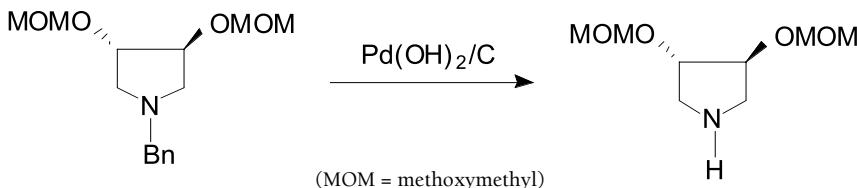


FIGURE 4.3



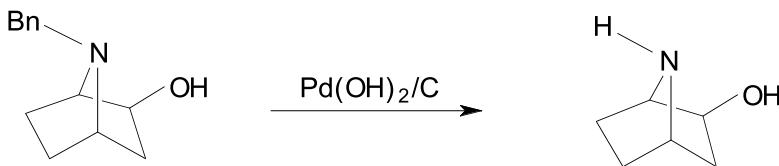
SCHEME 4.70

An *N*-benzyl group was removed by hydrogenolysis at 40 psi hydrogen using $\text{Pd}(\text{OH})_2/\text{C}$ catalyst (0.018 mol Pd/mol compound) in EtOH–HCl at 40°C for 6 hours (Scheme 4.71).³¹⁵

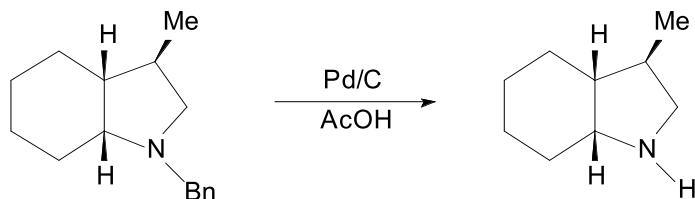
A benzyl group was hydrogenolyzed on 10% Pd/C (0.2 mol Pd/mol) in AcOH for 3 hours with a 55% overall yield (Scheme 4.72).³¹⁶

It was also reported that the other compound in the reaction mixture was hydrogenated on 10% Pd/C (0.2 mol Pd/mol) in AcOH for 5 hours with 80% yield without hydrogenolysis of the C–N bond (Scheme 4.73).³¹⁶

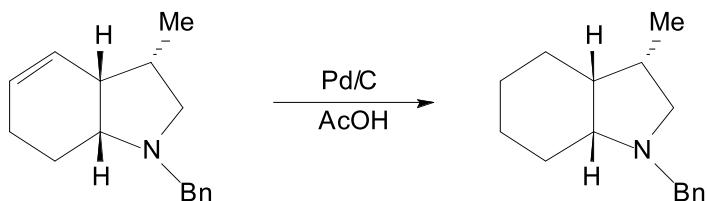
The lactone structure is a versatile synthetic intermediate that can be used to access a variety of 4-substituted pipecolic derivatives. Hydrogenolysis in methanolic HCl, followed by hydrolysis and desalting, gave 4-hydroxypipecolic



SCHEME 4.71



SCHEME 4.72



SCHEME 4.73

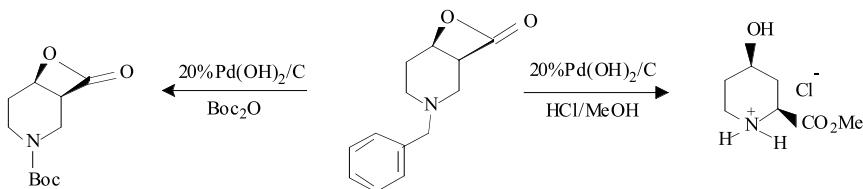
acid.³¹⁷ Hydrogenolysis in the presence of di-*tert*-butyldicarbamate and AcOEt as solvent gave N-Boc-protected lactone (Scheme 4.74).

Pipecolic acids substituted at the 2-position were obtained from lactones by simultaneous *O*- and *N*-deprotection on 10% Pd/C (0.08 mol Pd/mol) in EtOH–AcOH (2:1) for 1 hour (Scheme 4.75).³¹⁸

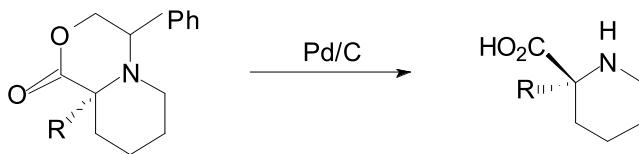
During the asymmetric synthesis of α -aminophosphonates (14 in Fig. 4.4), numerous attempts to cleave the benzylic C–N bond, involving catalytic or transfer hydrogenolysis, resulted in epimerization at the α -carbon.³¹⁹

The methyl and methoxymethyl ether derivatives, however, can be hydrogenolyzed without loss of enantiomeric purity (Scheme 4.76).³¹⁹

The highly diastereoselective 1,4-addition of lithiated chiral amines to α -, β -unsaturated esters, followed by hydrogenolysis of the benzylic-type C–N



SCHEME 4.74



SCHEME 4.75

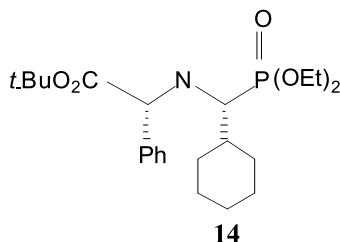
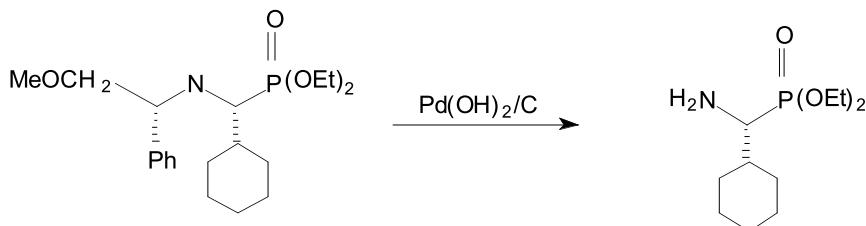
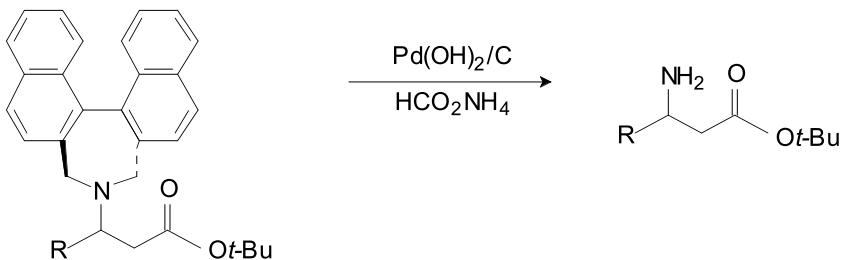


FIGURE 4.4

bonds of the 1,4-adducts, provides an asymmetric ammonia synthon for Michael additions.³²⁰ Various conditions were explored for the hydrogenolysis, and Pd(OH)₂/C in EtOH at 45°C with morpholinium formate or ammonium formate as the hydrogen donor gave the best results.³²¹ Moist commercial Pearlman's catalyst (Aldrich) had to be dried before use (60°C, 1 mm Hg, 3 h). Other Pd catalysts gave partial reduction of the naphthalene rings. No reaction occurred under 1 atm of hydrogen. Ammonium formate worked the best for substrates prone to β-elimination. Because of the Pd-catalyzed amine racemization,³²² the catalyst was always treated with the hydrogen donor before the substrate was added in order to avoid epimerization of the starting compound or racemization of the product. When Pearlman's catalyst was used before the



SCHEME 4.76



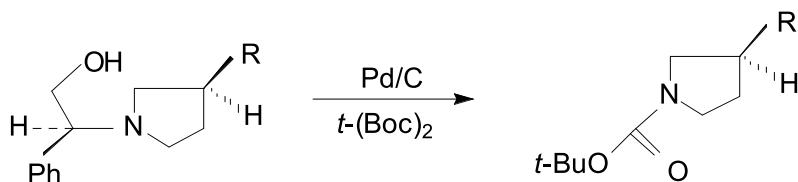
SCHEME 4.77

addition of the reducing agent, nearly racemic mixtures were obtained. Epimerization was completely avoided under the optimized conditions: dry 20% $\text{Pd}(\text{OH})_2/\text{C}$ (4.2 mol Pd/mol) was stirred in EtOH at 60°C and morpholinium formate (25 mol/mol) was added. After 30 minutes the protected compound dissolved in EtOH was added. The mixture was stirred for 5 hours at 60°C during which time morpholinium formate was added in four portions or formic acid was added and the mixture was stirred overnight at 60°C (Scheme 4.77).³²⁰

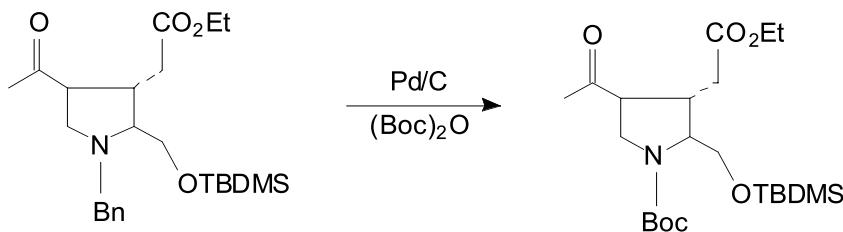
N-Substituted pyrrolidines were subjected to catalytic transfer hydrogenolysis affording pyrrolidines, but the yields were low. However, when di-*tert*-butyl dicarbonate was added to the *N*-substituted pyrrolidines before catalytic hydrogenolysis, the *N*-Boc derivatives were all formed in good yield (Scheme 4.78).^{323,324}

A nitrogen-protective benzyl group was hydrogenolytically removed and replaced by a *tert*-butyloxycarbonyl moiety in a single operation. The protected compound and $(\text{Boc})_2\text{O}$ in MeOH and 10% Pd/C were treated for 48 hours under 3 atm H_2 (Scheme 4.79).^{325,326}

Removal of the *N,N*-dibenzylamino protecting groups was performed in MeOH at atmospheric hydrogen pressure on 10% Pd/C (0.07 mol Pd/mol) for 16 hours or over $\text{Pd}(\text{OH})_2/\text{C}$ (0.3 mol Pd/mol) for 1 hour (Scheme 4.80).³²⁷



SCHEME 4.78

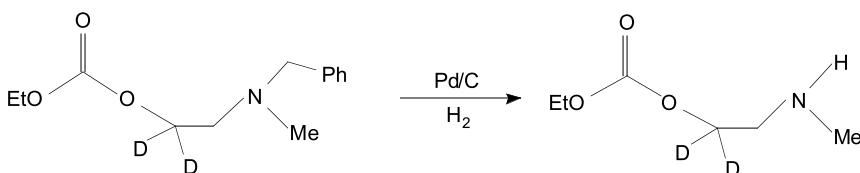
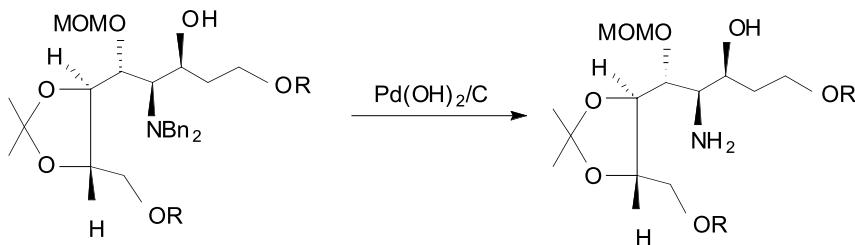


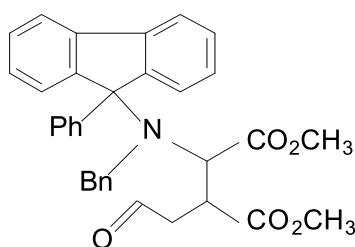
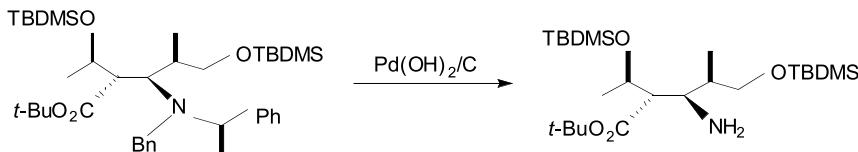
An N-benzyl-N-methyl carbonate in EtOH was hydrogenated on 10% Pd/C under 60 psi hydrogen for 20 hours.¹H NMR analysis indicated that no deuterium scrambling had occurred during debenzylation (Scheme 4.81).³²⁸

Benzyl and 1-phenylethyl groups were removed in AcOEt on Pd(OH)₂/C under hydrogen atmosphere for 5 days (Scheme 4.82).³²⁹

Benzyl and 9-phenylfluoren-9-yl (PhFI) protecting groups were removed in CH₂Cl₂–AcOEt–HCl–MeOH on 10% Pd/C (0.25 mol Pd/mol) at 52 psi H₂ for 24 hours (Scheme 4.84).³³⁰

Phenylfluorenyl protecting groups were removed by hydrogenolysis on 10% Pd/C in 10:1 EtOH–AcOH at 5 atm hydrogen pressure (Scheme 4.84).³³¹

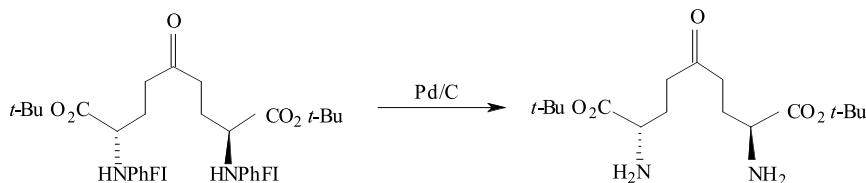


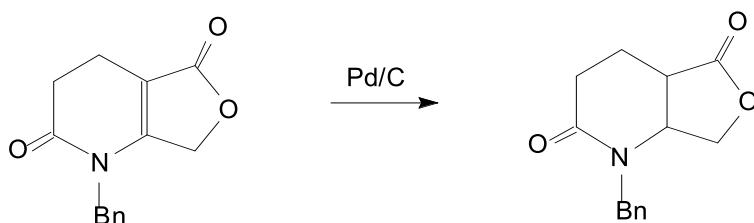
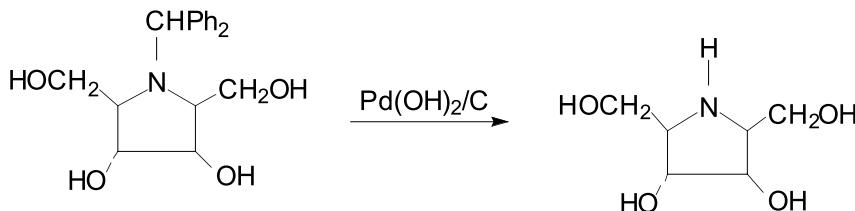


PhFI groups were also removed over 10% Pd/C (0.1 mol Pd/mol) in EtOH–AcOH for 24 hours,³³² on 10% Pd/C (0.12 mol Pd/mol), or on 10% Pd/C (0.15 mol/mol) in MeOH at 52 psi H₂ for 4.5 hours.³³³

The benzhydryl group from azasugars was removed in MeOH using Pd(OH)₂/C (0.03 mol Pd/mol compound) at 60 psi hydrogen overnight (Scheme 4.85).³³⁴

The C=C double bond in enamides was hydrogenated selectively without the cleavage of the C–N bond. A mixture of the enamide, sodium carbonate, and 10% Pd/C in EtOH was stirred under 1–3 atm hydrogen pressure for 16–48 hours (Scheme 4.86).³³⁵

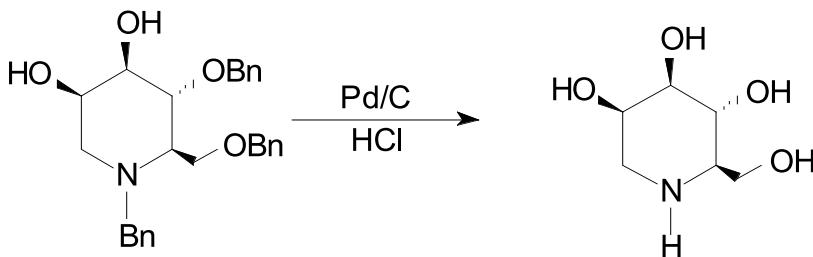


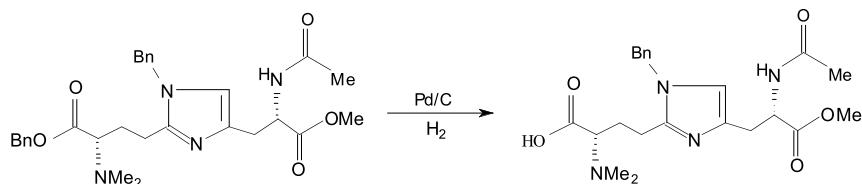


Both the *O*-benzyl and *N*-benzyl groups were removed using 10% Pd/C (0.09 mol Pd/mol compound) and concentrated HCl in EtOH under hydrogen for 14 hours (Scheme 4.87).³³⁵

O-Benzyl and *N*-benzyl groups were also removed in MeOH using 10% Pd/C (0.19 mol Pd/mol compound) at 3 atm hydrogen for 24 hours.³³⁶

The benzyl ester group was selectively hydrogenolyzed on 10% Pd/C in EtOH–H₂O (9:1) at 15 psi H₂ for 15 hours without concomitant removal of the imidazoyl benzyl moiety (Scheme 4.88).³³⁷



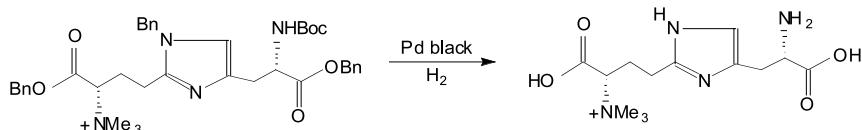


SCHEME 4.88

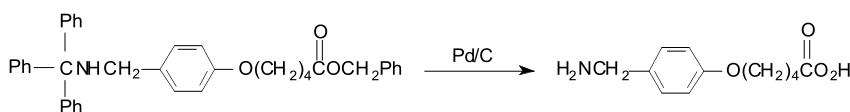
N-debenzylation was achieved with Pd black in AcOH–H₂O (4:1) at 50 psi hydrogen for 2–3 days. Removing of *O*-benzyl, *N*-benzyl, and *N*-Boc protecting groups was also achieved under these circumstances (Scheme 4.89).³³⁷

The triphenylmethyl function, also known as trityl (Trt), is a valuable bulky protecting group for peptide chemistry. Trityl groups confer acid-labile protection onto amines, but effective removal can also be achieved by catalytic hydrogenolysis.

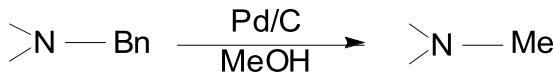
During the transformation of an *N*-tryphethylmethyl valeric acid ester derivative, the detritylation was the critical step. Removal of Trt under various acid conditions was unsuccessful in several ways, as emphasized by the unexpected finding that the ester could be cleaved while the tritylamine function remained unaffected. Harsher acid conditions gave rise to tritylamine from undesired *N*–CH₂ bond cleavage. The wanted removal of Trt was accomplished, however, readily by catalytic hydrogenolysis. In the cases of benzyl esters, a further simplification was possible because the catalytic hydrogenolysis removed the *N*-trityl and *O*-benzyl groups simultaneously (Scheme 4.90).³³⁸



SCHEME 4.89



SCHEME 4.90



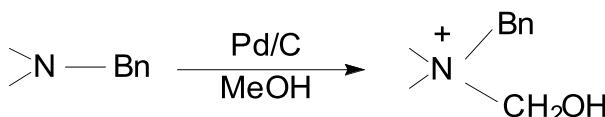
SCHEME 4.91

The suspension of the trityl precursor in a mixture of AcOEt and AcOH was hydrogenolyzed for 2 hours at 25°C at atmospheric hydrogen pressure in the presence of 10% Pd/C (0.01 mol Pd/mol).

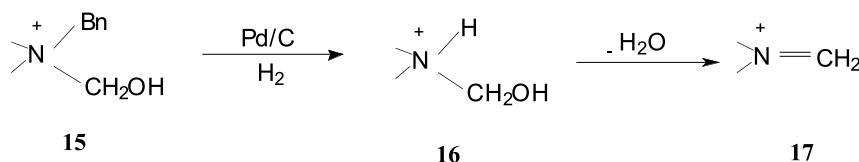
During the enantiospecific total synthesis of ajmalin-related alkaloids, (−)-suaveoline and (−)-raumacline, *N*-debenzylation of the hydrochloride salt of the alkaloids was performed with 10% Pd/C (0.12 mol Pd/mol compound) in absolute EtOH at room temperature and 1 atm of hydrogen for 1 or 2 hours. When this catalytic debenzylation was performed, however, using 10% Pd/C (0.28 mol Pd/mol compound) in MeOH for 5 hours, *N*-methyl derivatives were produced in good yield (Scheme 4.91).^{339,340}

This benzyl–methyl transfer reaction appears to be general in these systems. This process could involve the dehydrogenation of methanol on the surface of palladium, which produces formaldehyde. The formaldehyde could then add to the nitrogen atom to produce a quaternary carbinolamine (Scheme 4.92).

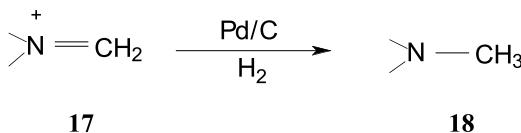
Debenzylation of the quaternary benzylamine (15) could provide a carbinolamine (16), followed by dehydration to form an iminium ion (17) (Scheme 4.93).



SCHEME 4.92



SCHEME 4.93



SCHEME 4.94

Reduction of the iminium intermediate (**17**) then would produce the *N*-methyl derivatives (**18**) (Scheme 4.94).

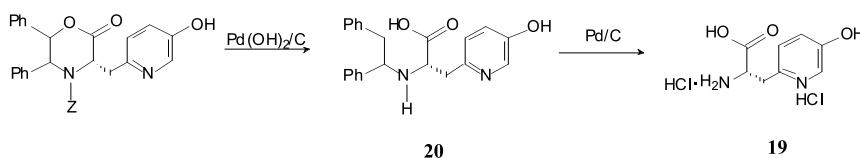
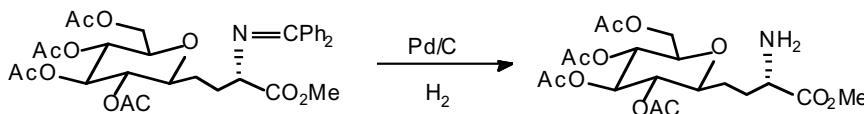
Deprotection of Schiff base glycosides has been accomplished using mildly acidic conditions or hydrogenolysis (Scheme 4.95).³⁴¹

The glycoside was dissolved in MeOH–HCl, 5% Pd/C was added, and the mixture was stirred under hydrogen for 2 hours.

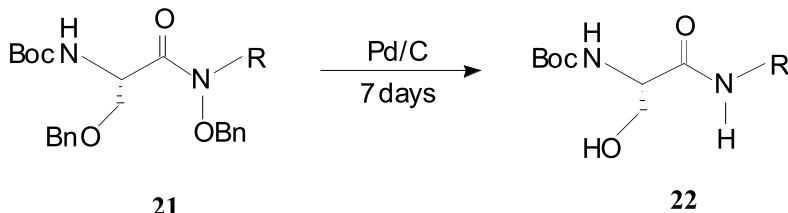
During the synthesis of *L*-azatyrosine (**19** in Scheme 4.96), hydrogenolytic removal of the carbobenzyloxy and diphenylethylene groups proved to be problematical. Hydrogenation over Pd(OH)₂/C at 50 psi H₂ for 24 hours yielded a variable mixture of *L*-azatyrosine and an intermediate (**20**). Extended hydrogenation yielded the saturated aromatic ring. This problem was circumvented by treating the mixture with HCl and continuing hydrogenation in water over 5% Pd/C for 30 minutes (Scheme 4.96).³⁴²

4.2.1.2. Hydrogenolysis of Benzyloxy–Nitrogen Bonds

N–O–CPh Both benzyl–oxygen and N–O bonds can undergo hydrogenolysis in the compounds containing benzyloxy–nitrogen bonds,



SCHEME 4.96



SCHEME 4.97

but in adequate circumstances the benzyl–oxygen bond can be cleaved selectively. However, hydrogenolysis of the N–O bond is usually concomitant with hydrogenolysis of the benzyl ether functionality.¹⁷⁶

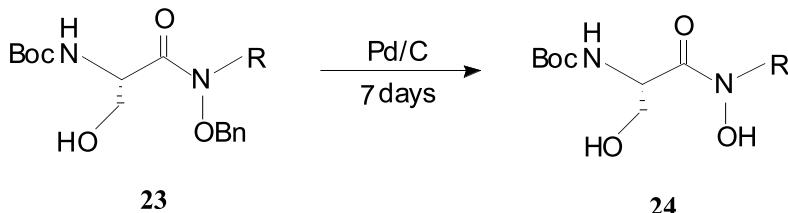
Catalytic hydrogenolysis of the bisbenzylated Boc-neonactin A (21) in Scheme 4.97) using 10% Pd/C provided an inseparable mixture of the debenzylated product and the N⁴-deshydroxy compound (22).³⁴³ Various manipulations of the reaction conditions including changing the solvent, the mol equivalents of Pd, and the reaction time proved unsuccessful. But with the use of an extended period of reaction time, the N–O bond can be completely removed. The bisbenzylated Boc-neonactin A and 10% Pd/C in EtOH were stirred under a hydrogen atmosphere for 7 days, providing the N⁴-deshydroxy compound in 70% yield (Scheme 4.97).

Catalytic hydrogenolysis of the monobenzylated compound (23), however, provided the desired Boc-neonactin A (24) in 76% yield (Scheme 4.98).

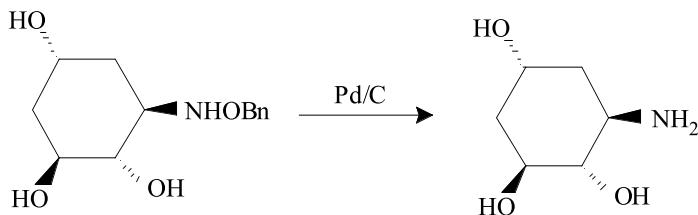
Hydrogenolysis of the N–O bond was also observed on Pd/C catalyst in MeOH (Scheme 4.99).³⁴⁴

4.2.1.3. Transfer Hydrogenolysis of Benzylic Compounds

Transfer hydrogenolysis using Pd/C and cyclohexene has been used for de-N-benzylation in peptide synthesis. This process, however, is not suitable



SCHEME 4.98



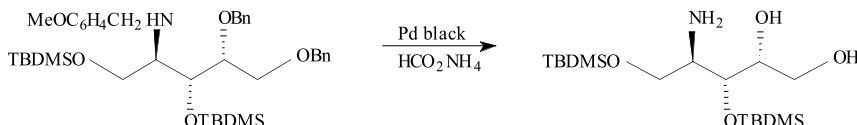
SCHEME 4.99

in the case of *tert*-butyl-derived protecting groups because they can undergo undesirable decomposition at the temperature of boiling ethanol. 1,4-Cyclohexadiene is a much more effective hydrogen donor and can be used at room temperature. Transfer hydrogenolysis appears to be preferable in several respects to catalytic hydrogenolysis but, of course, it has its own shortcomings. Probably the most important of these is the immiscibility of most peptides with the apolar hydrogen donors. Formic acid is a good solvent for most peptides and can be used as a convenient hydrogen donor for transfer hydrogenolysis of peptides.

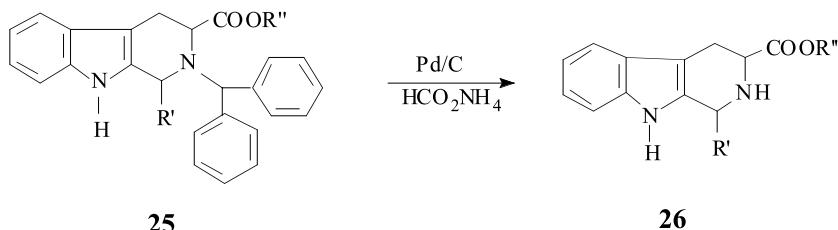
The benzyl and *p*-methoxyphenylmethyl protecting groups could be easily removed by refluxing the amine, Pd black, and ammonium formate in MeOH for 5 hours (Scheme 4.100).³⁴⁵

N-Benzyl protecting groups were removed by HCO₂H and Pd/C in MeOH,³⁴⁶ by HCO₂NH₄ and 10% Pd/C in EtOH,²⁵⁵ or by refluxing in MeOH-AcOEt for 3 hours using 10% Pd/C and HCO₂NH₄.³⁴⁷ Catalytic transfer hydrogenolysis of the 1,2,3-trisubstitutedtetrahydro- α -carbolines (25) afforded the 1,3-disubstituted species (26) (Scheme 4.101).³⁴⁸

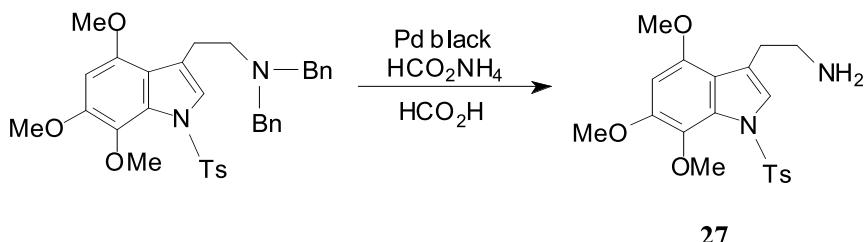
N,N-Deborylation was accomplished by Pd/C and HCO₂NH₄.³⁴⁹ Deborylation of an *N,N*-dibenzyltryptamine derivative was sluggish and incomplete using Pd/C as the catalyst. In contrast, transfer hydrogenolysis using ammonium formate-formic acid in the presence of Pd black efficiently afforded the free tryptamine (27) (Scheme 4.102).³⁵⁰



SCHEME 4.100



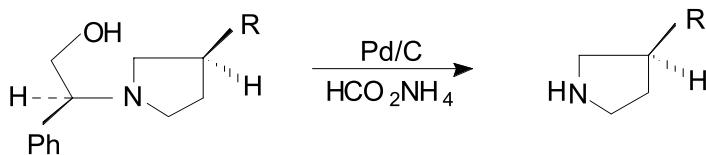
SCHEME 4.101



SCHEME 4.102

To the solution of the *N,N*-dibenzyltryptamine derivative in EtOH were added HCO_2NH_4 (15 mol/mol tryptamine) and Pd black (2 mol Pd/mol tryptamine) and the mixture was refluxed under N_2 for 12 hours. It was brought to room temperature and another batch of HCO_2NH_4 and Pd black was added with stirring. This was followed by the addition of formic acid, and the reaction mixture was refluxed for another 12 hours.³⁵⁰

N-Substituted pyrrolidines were subjected to catalytic transfer hydrogenolysis affording pyrrolidines, but the yields were low to moderate due to volatility, particularly in the case of the 3-*n*-butyl derivative (Scheme 4.103).³²⁴



SCHEME 4.103

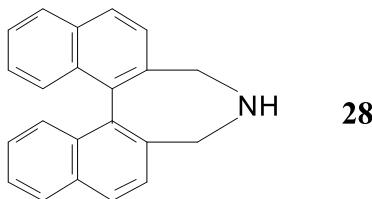


FIGURE 4.5

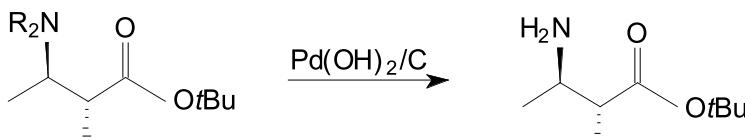
During the asymmetric synthesis of *erythro* and *threo* α -substituted β -amino esters, the dimethylbinaphthyl moiety (28 in Fig. 4.5) was removed using transfer hydrogenolysis.

An argon-purged flask was charged with dry 20% $\text{Pd}(\text{OH})_2/\text{C}$ (4 mol Pd/mol), EtOH and HCO_2NH_4 (25 mol/mol). The mixture was heated at 50°C for 30 minutes, treated with the protected compound dissolved in EtOH, and heated an additional 80 minutes (Scheme 4.104).³⁵¹

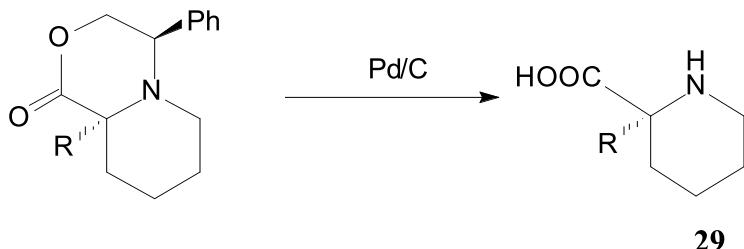
The benzyl C–N bond was hydrogenolyzed during a double O- and N-deprotection on Pd/C in mild acidic medium.³⁵² The reaction flask was charged with a solution of the substrate in a mixture of EtOH–AcOH (2:1). After the addition of 10% Pd/C (0.085 mol Pd/mol compound) the apparatus was charged with hydrogen. The reaction was complete within 30 min to 1 hour under stirring and enantiomerically pure (*S*)-pipecolic acid (29) was produced (Scheme 4.105).³⁵³

The detritylation of *N*-tryphenylmethylvaleric acid ester derivatives was accomplished by catalytic hydrogenolysis, both in the standard and catalytic transfer modes.³³⁸ The trityl precursor was suspended in a mixture of EtOH and AcOH, and HCO_2NH_4 was added. Reduction began with the addition of 10% Pd/C (0.05 mol Pd/mol) and continued for 50 hours at 25°C.

Both the benzylic C–O and the C–N bonds were cleaved during the synthesis of (+)-lactacystin. The hydrogenolysis of the oxazoline moiety on Pd/C, $\text{Pd}(\text{OH})_2/\text{C}$, or Pd black in MeOH proved unsuccessful, but catalytic transfer



SCHEME 4.104

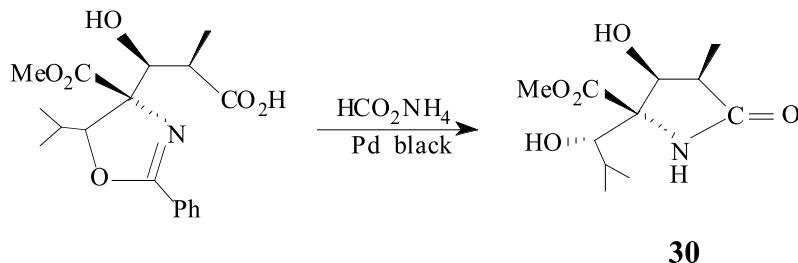


SCHEME 4.105

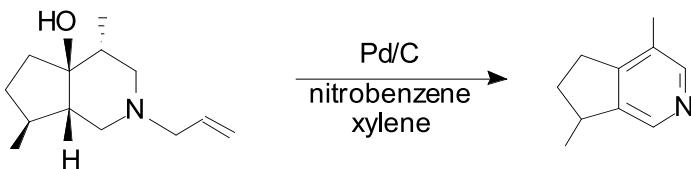
hydrogenolysis (Pd black, ammonium formate, AcOH, reflux) afforded γ -lactam ester (30) (Scheme 4.106).³⁵⁴

4.2.1.4. Hydrogenolysis of Other Activated C–N Bonds

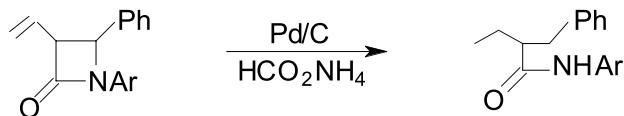
The N-allyl bond was hydrogenolyzed by heating the N-protected compound in a nitrobenzene-*p*-xylene mixture (1:1) in the presence of a catalytic amount of 10% Pd/C and molecular sieves (Scheme 4.107).^{355,356}



SCHEME 4.106



SCHEME 4.107

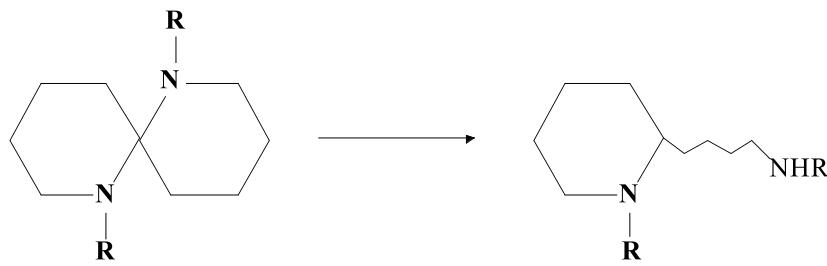


SCHEME 4.108

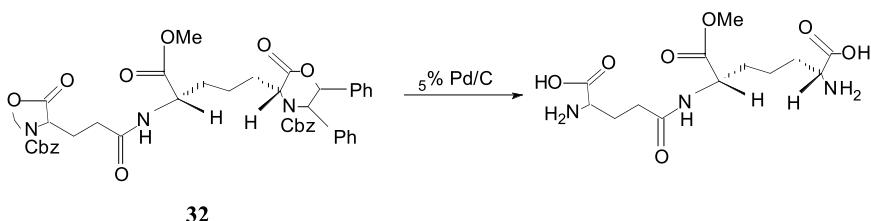
Microwave-induced organic reaction enhancement chemistry was used for the hydrogenolysis of the C–N bond in lactams. To a solution of α -vinyl β -lactams in ethylene glycol were added HCO_2NH_4 and 10% Pd/C catalyst; then this mixture was irradiated in a microwave oven (Scheme 4.108).³⁵⁷

Hydrogenolysis of one C–N bond in diazaspiroalkanes (31) can occur on platinum or nickel catalysts (Scheme 4.109).³⁵⁸

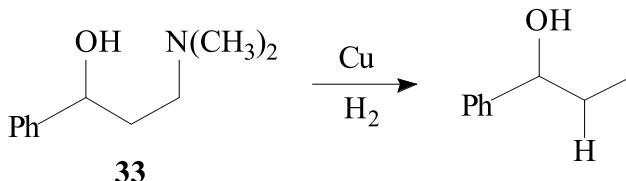
A fully protected peptide (32) was unmasked by catalytic hydrogenolysis on 5% Pd/C (0.4 mol Pd/mol) in CH_2Cl_2 –MeOH at 60 psi H_2 for 42 hours at room temperature (Scheme 4.110).³⁵⁹



SCHEME 4.109



SCHEME 4.110



SCHEME 4.111

1,3-Amino alcohols (33) were transformed to ketones on copper.^{360,361} The transformation involves the dehydrogenation of the hydroxyl group, the elimination of dimethylamine, and the hydrogenation of the unsaturated ketone (Scheme 4.111).

4.2.1.5. Ring Opening of C–N Containing Cyclic Compounds

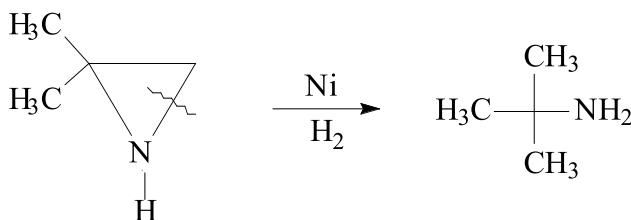
4.2.1.5.1. Hydrogenolysis of Aziridines

The ring opening of aziridines takes place easily because of the great strain in the three-membered ring. Pt, Pd, Rh, and Ni are used as catalysts. Usually the sterically less hindered C–N bond is ruptured (Scheme 4.112).

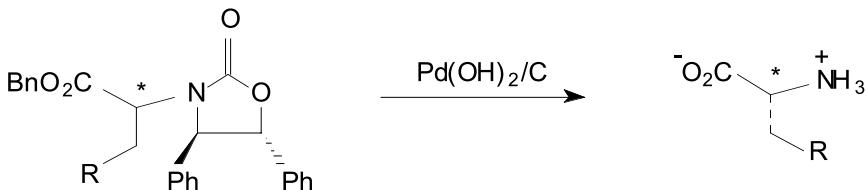
The catalytic hydrogenolysis of aziridines takes place with inversion on Pd, whereas on Pt and Ni, considerable racemization also occurs.³⁶²

4.2.1.5.2. Hydrogenolysis of Other Azacycloalkanes

Ring opening becomes more difficult as the ring size increases. The cleavage, however, takes place easier in the case of less stable ring structures. Reductive removal of the benzyl ester and the oxazolidinone gave the corresponding amino acid during the asymmetric synthesis of α -amino acids by conjugate addition of Grignard reagents (Scheme 4.113).³⁶³



SCHEME 4.112

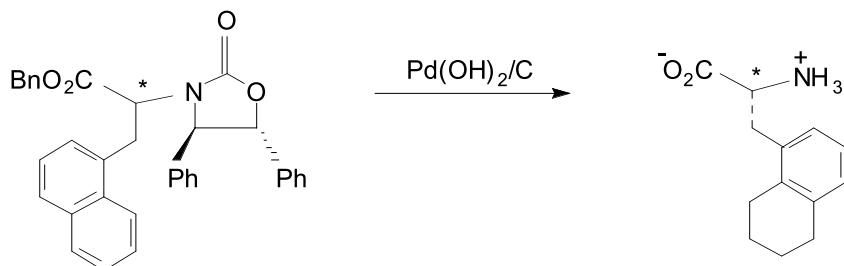


The $\text{Pd}(\text{OH})_2/\text{C}$ catalyst was added to the solution of the starting compounds in $\text{MeOH}-\text{THF}$ under argon. The mixture was purged with hydrogen four times followed by pressurizing to 60 psi of hydrogen. The reaction was stirred for 10–20 hours. As expected, the unsaturated groups were hydrogenated. Surprisingly, the remote ring of the naphthyl group was hydrogenated, whereas naphthalenes substituted in the 1-position were preferentially hydrogenated at the substituted ring (Scheme 4.114).³⁶³

4.3. HYDROGENOLYSIS OF C–S BONDS

Desulfurization of organic compounds over Ra-Ni is a well-known procedure.^{364–369} Ra-Ni exists in different forms (W1 to W8), differing in the preparation procedure and sometimes symbolized as Ni(H). Ra-Ni is sometimes called a catalyst; however, it is used usually in large excess and the reaction is stoichiometric. Ra-Ni can desulfurize every C-S bond containing compound but it can also hydrogenate a lot of other functional groups. Unwanted side reactions are sometimes suppressed by using deactivated Ra-Ni.

At the adsorption of benzenethiol on Ni(100), benzene and hydrogen are the only gas-phase products.³⁷⁰ Methanethiol adsorption has also been studied



SCHEME 4.114

on platinum,^{371,372} nickel,^{373–375} iron,³⁷⁶ and tungsten³⁷⁷ surfaces. Complete decomposition of methanethiol is observed, together with the formation of methane at higher exposures. On Cu, dimethyl sulfide adsorbs molecularly, whereas methyl thiolate is formed from methanethiol and dimethyl disulfide.³⁷⁸ 2-Methyl-2-propanethiol adsorbed on clean and sulfided Au surfaces undergoes S–H bond cleavage to form surface thiolate. Hydrogen sulfide formation is attributed to direct reaction between the thiol and the adsorbed sulfur, rather than to the recombination of adsorbed atomic hydrogen and sulfur.³⁷⁹ About one-half of the thiophenol adsorbed on Au also undergoes S–H bond cleavage.³⁸⁰

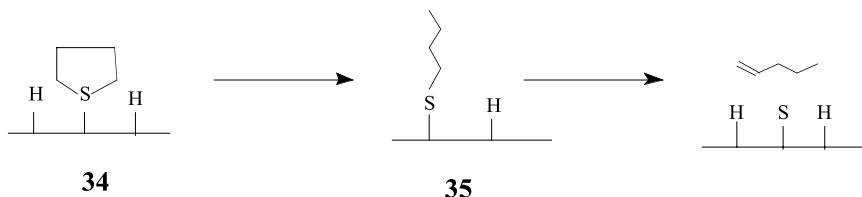
The initial step of the adsorption of thiols on a Mo(100) surface is the formation of adsorbed thiolate groups. Phenyl thiolate is formed upon adsorption of thiophenol at 120 K on a clean Mo(110) surface.³⁸¹ The thiolate intermediate subsequently undergoes competing C–S bond hydrogenolysis to form benzene, or C–S and C–H bond scission to form surface benzyne. The adsorption of thiophenol was also studied on a sulfur-covered Mo surface.³⁸² Phenyl disulfide is formed via S–H bond scission and S–S bond formation. The S–S linkage is oriented perpendicular and the phenyl ring parallel to the surface.

S–C Sulfides are hydrogenolyzed usually by Ra-Ni.^{383–391} Phenyl and methylthio groups were removed by Ra-Ni (10 mmol Ni/mmol) refluxing in ethanol for 2 hours.³⁹² A thio enol ether was desulfurized with Ra-Ni (100 mmol Ni/mmol) in MeOH at room temperature for 30 minutes.³⁹³ During the synthesis of 2-deoxy-β-glycosides the removal of the arylthio group was achieved using Ra-Ni with no problem.³⁹⁴

The initial step of the adsorption of cyclic sulfides on a Mo(100) surface is also the formation of adsorbed thiolate groups.^{395–397} Adsorbed alkyl thiolates decompose to adsorbed sulfur, carbon, and hydrogen on the clean Mo surface, but once the surface is deactivated by adsorbed sulfur, alkanes and alkenes evolve from the surface. Tetrahydrothiophene (34) and trimethylene sulfide decompose on Mo(110) to alkanes and alkenes by way of a common intermediate, which is proposed to be a surface thiolate (35). The thiolate undergoes hydrogenation or dehydrogenation, depending on the surface hydrogen concentration (Scheme 4.115).^{398,399}

A hydroxysulfoxide was desulfurized with Ra-Ni in MeOH for 30 minutes.⁴⁰⁰ Treatment with hydrogen in the presence of catalytic amounts of Ra-Ni in EtOH caused the desulfurization of a 2,6-anhydro-2-thio sugar, the reduction of an N-oxide, and the removal of benzyl and carbomethoxy groups at the same time.⁴⁰¹

According to the literature, desulfurization of thioic acids with Ra-Ni proceeds with retention of configuration.^{402,403} But use of the literature method invariably gave partially or completely racemized products.⁴⁰⁴ Finally, ultrasonic irradiation of a degassed mixture of the starting compound and Ra-Ni in

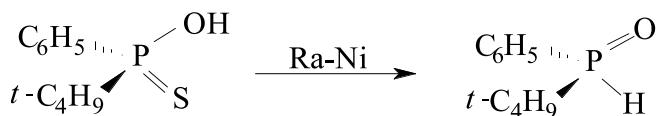


SCHEME 4.115

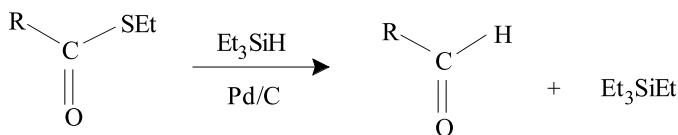
EtOH during 3 hours at 15–20°C with mechanical stirring provided the product with an enantiomeric purity of >99.6% (Scheme 4.116).

R-C-SR Hydrogenolysis of carboxylic acid thioesters over Ra-Ni deactivated by boiling in acetone is one of the classic syntheses of aldehydes.^{405–408} Without deactivation the Ra-Ni hydrogenolyzes the thioesters to alcohols.

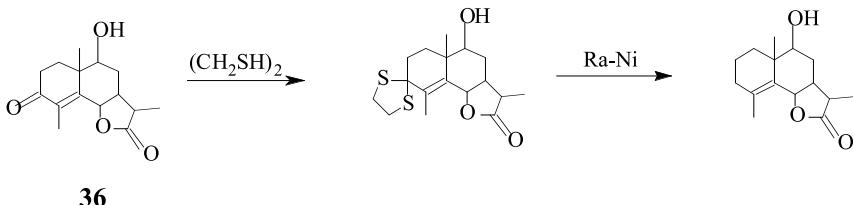
Thiol esters undergo smooth reduction to give aldehydes by the Fukuyama hydrosilylation procedure, which is an alternative way to transform carboxylic acids to aldehydes. Upon treatment with Et₃SiH and 10% Pd/C, a thioester underwent smooth reduction to give an aldehyde.^{409,410} For example, to a stirred mixture of thioester and Pd/C in acetone may be added Et₃SiH at room temperature under an Ar atmosphere. Stirring is continued until the hydrogenolysis is complete (0.5–1 h) (Scheme 4.117).



SCHEME 4.116



SCHEME 4.117



SCHEME 4.118

A keto thioester was also efficiently reduced to a keto aldehyde by the previously-mentioned Fukuyama hydrosilylation procedure using Lindlar's catalyst ($\text{Pd}/\text{CaCO}_3/\text{PbO}$) in acetone at room temperature.⁴¹¹

S-C-S The keto function is frequently deoxygenated via Ra-Ni-mediated desulfurization of thioacetals.⁴¹²⁻⁴¹⁴ That is, the ketone group can be removed from compound (36) by thioketalization followed by desulfurization with Ra-Ni (81 mmol Ni/mmol) in MeOH for 20 minutes (Scheme 4.118).⁴¹⁵

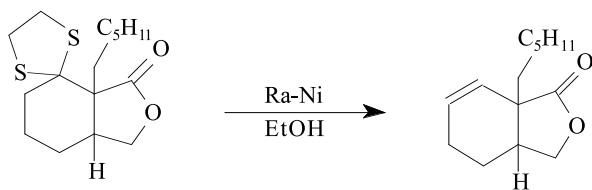
It has been found that dithioketals when refluxed with moderately active Ra-Ni in ketone solvents yield olefins as the main products.⁴¹⁶ Ethylene dithioacetal was refluxed in benzene-containing ethanol with Ra-Ni for 20 hours and was converted to olefin (Scheme 4.119).⁴¹⁷

Hydrogenolytic desulfurization was achieved with Ra-Ni (58 mmol Ni/mmol) refluxing in ethanol for 2 hours (Scheme 4.120).⁴¹⁸

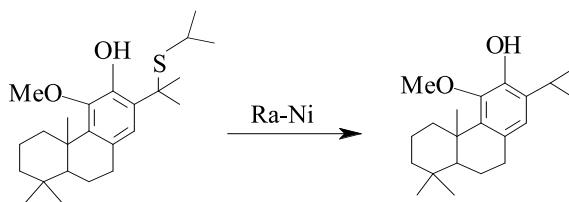
The use of an inadequate excess of Ra-Ni (170 mmol Ni/mmol) led to the isolation of a benzyl ethyl ether (37), which was hydrogenolyzed by Pd in the presence of acid (Scheme 4.121).

Substitution of methanol for ethanol gave a mixture that was inseparable by column chromatography. The new compound in the mixture exhibited a singlet as expected for the methyl ether.

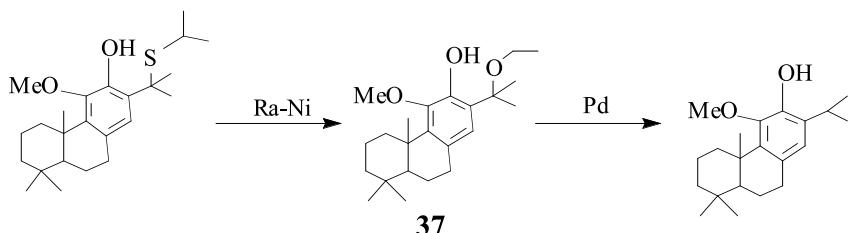
The elimination of the chiral auxiliary from hydroxy sulfoxides by hydrogenolysis of the C-S bond with Ra-Ni did not give the expected desulfurized



SCHEME 4.119



SCHEME 4.120

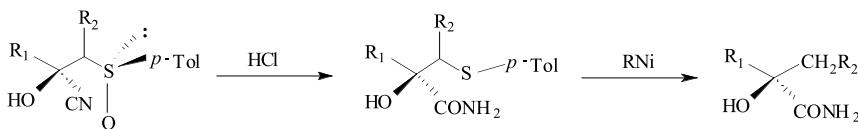


SCHEME 4.121

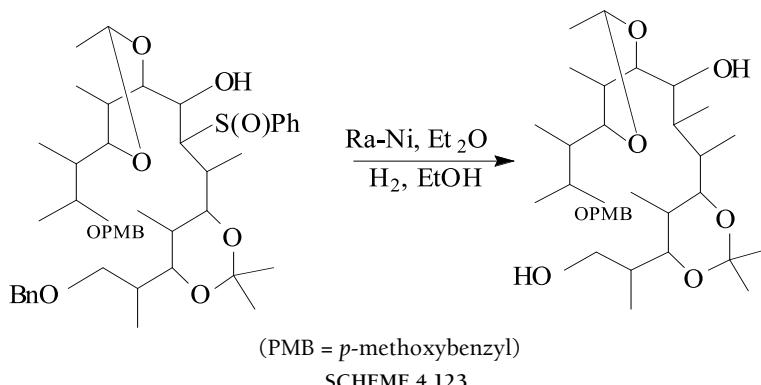
cyanohydrins.⁴¹⁹ The hydrolysis of the CN group by using an ether solution saturated with HCl resulted in the concomitant hydrogenolysis of the sulfenyl group, yielding the sulfenyl hydroxy amides. Vigorously stirring these compounds with an excess of Ra-Ni in anhydrous ethanol under argon at room temperature for 2 hours afforded the desired optically pure α -hydroxy amides (Scheme 4.122).

Desulfoxidation was achieved using Ra-Ni in ether. This was followed by selective hydrogenolysis of the benzyl group on W2 Ra-Ni under a hydrogen atmosphere in EtOH.^{420–422} Desulfoxidation had to be performed in ether; use of ethanol as the solvent in desulfoxidation led to cleavage of a C-7–C-8 bond (Scheme 4.123).

Hydrogenolysis of *para*-methoxybenzyl ether was made on 10% Pd/C in EtOH under a hydrogen atmosphere.



SCHEME 4.122



S-Aryl-*N,N*-dialkylthiocarbamates and phenyl mercaptans were readily desulfurized by Ra-Ni in EtOH at room temperature.²⁶ Thiolactams were desulfurized with Ra-Ni in THF.^{423,424} Desulfurization of a thiolactam containing a secondary hydroxyl group with Ra-Ni caused the deoxygenation of the alcohol function, too. Dehydration of the alcohol gave α , β -unsaturated thiolactam, which when treated with Ra-Ni under a variety of conditions, hydrogenated the C=C bond and resulted in the appearance of one stereoisomer. Desulfurization with deactivated Ra-Ni in acetone gave the alkene, which upon hydrogenation on 10% Pd/C gave a mixture of diastereomers.⁴²⁵

4.4. HYDROGENOLYSIS OF C–Se BONDS

Since the chemistry of the C–Se bond is very similar to the chemistry of the C–S bond, the deselenation procedures are also very similar to the desulfurization methods. Thus, Ra-Ni is an efficient reagent in hydrogenolytic deselenations, but the outcome of the reaction depends on the preparation of the catalyst.^{426–428}

A phenylselenenyl group was eliminated by deactivated Ra-Ni. Deactivation was achieved by heating the ethanolic suspension at 60°C for 3–4 days after which the starting compound was treated with this ethanolic Ra-Ni suspension for 30 minutes.^{415,429}

4.5. HYDROGENOLYSIS OF C–HALOGEN BONDS

Breaking carbon–halogen bonds is very important because halogenated hydrocarbons are well-known environmental pollutants, and their fundamental

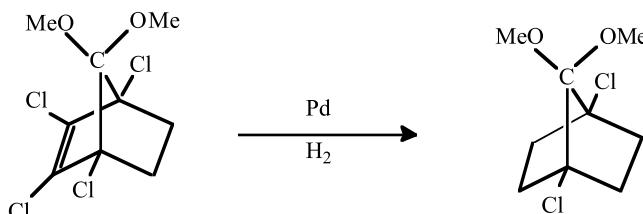
chemistry on catalyst surfaces is relevant to environmental protection and cleanup technologies. Alkyl halides are much less readily hydrogenolyzed than vinyl, aryl, and especially benzyl or allyl halides. The order of ease of dehalogenation is I > Br ≈ Cl » F. According to this sequence, alkyl fluorides are very difficult to remove by catalytic hydrogenation.

C–X The hydrogenolysis of alkyl halides to alkanes can be achieved in the presence of Pd/C and Ra-Ni catalysts. Hydrogen halides produced during the reaction can deactivate the catalysts. Hydrogen ion is a particularly strong poison; therefore, the reaction is usually carried out in the presence of bases. Sodium hydroxide is used frequently, whereas amines are used often for base-labile compounds. The reactivity of alkyl halides follows the next sequence: tertiary > secondary > primary. Ra-Ni is an active catalyst for dehalogenations but is readily deactivated by the halide ions, whereas Pd/C is less susceptible to this poisoning effect. The C–Cl bond of a chloromethyl group was ruptured using Ra-Ni in EtOH under reflux for 2 hours.⁴³⁰ The bond of a Cl and a tertiary carbon was cleaved by Pd/C and H₂.⁴³¹

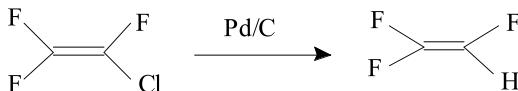
C=C–X The C–X bond connected to vinyl groups is activated enough for facile hydrogenolysis. The outcome of the reaction depends on the relative rates of hydrogenolysis versus hydrogenation. If the C=C bond hydrogenates first, hydrogenolysis of the saturated C–O bond takes place slowly. The rates of hydrogenolyses increase in the order Ru, Rh << Pt, Pd, but the solvent can also influence the outcome, and the ratio of hydrogenolysis to hydrogenation increases with increasing acidity and polarity. In the example shown in Scheme 4.124, the vinyl C–Cl bonds were hydrogenolyzed using a Pd catalyst.⁴³²

During hydrogenation of vinylic chlorides, both saturation of the double bond and hydrogenolysis of the C–Cl bond take place.^{433–435} Also, selective hydrogenolysis of chlorine occurs in the presence of fluorine atoms on a Pd/C catalyst (Scheme 4.125).⁴³⁶

Continuing this trend, vinylic bromine can be much more easily hydrogenolyzed than vinylic chlorine over a palladium catalyst.⁴³⁷

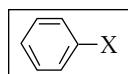


SCHEME 4.124



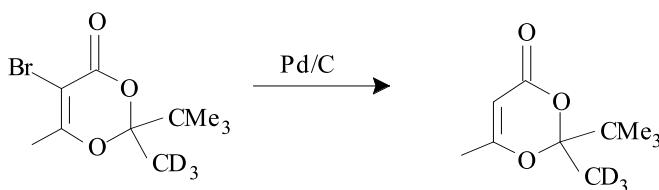
SCHEME 4.125

The cleavage of the C–Br bond in a chiral allene was performed with a Zn–Cu couple in THF–MeOH.⁴³⁸ Debromination was achieved in EtOH using 10% Pd/C and triethylamine as base under a hydrogen atmosphere (Scheme 4.126).⁴³⁹



It is well known that halogenated benzene derivatives can be hydrogenolyzed to benzene. Compared with other detoxification methods, hydrodechlorination reactions are gaining in importance because they allow the polyhalogenated aromatics to be hydrogenolyzed to the parent hydrocarbons without the production of waste. Hydrodehalogenations have been reported by supported Pd catalysts^{440–443} and transfer hydrogenolyses using formate salts,^{444–446} sodium hypophosphite in protic solvents (methanol, ethanol, and water)⁴⁴⁷ and indoline.⁴⁴⁸ Hydrodehalogenation with Pd/C occurs preferentially with aromatic rather than aliphatic compounds.⁴⁴⁹ It has been reported that the hydrodehalogenation of the aryl halides follows the order PhI < PhBr < PhCl when Pd/C⁴⁴⁵ is the catalyst, whereas this order is reversed with Ra–Ni.⁴⁵⁰ It has been reported that the hydrodehalogenation of chlorobenzene by Pd/C proceeds through dissociative adsorption of the molecule on the surface followed by the addition of hydrogen.⁴⁵¹

A multiphase system consisting of a hydrocarbon solvent, a strong alkaline solution, and a quaternary onium salt, in the presence of a Pd/C catalyst with hydrogen that was bubbled at atmospheric pressure through the organic phase, allows the rapid displacement of chlorine from polyhalogenated benzenes. The onium salt, insoluble in both phases, is localized in the interfaces, coats the Pd/C catalyst, and constitutes the phase in which the reaction takes

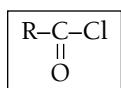


SCHEME 4.126

place. Halogenated compounds are partitioned between the hydrocarbon solution and the liquid phase of the phase-transfer agent. Rapid removal of HCl adsorbed on Pd/C is effected by neutralization with the alkaline solution. The enhancement of the reaction rate compared with the known methods might be attributed to the facile adsorption of H₂ by the catalyst under the reaction conditions.⁴⁵² Hydrodehalogenation of polyhalogenated aromatics with Pd/C catalyst carried out in the presence of onium salt follows zero-order kinetics in the substrate and first-order kinetics in the Pd/C catalyst.⁴⁵³

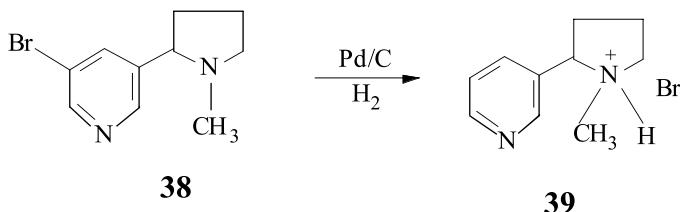
Hydrodehalogenations of chloro-, bromo-, and iodobenzene were carried out individually as well as in competitive reactions. When the reactions were carried out separately, the reduction of chlorobenzene closely paralleled that of bromobenzene, whereas the reduction of iodobenzene was slower. When they were allowed to react competitively, the reduction was highly selective, and the reaction was delayed, but iodobenzene reacted first followed by bromobenzene and then chlorobenzene.

Dehalogenation of aromatic amines using catalytic hydrogenolysis takes place easily, usually without the reduction of C=C, COO, C≡N, and NO₂ groups.^{454,455} The hydrogenolysis of 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (38) on Pd/C in EtOH produces nicotine hydrobromide (39) (Scheme 4.127).⁴⁵⁶

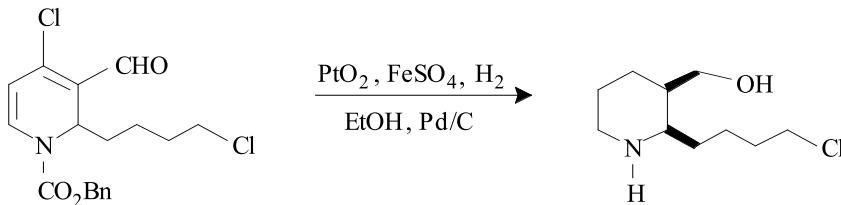


Carboxylic acid chlorides can be converted to aldehydes by hydrogenolysis on a poisoned Pd/BaSO₄ catalyst. This is the classic Rosenmund reduction. Over more active catalysts, further hydrogenation gives the corresponding alcohols. Bases are used to react with the HCl. For example, 2,5-dimethylpyridine was used as base in a Rosenmund reduction.⁴⁵⁷

Pt/C and Li₂CO₃ in AcOEt were used to remove chlorine from 4-chloro-1,2-dihydropyridine.⁴⁵⁸ Pd/C was used in combination with Pt/C to remove the benzyl protecting group. It was anticipated that during the hydrogenolysis of the chlorobutyl-containing compound, the axial group would sterically hinder the catalytic hydrogenation from the top face, producing the *cis*-piperidine



SCHEME 4.127



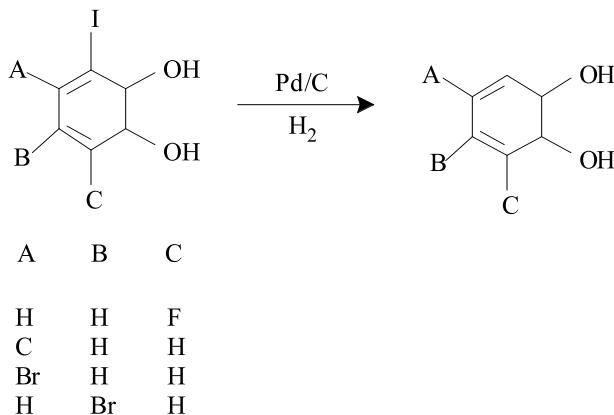
SCHEME 4.128

alcohol. Initial attempts using PtO_2 and Pd/C were successful but only with low stereoselectivity. The selectivity was increased in the presence of ferrous sulfate, which is a known promoter in the catalytic reduction of α,β -unsaturated aldehydes (Scheme 4.128).⁴⁵⁹

PtO_2 and H_2 were used in 0.5% HCl to remove the Cl and reduce a nitro group to provide a cyclohexylammonium salt.⁴⁶⁰

C–Br Pd/C catalyst and sodium acetate in acetic acid⁴⁶¹ or Et_3N in EtOH –benzene⁴⁶² or in MeOH ⁴⁶³ were used in a hydrogen atmosphere for debromination. Transfer hydrogenolysis can also be used for the cleavage of C–Br bond. A bromonaphthalene, 10% Pd/C , and HCO_2H in DMF was stirred at 150°C for 5 hours.⁴⁶⁴ Ammonium formate can also be used as the hydrogen donor.⁴⁶⁵

C–I Replacement of the iodine substituent by a hydrogen atom was achieved via selective catalytic hydrogenolysis using 3% Pd/C in MeOH containing AcONa and traces of quinoline at room temperature and 1 atm hydrogen pressure (Scheme 4.129).⁴⁶⁶



SCHEME 4.129

Selective removal of the iodine from fluorinated compounds was performed by 5% Pd/C catalyzed hydrogenolysis in the presence of triethylamine or sodium acetate.⁴⁶⁷ Ra-Ni and 1% NaOH were used for the cleavage of the C–I bond.⁴⁶⁸ The adsorption of chloroiodomethane was studied on a Pt(111) surface. Dissociation began with C–I bond cleavage at about 150 K. Co-adsorbed deuterium atoms weaken the bonding between the starting compound and the surface and decrease the amount of dissociated molecules.⁴⁶⁹

4.6. HYDROGENOLYSIS OF C–Si BONDS

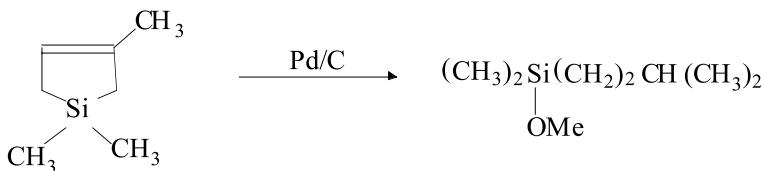
In the case of a C=C bond containing organosilicon compounds, the presence of a Si atom does not exert any appreciable influence on addition in an apolar solvent. In a polar solvent, however, the rupture of the C–Si bond also occurs (Scheme 4.130).⁴⁷⁰

C–Si bond breaking was observed at the transformation of tetramethylsilane on Pt and Pd catalysts.^{471,472} C–Si hydrogenolysis occurred on Pd,⁴⁷³ over W and Fe,⁴⁷⁴ on Au and Mo,⁴⁷⁵ and over Ni and Rh.⁴⁷⁶ Copper catalysts can catalyze the epimerization of 1,2-dimethylsilacyclopentane.^{477,478} Over metal catalysts, triethylsilane hydrogenolyses in stages, losing one ethyl group at a time until only strongly adsorbed Si remains on the metal surface. This strongly adsorbed Si can poison the catalytic activity.⁴⁷⁹ Alkene hydrogenation activity can restore by oxidation. The oxidation produces a new reconstructed surface for hydrogenation.⁴⁸⁰

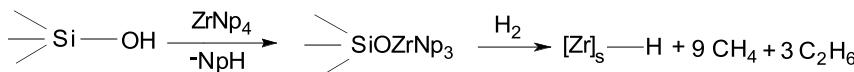
The *t*-butyldiphenylsilyl protecting group together with benzyl and benzylloximethyl protecting groups were removed using Pd(OH)₂ in MeOH–acetone under a hydrogen atmosphere.⁴⁸¹

4.7. HYDROGENOLYSIS OF C–C BONDS

Hydrogenolysis of the C–C bond takes place on different metal catalysts but the rupture of the nonpolarized C–C bond is more difficult than cleavage of the more polarized carbon–heteroatom bonds.^{482–486}



Scheme 4.130



SCHEME 4.131

Because of the unreactivity of the alkenes, their activation and functionalization are among the challenges of catalytic chemistry. Tetrakis(neopentyl)zirconium can react with a silica surface at 773 K leading to a surface species that can be transformed to surface zirconium hydride (Scheme 4.131).^{487,488}

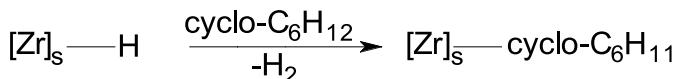
This highly electron deficient Zr(IV) surface hydride can activate the C–H bond of alkanes at room temperature (Scheme 4.132).

Above 323 K, the surface hydride catalyzes the hydrogenolysis of neopentane, isobutane, and propane, whereas ethane does not undergo any significant hydrogenolysis. The first step of the reaction is the activation of the C–H bond, whereas the next step is the activation of the C–C bond of the alkyl groups via β -methyl migration steps.

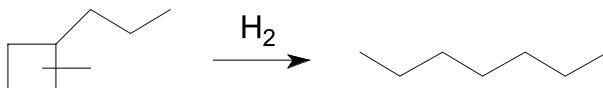
Hydrogenolysis of cyclic alkanes differs from that of normal alkanes. The bond angles in small rings are different from a tetrahedral angle and the angle strain makes these molecules very reactive. Because of their unique reactivity, sometime the term *hydrogenative addition* is used for hydrogenolysis of small rings.^{489,490} The angle strain is much smaller or does not exist at all in the case of five- and six-membered rings. In spite of this, the ring opening of these molecules is faster than hydrogenolysis of the normal alkanes.

Methylcyclopentane is a powerful probe molecule for the study of metal surfaces. The product distribution on platinum depends on the following factors: particle size,⁴⁹¹ reaction conditions,^{492–494} carbonaceous residues,^{492,493,495} and the extent of the interface between the metal and the support.^{492,493,495} The hydrogenolysis rate of methylcyclopentane depends on the hydrogen pressure.^{496,497} The rate exhibits a maximal value as a function of hydrogen pressure on EuroPt catalysts.⁴⁹⁸ The hydrogenolysis of methylcyclopentane has also been studied over Pt–Ru bimetallic catalysts.⁴⁹⁹

In the presence of hydrogen the configurational isomerization of the dialkylcyclopentanes and the dialkylcyclohexanes can also occur on the cata-



SCHEME 4.132



SCHEME 4.133

lytic surface.⁵⁰⁰ Adsorbed cyclopropanes are thought to be intermediates in bond shifts, whereas the adsorbed five-membered rings play important roles in catalytic reforming. Therefore, many papers are devoted to the study of substituted cyclopropanes and cyclopentanes.^{501–505} In contrast, only a few publications have dealt with alkyl-substituted cyclobutanes.⁵⁰⁶

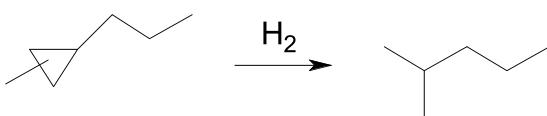
The selectivity of the ring opening of methylcyclobutane over Pt/SiO₂ and Pd/SiO₂ was close to statistical whereas on Rh/SiO₂ and Ni/SiO₂ catalysts the rupture of the sterically less hindered bond was the main reaction route.^{507–508} In contrast, the main direction of the ring-opening of propylcyclobutane on Pt/SiO₂ and Pd/SiO₂ catalysts is the cleavage of the more hindered C–C bond (Scheme 4.133).^{489,509,510}

However, cleavage of the sterically less hindered bond was the major reaction pathway in the hydrogenolysis of propylcyclopropane on palladium and platinum catalysts (Scheme 4.134).⁵¹¹

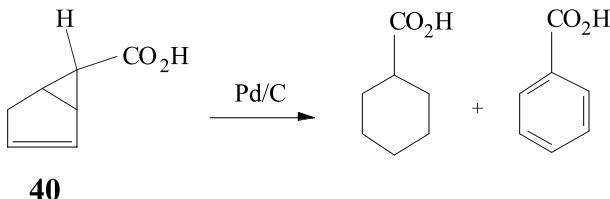
The unusual regioselectivity in the case of substituted cyclobutanes can be attributed to the simultaneous adsorption of the ring and the propyl group on the surface. Also metal–carbonaceous interfaces are thought to play a role because they provide anchoring sites for the side-chain adsorption. The resulting fixed geometry leads to the unusual regioselectivity.⁵¹² On Pt/SiO₂ at 373 K, the ring opens in the sterically more hindered direction, whereas the selectivity is lost at 573 K.⁵¹³

Aromatization and ring enlargement of propylcyclobutane were observed over Pt/SiO₂, whereas only aromatization took place on Pd/SiO₂ and Rh/SiO₂.⁵¹⁴ Aromatization was also found during the hydrogenolysis of bicyclo[3.1.0]hex-2-ene-endo-6-carboxylic acid (40), where cyclohexane carboxylic acid and benzoic acid were the products (Scheme 4.135).⁵¹⁵

Mostly, the sterically less hindered bond was cleaved in the case of methylcyclobutane on Ni, whereas for the propylcyclobutane, the selectivity was



SCHEME 4.134



SCHEME 4.135

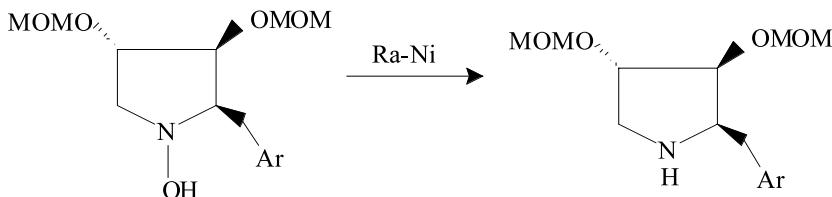
close to statistical.⁵¹⁶ The analysis of the hydrogen-pressure-versus-turnover-frequency curves made it possible to discuss the mechanism of the transformations on platinum,^{507,511,512} palladium,^{511,512} nickel,⁵¹⁶ and rhodium⁵¹⁷ catalysts. The hydrogen-pressure-dependence curves show that on Pt/SiO₂ at 373 K, the initial surface is not very different from the working one, whereas at 573 K the actually reacted species differ from those initially formed.⁵¹² The steady-state surface was also different on Pd/SiO₂.⁵¹⁰

4.8. HYDROGENOLYSIS OF N–O BONDS

The nitrogen–oxygen bond is usually cleaved readily by catalytic hydrogenolysis and the reaction has wide synthetic utility.

 **Nitro Compounds.** Under mild conditions, aromatic nitro compounds are hydrogenated easily to amines.⁵¹⁸ The reaction may give partially reduced products, according to the circumstances. Palladium, platinum, and nickel are used frequently for this reaction. For example, nitro and benzyl ester functions are reduced on Pd(OH)₂/C on THF and on Pd/C in EtOH.⁵¹⁹ Aliphatic nitro groups are reduced more slowly.

The reduction of aromatic nitro compounds to amines can also be achieved by transfer hydrogenolysis using hydrazine as the hydrogen donor and Pd or other metal catalysts.^{520,521} Formic acid is a more active hydrogen donor, but in the presence of a halogen substituent the *in situ* generated haloid anion poisons the catalyst,⁵²² and formate salts have to be used for the reduction of these compounds.⁵²³ Ammonium formate is a good hydrogen transfer agent for the selective reduction of nitro groups in the presence of acids, esters, amides, and halogen groups.⁵²⁴ It was reported that potassium formate was better than sodium formate, which in turn was better than formic acid as the hydrogen donor for nitrotoluene reduction.⁵²⁵ Nitroarenes containing benzyl groups can be hydrogenated without debenzylation in the presence of hydrazine hydrate and Ra-Ni.⁵²⁶ Ammonium formate can also be used for the



SCHEME 4.136

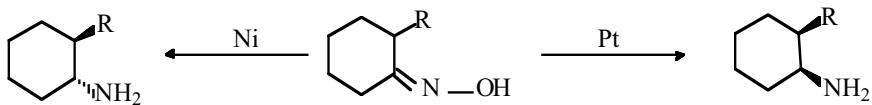
reduction of aliphatic nitro compounds to amines. The method is selective and sterospecific and proceeds with retention of configuration.^{526,527}

Pyrrolidine derivatives Catalytic hydrogenolysis of the N–OH bond producing pyrrolidine was performed in the presence of Ra-Ni (Scheme 4.136).⁵²⁸

C=N–OH **Oximes** Amines can be prepared by the catalytic hydrogenation-hydrogenolysis of oximes over nickel or noble metal catalysts. Nickel is used usually in the presence of ammonia. Noble metals are used under mild conditions. The stereochemistry of the reaction depends on the circumstances. On Ra-Ni the *trans*-2-alkylcyclohexylamine (41) was the main product,⁵²⁹ whereas on palladium the *cis* product (42) was produced (Scheme 4.137).⁵³⁰

Hydrogenolysis of hydroxybenzamidines to benzamidines has always been of interest to the hydrogenation chemists. The hydrogenolysis of the N–O bond in these compounds was performed on 4% Pd/C in AcOH at 60°C and 60 psi hydrogen pressure (Scheme 4.138).^{531,532}

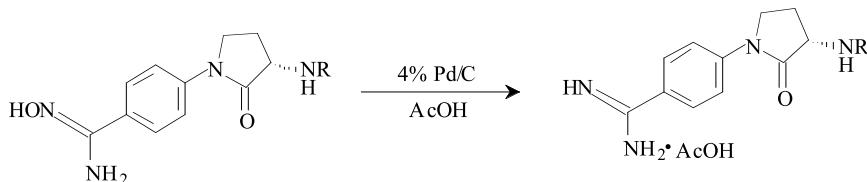
Amine Oxides Catalytic hydrogenolyses of aromatic N-oxides occurs easily except if the N–O bond is hindered. Rh/C is the most active catalyst compared with Ru/C, Pt/C, and Pd/C, but this catalyst is unselective and reduces aromatic rings as well. N-Oxides can also be reduced in EtOH with a catalytic amount of Ra-Ni under hydrogen at 40°C for 1.5 hours.⁵³³



41

42

SCHEME 4.137



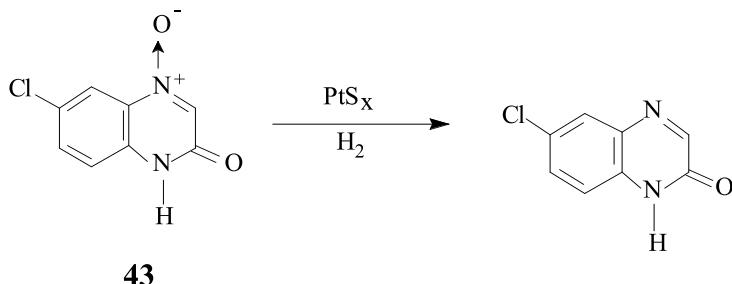
SCHEME 4.138

On Pd/C, carbon–carbon double bonds and halogens are usually reduced before the N-oxides. The final selectivity in the hydrogenation of N-oxides has been shown to depend on the pH, the catalyst system used, and the functional groups present and their position. PtS_x was a superior catalyst with a higher assay and yield in the selective hydrogenation of 6-chloro-2(1H)-hydroxyquinoxaline-4-oxides (43) (Scheme 4.139).⁵³⁴

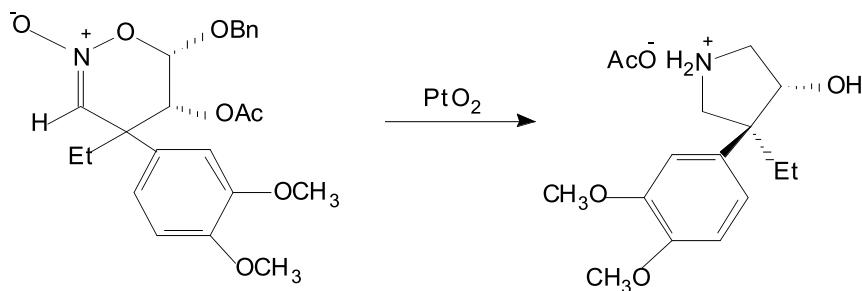
=N→O Nitrones represent a versatile class of compounds in organic synthesis since they are useful 1,3-dipoles suitable for cycloaddition reactions.⁵³⁵ It was found that catalytic hydrogenolyses of nitronates employing PtO₂ at elevated pressures provide a route to substituted pyrrolidines.^{536,537} The nitronates are usually reduced in the presence of 15 mol % PtO₂ at 160 psi hydrogen pressure. During hydrogenation of acetoxy nitronates, partial saponification of the acetate occurred, liberating acetic acid and trapping the pyrrolidine product (Scheme 4.140).⁵³⁸

Isoxazole Derivatives Isoxazoles may be considered as masked α -diketones and undergo hydrogenolysis readily (Scheme 4.141).⁵³⁹

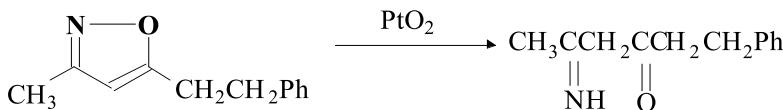
Hydrogenolysis of the isoxazoline ring with Ra-Ni in the presence of hydrogen results in conversion to a hydroxymethyl ketone (Scheme 4.142).⁵⁴⁰



SCHEME 4.139



SCHEME 4.140



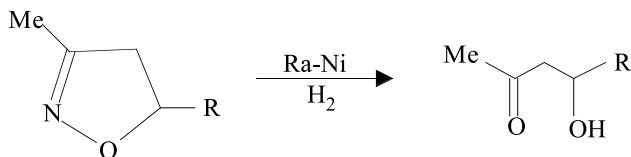
SCHEME 4.141

However, in the case of a compound containing the electron withdrawing benzoyl group, β -elimination of the benzyloxy group occurred and an enone was obtained in the presence of hydrogen and boric acid (Scheme 4.143).⁵⁴¹

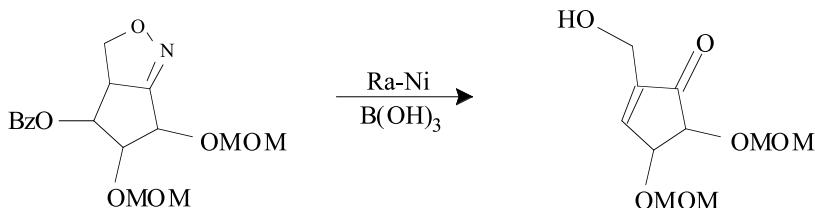
N-O Isoxazolidines can be converted easily to tetrasubstituted cyclobutylamines. This transformation involves a one-pot, two-stage reaction involving hydrogenolysis of the isoxazolidine ring on Pd/C in AcOEt and the N-*tert*-butoxicarbonylation of the resulting amino group (Scheme 4.144).⁵⁴²

The 2,3,5,5-tetraphenylisoxazolidine (44) was reduced by 5% Pd/C in MeOH for 12 hours under a hydrogen atmosphere (Scheme 4.145).⁵⁴⁴

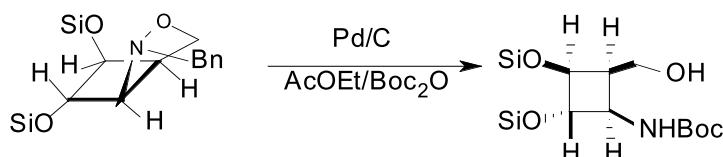
The N-O bond in an isoxazolidine ring was hydrogenolyzed on 5% Pd/C in MeOH for 12 hours in a hydrogen atmosphere at room temperature.⁵⁴⁴



SCHEME 4.142

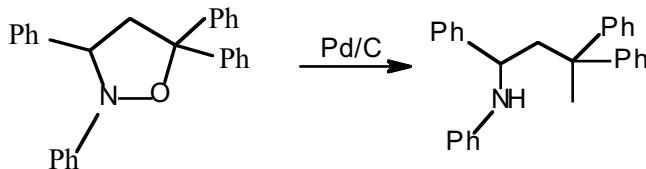


SCHEME 4.143



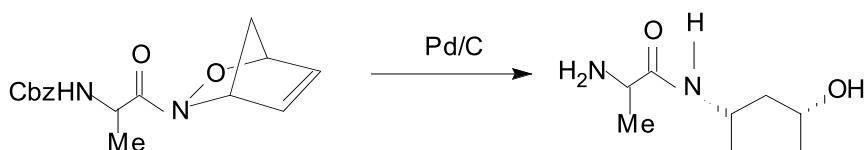
SCHEME 4.144

Oxazines During the hydrogenolysis of an unsaturated oxazine ring the double bond was also hydrogenated (Scheme 4.146). With sodium amalgam, the double bond was not saturated.⁵⁴⁵

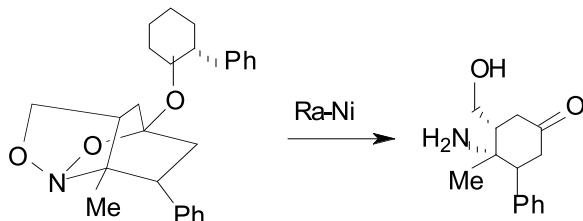


44

SCHEME 4.145



SCHEME 4.146

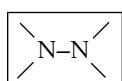


SCHEME 4.147

Nitroso Acetals Hydrogenation of a nitroso acetal on Ra-Ni at 1 atm H₂ for 1 hour afforded a ketone via the hydrogenolysis of the N–O bonds and the cyclohexyl C–O bond (Scheme 4.147).⁵⁴⁶

During the hydrogenation of the butyl derivative, however, the hydrogenolysis of the other C–O bond occurred and the product was not the expected ketone but rather an alcohol (Scheme 4.148).

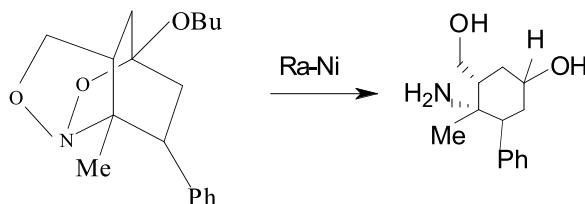
4.9. HYDROGENOLYSIS OF N–N BONDS



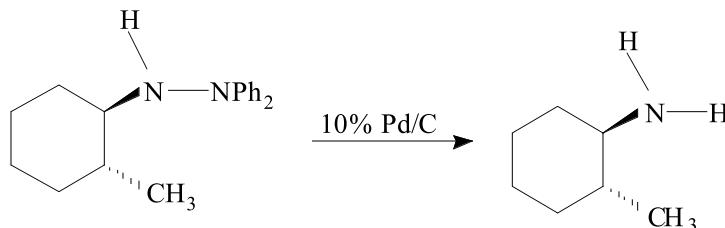
Hydrazines and compounds that can be hydrogenated to hydrazines undergo N–N bond rupture on noble metal catalysts. Pd seems to be the best catalyst for the hydrogenolysis of the N–N bonds in aromatic hydrazines, whereas Rh seems best for the aliphatic ones. Ni is also useful for the hydrogenolysis of N–N bonds in hydrazines.

A 1,1-dimethylhydrazine derivative was hydrogenolyzed on Ra-Ni (85 mol Ni/mol hydrazine) at 4 atm H₂ in MeOH for 48 hours.⁵⁴⁷ Also 1,1-diphenylhydrazine derivatives were hydrogenolyzed into amines on 10% Pd/C (Scheme 4.149).^{548,549}

2-Phenyl-2-butylhydrazine was hydrogenolyzed on PtO₂.⁵⁵⁰ Because the benzyl C–N bond is hydrogenolyzed easily, the hydrazones of the aromatic ketones can be converted directly to hydrocarbons.



SCHEME 4.148



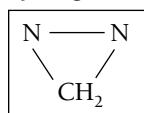
SCHEME 4.149

Catalytic hydrogenation of azo compounds over Pt or Ra-Ni often leads to hydrogenolysis.⁵⁵¹ Catalytic transfer hydrogenolysis using cyclohexene and Pd is also used for the conversion of azobenzenes to anilines.⁵⁵²

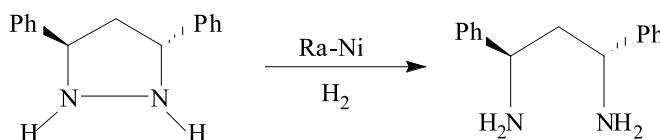
The N–N bond in a pyrrolidine ring was hydrogenolyzed on Ra-Ni with the assistance of ultrasound (Scheme 4.150).⁵⁵³

The *N,N*-dimethylpyrrolidine did not react at the same conditions; that is, the tetrasubstituted nature of the hydrazine functionality prevents the cleavage of the N–N bond. It is likely that the rupture of the N–N bond needs the dissociative adsorption (N–H bond rupture) of at least one nitrogen atom.

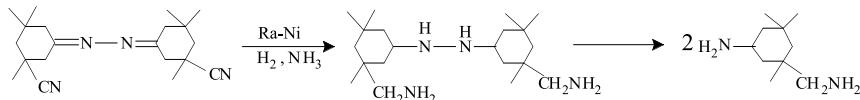
Isophorone diamine is synthesized traditionally by aminoreduction of isophoronenitrile. Raney cobalt was used for this process. More recently, a new two-step process was patented. The first step consists of synthesizing the imine and the second one of hydrogenating the latter. Ra-Ni was used as catalyst at 150°C and 60 bar hydrogen pressure. Under these conditions, the catalyst reduces the nitrile groups and is able to cleave the N–N bonds, too. Ammonia is required to promote primary amine formation during nitrile hydrogenation (Scheme 4.151).⁵⁵⁴



Diazirine is a cyclic isomer of diazomethane. According to the organometallic literature, scission of both C–N and N–N bonds can occur when diazirines interact with metal complexes. The formation of carbene ligands arises from selective cleavage of the C–N bond, whereas selective N–N bond scission results in the formation

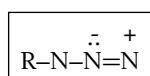


SCHEME 4.151



SCHEME 4.151

of alkylideneimino (R_2CN) ligands. Dissociative adsorption of diazirine on Cu(100) at 124 K involves totally selective N–N bond scission,⁵⁵⁵ whereas on Pd(110) both C–N and N–N bond scission are observed.^{556,557}

 Azides are organic derivatives of the unstable hydrazoic acid (HN_3). They are useful intermediates for the synthesis of N-containing compounds, because the azido group is stable toward a variety of reagents and can be easily hydrogenated–hydrogenolyzed to primary amines. The azide hydrogenation–hydrogenolysis needs both the hydrogenation of the double bond and the hydrogenolysis of the N–N single bond. Palladium, nickel, and platinum have been used frequently for the hydrogenation–hydrogenolysis of the azido group. Because the reaction evolves one N_2 molecule for every reacted H_2 molecule, sometimes it is advantageous to evacuate the hydrogenation apparatus and refill with hydrogen.

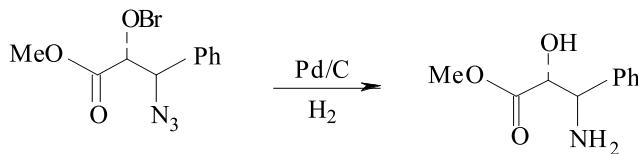
Pd/C is a frequently used catalyst for the hydrogenation–hydrogenolysis of azides.^{558–563} Pd/C, 10% (0.037 mol Pd/mol azide) was stirred in MeOH in an atmosphere of hydrogen for 30 minutes⁵⁶⁴ or for 6 days.⁵⁶⁵ MeOH is a frequently used solvent.^{566–569} MeOH and a few drops of AcOH were used for azide hydrogenolysis.⁵⁷⁰ EtOH,^{571–576} AcOEt,^{577–580} and THF^{581,582} are also popular solvents. In the presence of $(Boc)_2O$ and 10% Pd/C in THF, *in situ* protection of the resulting amine occurred.^{583,584} The hydrogenation–hydrogenolysis of the azido group was also accomplished with 10% Pd/C using 1 N aqueous hydrochloric acid,⁵⁸⁵ acetic acid,^{586,587} a MeOH–AcOH mixture,^{588,589} or *t*-BuOH⁵⁹⁰ as solvents.

The oxygen–carbon bond was also hydrogenolyzed during the reduction of the azido group (Scheme 4.152).⁵⁹¹

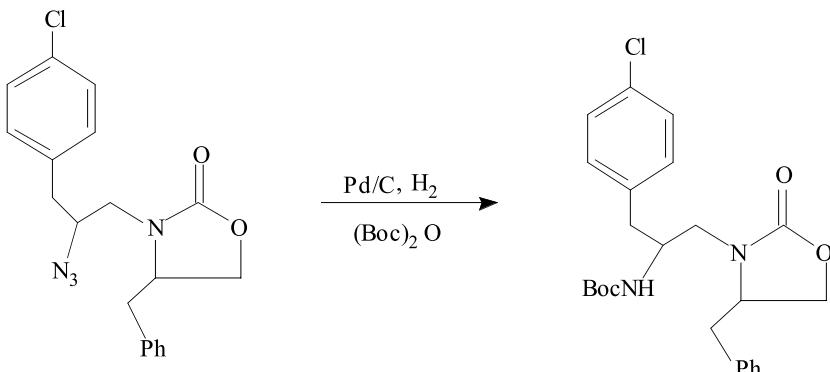
The oxazolidine ring proved to be stable toward hydrogenation conditions using 10% Pd/C and $(Boc)_2O$ in CH_2Cl_2 (Scheme 4.153).⁵⁹²

Pd(OH)₂/C catalyst was also used for the reduction of azides.^{593–595} Ra-Ni^{596,597} and PtO₂⁵⁹⁸ were also used for the reduction of azides. Lindlar's catalyst was used for the reduction in the presence of double bonds (Scheme 4.154).^{599–601}

The 9-phenylfluoren-9-yl (PhFI) group is very useful for protection of the amino group. Pd/C can remove the Ph group and reduce the amido group,



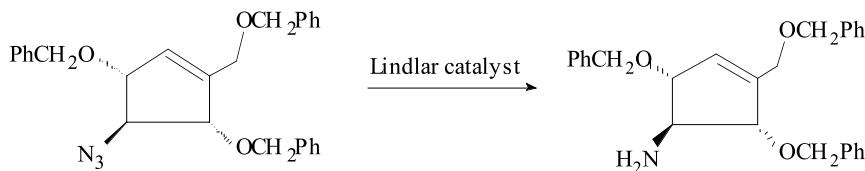
SCHEME 4.152



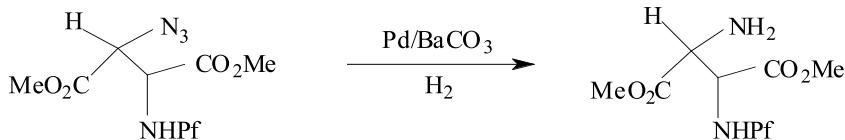
SCHEME 4.153

whereas with the use of Pd/BaCO_3 in MeOH , the chemoselective reduction of the azido group can be achieved (Scheme 4.155).⁶⁰²

Transfer hydrogenation is also useful for the reduction of the azido group. The azide was treated 10% Pd/C and ammonium formate in MeOH under an inert atmosphere for 2.5 hours.⁶⁰³



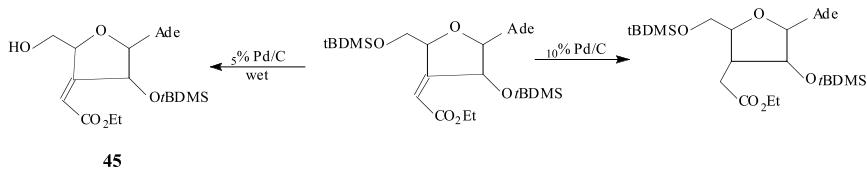
SCHEME 4.154



SCHEME 4.155

4.10. HYDROGENOLYSIS OF Si–O BONDS

The double bond in a *D*-ribofuranosyl derivative containing *tert*-butyldimethylsilyl groups was hydrogenated on 10% Pd/C in MeOH for 3 days under hydrogen and the reduction gave a single product, which was assigned as the α -isomer. Surprisingly, when the olefin was treated with H₂ and a wet 5% Pd/C (Degussa type), the only observed product was the 5'-deprotected olefin (45) (Scheme 4.156). This method was found to be applicable for the selective 5'-desilylation.⁶⁰⁴



SCHEME 4.156

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Bond Breaking Reactions

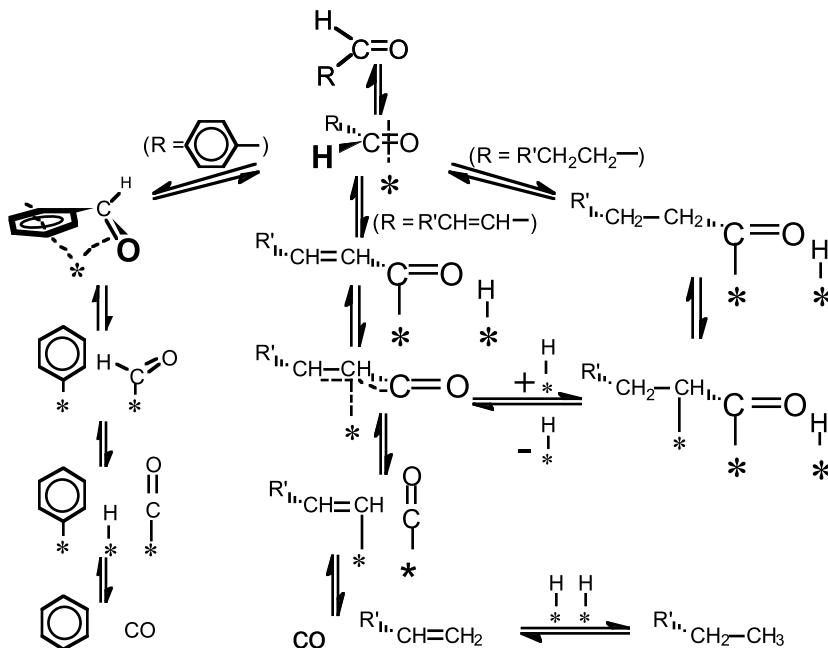
- 5.1. Breaking Carbon–Carbon Bonds: Decarbonylation
- 5.2. Breaking C–O and C–H Bonds: Dehydration
- 5.3. Breaking H–C Bonds, Dehydrogenation
- 5.4. Breaking S–H Bonds

References

5.1. BREAKING CARBON–CARBON BONDS: DECARBONYLATION

5.1.1. GENERAL

Decarbonylation of aldehydes occurs over the Pt metals. Traditionally, Pd supported on charcoal or barium sulfate is used.¹ The reaction mechanism is not fully understood, and several mechanisms have been proposed.² Different pathways seem to be followed by the different possible structural aldehydes (Scheme 5.1).³ The reaction is mildly structure-sensitive with the highest activity exhibited by the smaller crystallites; however, selectivity for alkene production rather than alkane production is highest on the larger crystallites. If the desired product is an alkene, larger crystallites may be preferred because smaller crystallites catalyze double bond isomerization better than large crystallites. Additionally, to avoid such isomerization the product alkene must be rapidly removed from the catalyst. For example, to minimize racemization in the synthesis of (+)-apopinene from decarbonylation of (+)-myrtenal,⁴ expeditious removal of apopinene was accomplished by rapid distillation through a



SCHEME 5.1

short-path head from a mixture of 35 g of (+)-myrtenal and 3.5 g of 5% Pd/BaSO₄ (Aldrich) under helium in a 250-ml flask immersed in an oil bath pre-heated to 196°C and gradually increased to 234°C during the reaction and distillation. Within 15 minutes, three fractions were collected at 130, 160, and 154°C and a final fraction was collected at 154°C with a continuously decreasing temperature over the next 30 minutes. After gas chromatography purification, these fractions exhibited optical rotations $[\alpha]_D^{25}$ of +54.2°, +52.5°, +51.7°, and +37.3°, respectively.⁵ Since decarbonylation of aldehydes occurs on Pd, it might be expected that catalyst deactivation may occur during the hydrogenation of aldehydes due to carbon monoxide poisoning.

5.1.2. CATALYST DEACTIVATION, REACTIVATION, AND PROTECTION FROM DEACTIVATION

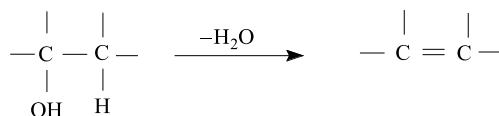
During hydrogenation of aldehydes, especially over platinum oxide, catalyst deactivation occurs. The reasons for this deactivation are not well understood and several theories exist.⁶

Because the catalyst can be rejuvenated by shaking in air (after the removal of hydrogen, of course) possible poisons may be carbonaceous deposits or adsorbed CO. Exclusion of the possibility that CO is the poison on the grounds that decarbonylation does not occur at hydrogenation temperatures³ may well be erroneous because CO does not desorb from Pd and Pt below 125°C.⁷ So decarbonylation could occur and CO could deactivate the catalyst without any significant amounts of decarbonylation products appearing in the reaction medium. On the other hand, deactivation during hydrogenation of other functional groups may be overcome by shaking the deactivated catalysts with air, a practice that suggests deactivation by carbonaceous deposits.⁸

Protection from deactivation has taken several strategies.⁶ Small amounts of salts, particularly ferrous chloride or stannous chloride, are effective provided they are not present in large amounts. Possibly, these salts get reduced to form bimetallic surface alloys with the platinum metals and these new catalysts are resistant to the particular poisoning resulting from hydrogenation of aldehydes; however, recent evidence suggests that the metal ions are responsible for selectivity.⁹ Another successful strategy for preventing deactivation is mixing a small amount (1%) of oxygen with the hydrogen.¹⁰ (The explosion concentration of oxygen in hydrogen is approximately 5%, so keeping the oxygen level low is essential.) Over platinum metals, hydrogen and oxygen form hydrogen peroxide, which could well keep the surface clean of carbonaceous deposits. Adding oxygen to hydrogen actually increases hydrogenation rates, but the strategy works only for aldehydes and causes rate reductions in other hydrogenations. This seems to contradict the general practice of rejuvenating a deactivated catalyst by shaking with air, but the two procedures are different. In the case of aldehyde deactivation, the poison removed may be CO, or some specific decomposition product from aldehydes, plus carbonaceous materials, whereas in the general case, only the removal of carbonaceous materials may be involved.

5.2. BREAKING C–O AND C–H BONDS: DEHYDRATION

During the dehydration of alcohols, cleavage of both the C–O and the C–H bonds occurs (Scheme 5.2).



SCHEME 5.2

5.2.1. DEHYDRATION OF ALCOHOLS

Dehydration of alcohols occurs on acidic catalysts. For example, zeolites, clays, and metal oxides, mainly $\gamma\text{-Al}_2\text{O}_3$, are widely used dehydration catalysts. The Lewis acid sites (Al^{3+} ions) are not involved in the dehydration reaction but the reaction needs surface oxygen ions. The alcohol binds to the surface by hydrogen bonds. A proton is transferred from a surface OH group to the oxygen of the alcohol, facilitating the transfer of a proton from the neighbouring carbon to a basic surface oxygen atom.¹¹ Alcohol dehydration to give ethers also occurs on the $\gamma\text{-Al}_2\text{O}_3$ surface. It is likely that in this case an alkoxide reacts with a neighbouring adsorbed hydrogen-bonded intermediate.

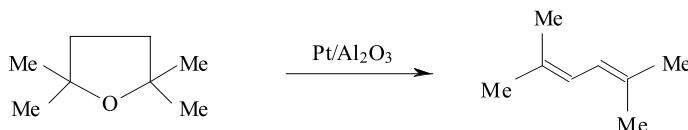
Dehydration of alcohols, however, can occur on metal catalysts, too. This reaction takes place mainly in the case of tertiary alcohols, where dehydrogenation to ketones cannot occur.

Alkane formation from alcohols through alkenes may occur also on catalysts having acidic sites. Alkane formation was found on Ni/SiO_2 ^{12–14} and Pd/SiO_2 ,¹⁵ to a lesser extent for primary, but to a greater extent for secondary, alcohols. These dehydrations may occur on acidic centers. Alkane has also been found on a Pt/C catalyst,¹⁶ but in this case the dehydration is considered to take place on the carbon support.¹⁷ Primary alcohols do not undergo hydrolysis on $\text{Ni/Al}_2\text{O}_3$ catalysts, whereas secondary and tertiary alcohols do.¹⁸ This may also be explained in terms of dehydration. Unsupported Cu and Ni are also capable of dehydration of alcohols. Still, in this case the alcohols can probably oxidize the metals and the resulting metal ions may be responsible for the dehydration activity.^{19,20}

The favorite method of dehydrogenating alcohols to aldehydes and ketones uses MnO_2 , but whether this is a catalytic reaction is uncertain. Although the mechanism has not been established and is likely stoichiometric, we present some examples here because it is frequently considered catalytic by many organic chemists. Always MnO_2 is used in large excess, and usually its preparation method and history are not given. Manganese oxide has been reported as just MnO_2 ,^{21–24} activated MnO_2 ,^{25–28} activated black MnO_2 ,²⁹ $\gamma\text{-MnO}_2$ (sonicated),³⁰ and MnO_2 (Aldrich, manganese(IV) oxide “activated”).³¹ Other dehydrogenation catalysts are Pd/C³² and Pt/C,³³ both used with oxygen.

5.2.2. DEHYDRATION OF OXACYCLOALKANES

The most studied area in this field is the dehydration of oxolanes to butadiene. This type of dehydration is catalyzed by various acidic heterogeneous catalysts. For example, 2,2,5,5-tetramethyloxolane can be dehydrated on $\text{Pt/Al}_2\text{O}_3$ to 2,5-dimethyl-2,4-hexadiene in good yield (Scheme 5.3).³⁴



SCHEME 5.3

5.2.3. DEHYDRATION DURING REDUCTIVE AMINATION

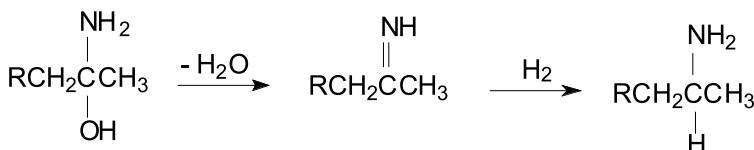
Amines can be synthesized by the treatment of a ketone or aldehyde with an amine in the presence of hydrogen and a noble metal catalyst. During this reductive amination, the intermediate loses water to give an imine that is reduced to yield the amine product (Scheme 5.4).

Azasugars can be synthesized by intramolecular reductive amination via catalytic hydrogenation with hydrogen and platinum. In the double reductive amination of 5-keto-D-fructose, however, the only reducing agent that worked well was NaBH₃CN. Catalytic conditions using hydrogen and noble metal catalysts were unsuccessful, even though numerous reaction conditions (modifying the pH, solvent, and temperature) and reagents (Pt, Pd, Raney Ni) were employed. No reaction occurred under neutral conditions when noble metal catalysts were used, whereas under basic conditions there was clear imine formation but no observed formation of the desired pyrrolidine products.³⁵

5.3. BREAKING H–C BONDS: DEHYDROGENATION

5.3.1. ALCOHOLS TO ALDEHYDES AND KETONES

As a synthetic tool, heterogeneous catalytic dehydrogenations offer selective conversions of functional groups. Most popular dehydrogenations involve



SCHEME 5.4

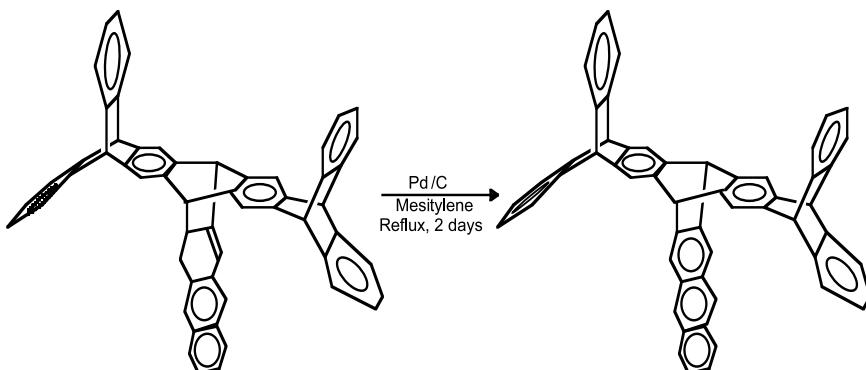
dehydrogenations of alcohols to either aldehydes or ketones and aromatization of six-membered cyclic systems. Examples of dehydrogenations have already been included in Section 2.4.1. and Section 2.4.2. They are also included in Chapter 6.

5.3.2. AROMATIZATIONS

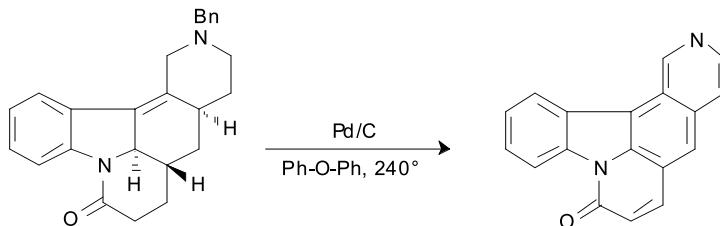
Dehydrogenating six-membered ring compounds into aromatics is fairly easy. Pd/C is the most frequently used catalyst for this purpose to make benzenes³⁶⁻⁴² or pyridines.^{43,44} The reaction has been studied over single crystals of Pt with the conclusion that Pt corners and edges contain the most favorable sites.⁴⁵ Interestingly, aromatization of *n*-heptane on single crystals shows Pt(111) planes to be most active⁴⁶ (see Section 1.1.2.4. for further discussion). Perhaps the edge and corner atoms are more active for removing hydrogens from the ring but the plane sites are required to line up the atoms in a six-membered ring.

The nature of the dehydrogenation on Pd is not so clear; however, if planes are important, it is not obvious from the aromatization of the highly congested compound shown in Scheme 5.5.⁴⁷ Clearly, edges or corners must be involved, which points out the probability that all surface atoms catalyze these reactions, some better than others. In this case, the newly forming benzene ring cannot adsorb flat onto a plane (edgewise is a possibility) but it certainly could hang the protruding appendages over an edge.

A curious mechanistic phenomenon found in hydrogenation is also found in dehydrogenation. Once again, we see an example of a reaction occurring on both sides of a six-membered ring. A clear example of *trans* dehydrogenation occurs during the Pd-catalyzed aromatization of the compound in Scheme 5.6.⁴⁸ See Section 2.1.3.2. for a discussion of *trans* addition.



SCHEME 5.5



SCHEME 5.6

5.4. BREAKING S–H BONDS

The initial step of the adsorption of thiols on Mo(100) surface is the formation of adsorbed thiolate groups. Phenyl thiolate is formed upon the adsorption of benzenethiol at 120 K on a clean Mo(110) surface.⁴⁹ The thiolate intermediate subsequently undergoes competing C–S bond hydrogenolysis to form benzene, or C–S and C–H bond scission to form surface benzyne. The adsorption of benzenethiol was also studied on a sulfur-covered Mo surface.⁵⁰ Phenyl disulfide is formed via S–H bond scission and S–S bond formation. The S–S linkage is oriented perpendicular and the phenyl ring parallel to the surface.

At the adsorption of benzenethiol on Ni(100), benzene and hydrogen are the only gas-phase products.⁵¹ Methanethiol adsorption has also been studied on Pt,^{52,53} Ni,^{54–56} Fe,⁵⁷ and W⁵⁸ surfaces. Complete decomposition of methanethiol is observed, together with the formation of methane at higher exposures. On Cu, dimethyl sulfide adsorbs molecularly, whereas methyl thiolate was formed from methanethiol and dimethyl disulfide.⁵⁹ *Tert*-Butyl thioalcohol adsorbed on clean and sulfided Au surfaces undergoes S–H bond cleavage to form surface thiolate. Hydrogen sulfide formation is attributed to a direct reaction between the thiol and the adsorbed sulfur, rather than the recombination of adsorbed atomic hydrogen and sulfur.⁶⁰ About one-half of the benzenethiol adsorbed on Au also undergoes S–H bond cleavage.⁶¹

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Oxidations

- 6.1. Oxidations with Hydrogen Peroxide
- 6.2. Oxidations with O₂, O₃, and Other Reagents

References

One of the exciting results to come out of heterogeneous catalysis research since the early 1980s is the discovery and development of catalysts that employ hydrogen peroxide to selectively oxidize organic compounds at low temperatures in the liquid phase. These catalysts are based on titanium, and the important discovery was a way to isolate titanium in framework locations of the inner cavities of zeolites (molecular sieves). Thus, mild oxidations may be run in water or water-soluble solvents. Practicing organic chemists now have a way to catalytically oxidize benzene to phenols; alkanes to alcohols and ketones; primary alcohols to aldehydes, acids, esters, and acetals; secondary alcohols to ketones; primary amines to oximes; secondary amines to hydroxylamines; and tertiary amines to amine oxides.

Since the initial discovery, much work has gone into improving the catalyst. The original zeolite contained small pores that limited oxidations to relatively small molecules with shapes that allowed them to move in and out of that pore system. One modification has been to isolate titanium in zeolites with larger pores so larger molecules can be oxidized. Another modification has been to incorporate other metal ions into the frameworks of different zeolites with

differing results. Also, of course, several studies have examined the mechanism of action of the framework metal ions, hydrogen peroxide (and sometimes dioxygen), and substrates. We examine each of these aspects.

6.1. OXIDATIONS WITH HYDROGEN PEROXIDE

Listed in the Table 6.1 are some of the more common sources of oxygen employed for oxidations of organic compounds. Dioxygen is not listed because it requires a catalyst for oxidation at low temperatures. Likewise, hydrogen peroxide and ozone exhibit different activities when used with the proper heterogeneous catalyst.

There are several advantages of using hydrogen peroxide for oxidation.

It furnishes 47% of its weight as oxidant, which is much more than other common oxidants such as NaClO, KHSO₅, and ROOH.

Hydrogen peroxide is the ultimate “green” reagent because water is the only by-product, so no inorganic salts are produced in its reaction.

Aqueous H₂O₂ is a stable reagent. However, it should be noted that its safe use in industry is possible only if H₂O₂-decomposition catalysts, like Fe salts, are rigorously excluded.

TABLE 6.1 Some Common Oxidizing Agents

Oxidant	Sources of oxygen for chemical oxidations	
	Active oxygen	Co-product
H ₂ O ₂	47.1	H ₂ O
O ₃	33.3	O ₂
HNO ₃	25.4	NO _x
NaClO	21.6	NaCl
NaClO ₂	19.2	NaCl
t-BuOOH	17.8	t-BuOH
C ₅ H ₁₁ NO ₂	13.7	C ₅ H ₁₁ NO
NaBrO	13.4	NaBr
KHSO ₅	10.5	KHSO ₄
PhlO	7.3	Phl
NalO ₄	7.2	Nal

In spite of these advantages, problems have existed that complicated the use of H₂O₂ as an oxidant.

Most valuable organic substrates and aqueous H₂O₂ are mutually insoluble.

Water and polar solvents poisoned the early catalysts used.

Water-sensitive products, such as epoxides, are decomposed by water under the reaction conditions of the early catalyst systems.

Many of these problems disappeared in 1983 when Taramasso, Perego, and Notari synthesized titanium silicalite-1 (TS-1),¹ which greatly affected the use of zeolite catalysts for practical oxidation chemistry. This catalyst shows outstanding activity, selectivity, and stability below 100°C.

6.1.1. TITANIUM SILICALITE CATALYSTS

TS-1 and titanium silicalite-2 (TS-2) are microporous solid materials made of SiO₂ and TiO₂ that have silicalite structures (TS-1 has the ZSM-5 structure and TS-2, the ZSM-11 structure) modified by isomorphous substitution of Si(IV) with Ti(IV). TS-1 and TS-2, the former being most studied, show similar properties in catalysis of H₂O₂ oxidations.

Several methods have been employed for the synthesis of TS-1.^{1–3} A typical method begins with the addition of tetraethylorthotitanate (TEOT) to tetraethylorthosilicate followed by the addition of a certain concentration of tetrapropylammonium hydroxide. The resulting mixture is stirred until clear, heated to remove alcohol, put into an autoclave, and heated to 175°C for 24 hours.⁴ Other methods use Ti(OBu)₄^{5,6} or TiF₄⁷ instead of TEOT. TS-2 contains a slightly larger cavity and is prepared in a similar manner.^{8,9}

Not only has the Ti precursor been investigated, but also the structure of the molecular sieve has been heavily investigated. Thus we now have an array of silica and silica-alumina molecular sieve supported Ti catalysts. These include Ti on amorphous SiO₂,^{10,11} Ti on a variety of SiO₂ mixed oxides,¹² Ti-β (titanium-beta),^{13–17} Ti-MCM-48,¹⁸ Ti-MCM-41,¹⁹ Ti-HMS,¹⁸ titanium-mordenite,²⁰ titanium on fibrous silicalite,²¹ and titanium boralites.²² As might be expected, the usual inventory of physical characterizations have been applied to these catalysts: X-ray diffraction,^{18,23–27} Fourier transform infrared,^{18,23–27} FT Raman,^{18,23–26} ultraviolet (UV)^{18,24,26–28} XANES,^{22,29} EXAFS,^{22,29} Si MAS nuclear magnetic resonance (NMR),²³ ¹H→²⁹Si CP MAS nuclear magnetic resonance (NMR),²³ adsorption microcalorimetry,^{25,28} UV-visible diffuse reflectance spectroscopy,²⁶ transmission electron microscopy²⁷ with X-ray energy dispersion spectrometry,²⁴ ¹²⁹Xe NMR,²⁴ scanning electron microscopy,²⁵ N₂-physisorption,^{18,26} and electron diffraction.²⁷ A recent comprehensive review compares and discusses much of the information pertaining to the

structure and properties of the Ti silicalites and speculations on how these properties influence activities and selectivities.³⁰

6.1.2. TS-1-CATALYZED REACTIONS

This popular and rapidly maturing field has generated several reviews,^{31–37} which contain many references. The types of reactions typical of the titanium silicalites and similar titanium-incorporated catalytic systems are summarized in the following paragraphs.

By 1990, most of the catalytic reactions of TS-1 had been discovered. The wide scope of these reactions is shown in Fig. 6.1.³⁵ Conversions include olefins and diolefins to epoxides,^{6,7,12,16,19,21,24,34,36,38–45} aromatic compounds to phenols,^{7,9,19,25,27,36} ketones to oximes,^{11,20,34,46} primary alcohols to aldehydes and then to acids, secondary alcohols to ketones,^{34–36,42,47–50} and alkanes to secondary and tertiary alcohols and ketones.^{6,34,45,51,52}

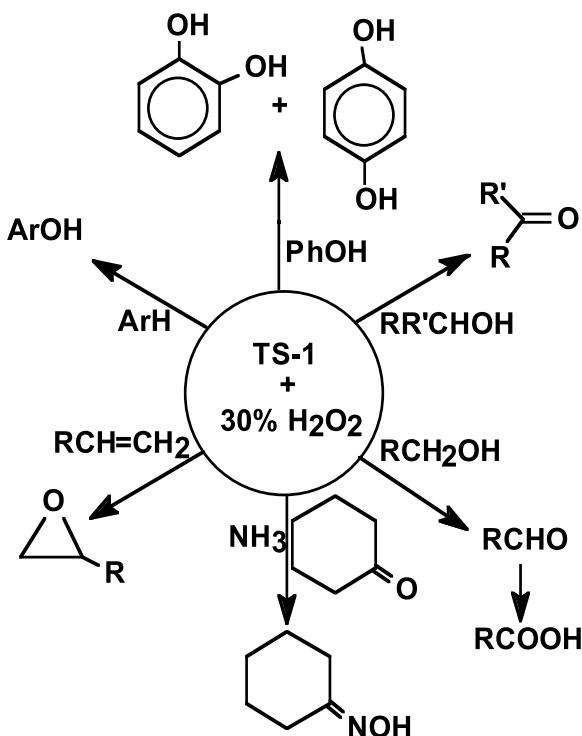


FIGURE 6.1 General scope of reactions catalyzed by TS-1.³⁵

The hydroxylation of aromatic rings has been a special focus because of its commercial importance. In anhydrous solvents (one liquid phase), benzene itself undergoes oxidation to phenol but overoxidation to *p*-benzoquinone may occur. Likewise, phenol may be oxidized to hydroquinone and catechol (Fig. 6.2),^{9,25,35,36,53,54} and monosubstituted benzenes, such as anisole, are hydroxylated. In the absence of solvents (two liquid phases, benzene and aqueous H₂O₂), faster rates, higher conversions, and higher selectivities to phenol (95%) are obtained.⁵⁵ However, electron-withdrawing substituents greatly inhibit aromatic ring hydroxylations.³⁶ Also, shape selectivity, due to the narrow sizes of the zeolite channels, directs the hydroxylations of phenol to produce more of the para isomer than usually is obtained from homogeneous oxidations, but the product mixture depends somewhat on the Ti atom percentage, 100(Ti/(Ti + Si)), that is incorporated into the framework.²⁵

Based on this technology, an industrial process for producing hydroquinone and catechol was developed by EniChem Synthesis starting at 10,000 tons per year (Fig. 6.3).³⁶

Alkyl-substituted benzenes are oxidized both on the benzene ring and on the side chain. Additionally, some dimerization occurs.³⁶ Alkylbenzenes containing linear alkyl groups are oxidized preferentially at the side chain³³ nearest the benzene ring; for example, ethylbenzene oxidizes first to 1-phenyl ethanol and then to acetophenone.³⁶

As shown in Fig. 6.4, primary amines are converted to oximes, secondary amines to hydroxylamines, and tertiary amines to *N*-oxides.³⁴

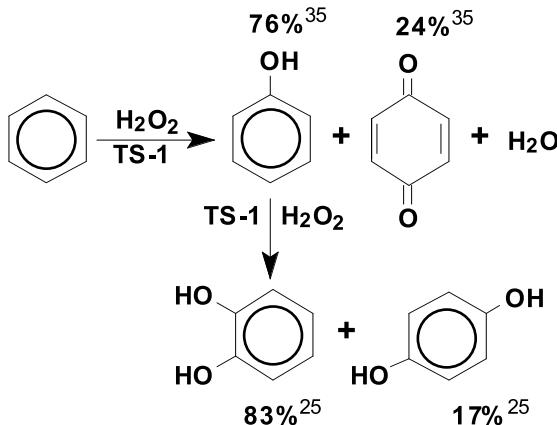
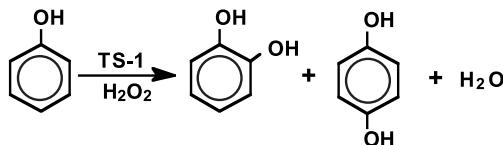


FIGURE 6.2 Hydroxylations of benzene and phenol in organic solvents.

Selectivity depends on catalyst concentration, temperature, and solvent



- Phenol conversion: 20–30%
- H_2O_2 conversion: 100%
- Yield of converted phenol: 92%
- Selectivity (ortho/para): 1.3–0.5
- Solvent media: H_2O , MeOH, H_2O –acetone (60:40)
- Temperature: reflux
- H_2O_2 /phenol molar ratio: 0.25–0.35
- By-products: tars, CO_2 , O_2 , carboxylic acids

10,000 ton/year plant in Ravenna, Italy, in 1986

FIGURE 6.3 Early commercialization of TS-1 hydroxylation of phenol.³⁶

The oxidation of alcohols has been extensively studied.^{34–36,42,47–49} Fig. 6.5 summarizes these reactions.

Reaction rates proceed according to the following trend: secondary alcohols oxidize faster than primary, which oxidize much faster than methanol, which is unique. Methanol is slowly oxidized, presumably because it complexes strongly with the active Ti site. Moreover, methanol acts as a co-catalyst, increasing the rates of alkene^{4,37} and alkane⁵¹ oxidations. Thus methanol is a

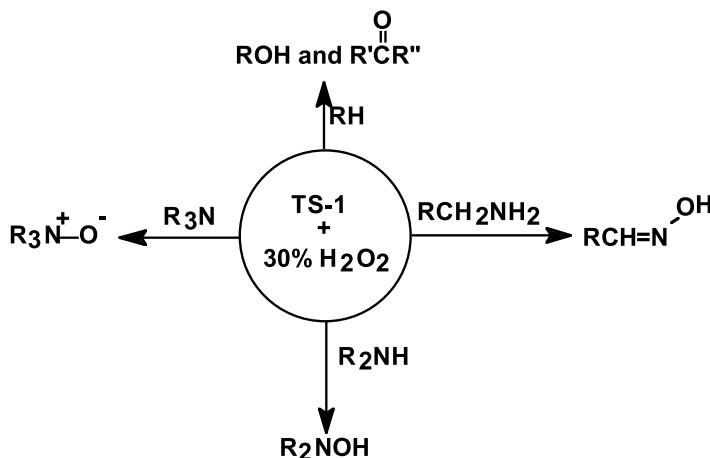


FIGURE 6.4 Oxidations of amines and alkanes over TS-1.

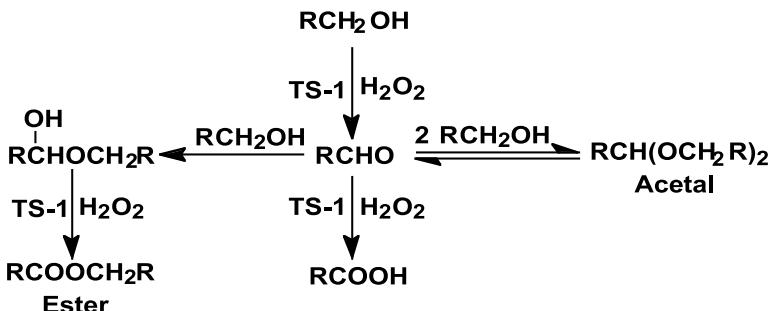


FIGURE 6.5 TS-1-catalyzed oxidations of alcohols.

good solvent for TS-1-oxidations with H_2O_2 . Likewise, tertiary alcohols react very slowly, but this is likely due to their size. So *tert*-butanol is a good solvent for TS-1 catalyzed oxidations. The position of the OH group along the chain exerts an important effect on the rate and OH groups near the end oxidize faster than those far from the end. Chain length seems to have a minor effect on rate. But branched alkyl chains lower oxidation rates compared with linear chains.⁴⁷

Alkanes are oxidized first to alcohols and then to ketones^{6,34,45,51,52} as shown in Fig. 6.6. The order of reactivity is tertiary C–H > secondary C–H >> primary C–H. In many cases oxidation of primary C–H bonds is below detection.⁵²

As detailed in Fig. 6.6, an increase in the chain length decreases the turnover number (TON), which parallels the compounds' decrease in diffusivity in zeolites. Oxidation occurs approximately statistically along the straight chain; attaching methyl side groups to the chain reduces TONs; and *gem*-dimethyl groups (*a tert*-butyl group) restrict entrance to the zeolite channel (~5.5 Å).⁵¹ Electron-withdrawing groups inhibit oxidation at adjacent positions.³⁰

In the linear versus cyclic case, *n*-hexane oxidizes 18.9 times as fast as cyclohexane (see Fig. 6-6); however, under slightly different conditions (same temperature and pressure, acetone solvent) and a slightly different preparation of TS-1, *n*-hexane oxidizes only 4.8 times as fast as cyclohexane.⁴⁵ These differences in TOFs between the linear and cyclic isomers are also attributed to the size restrictions of the zeolite. When the channel diameter is increased, as in the Ti-β catalyst (~6.5 Å), larger cycloalkanes, such as cyclododecane, can be oxidized.⁴⁵

An interesting influence of methanol has been observed in the oxidation of *n*-hexane as shown in Fig. 6.7.⁵¹ To this two-phase system (10 ml *n*-hexane, 10

	TON ^b	Percentage Products ^a									
		1-ol	2-ol	3-ol	4-ol	5-ol	1-one	2-one	3-one	4-one	5-one
	7.0	—	17	39	—	—	—	34	10	—	—
	0.37	50	—	—	—	—	50	—	—	—	—
	0.24	—	—	—	—	—	—	100	—	—	—
	0.26	—	—	—	—	—	—	100	—	—	—
	0	—	—	—	—	—	—	—	—	—	—
	4.5	—	16	47	17	—	—	10	8.0	2.0	—
	0.50	28	34	22	—	—	—	9.0	4.0	3.0	—
	0.10	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c

^a Conditions: TS-1 0.05 g (except 1.0 g for *n*-C₇, *n*-C₈, *n*-C₉), H₂O₂ (30%) 10 ml, alkane 10 ml, 50°C, 3h.

^b Mols product/mols Ti.

^c Not measured.

FIGURE 6.6 TS-1-catalyzed oxidations of alkanes.⁵¹

ml 30% H₂O₂), a small amount of methanol causes a large increase in TON; however, increasing amounts of methanol cause a maximum in TON followed by lower TONs.

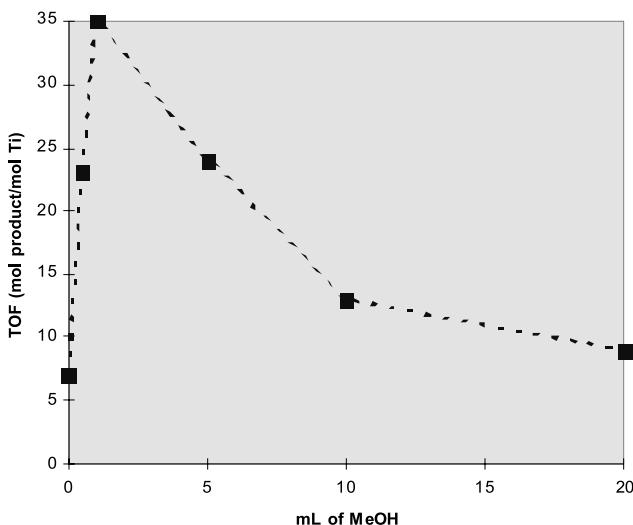


FIGURE 6.7 Effect of methanol on TON of *n*-hexane oxidation by H₂O₂ over TS-1.⁵¹

6.1.3. REACTION MECHANISMS

Although the complete mechanism for each of the previously described reactions is not known, substantial details have been worked out. First, it is clear that Ti is incorporated into the framework of the silicalite structure. Too much Ti (more than about 2.5%) in the preparation steps forms nonframework TiO_2 crystallites, which decompose H_2O_2 . Second, the rate enhancement due to methanol suggests a tight association at the Ti active site as shown in Fig. 6.8.^{37,38} This is supported by the fact that methanol oxidizes much more slowly than other alcohols.⁴⁷ This tight coordination of methanol is proposed to increase the electrophilicity of the Ti-coordinated H_2O_2 and facilitate oxygen transfer to the alkene.³¹

To account for stereochemical results for the epoxidation of allyl alcohols, a slightly different intermediate has been proposed as shown in Fig. 6.9.¹⁶ The authors propose an intermediate (A) analogous to the intermediate in peracid oxidations. A small molecule of alcohol or water is coordinated to Ti with deprotonation and another is coordinatively ligated to Ti without deprotonation to achieve a pentacoordinated ligand sphere. During epoxidation, the allyl alcohol substrate is held in position by a hydrogen bond.

In the absence of alkene, alcohols lose hydrogen to the $\text{Ti}-\text{H}_2\text{O}_2$ complex to form water and ketone or aldehyde as shown in Fig. 6–10.^{47,49}

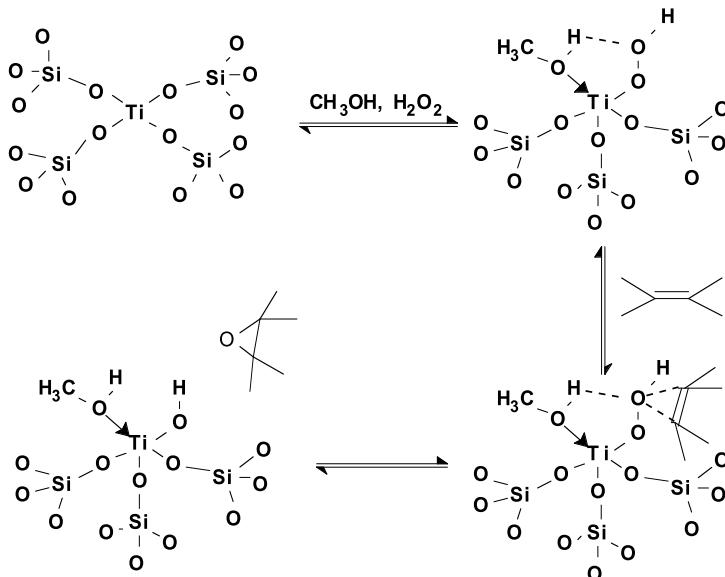
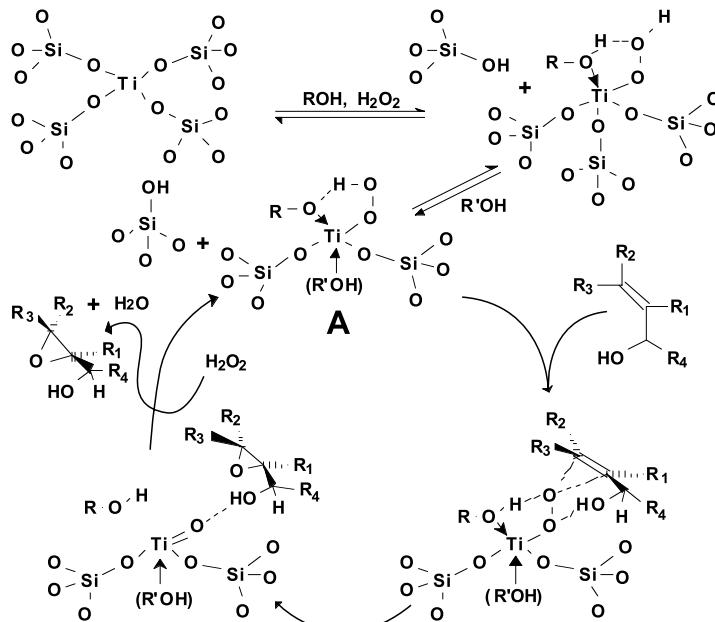
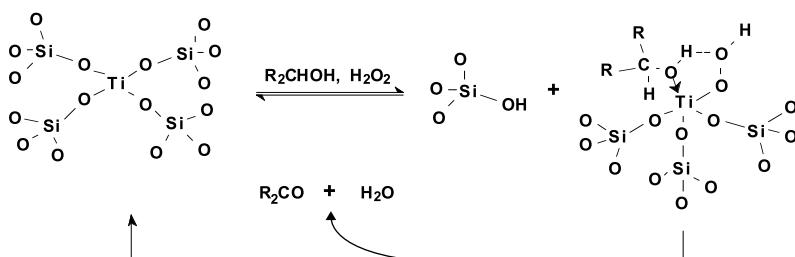


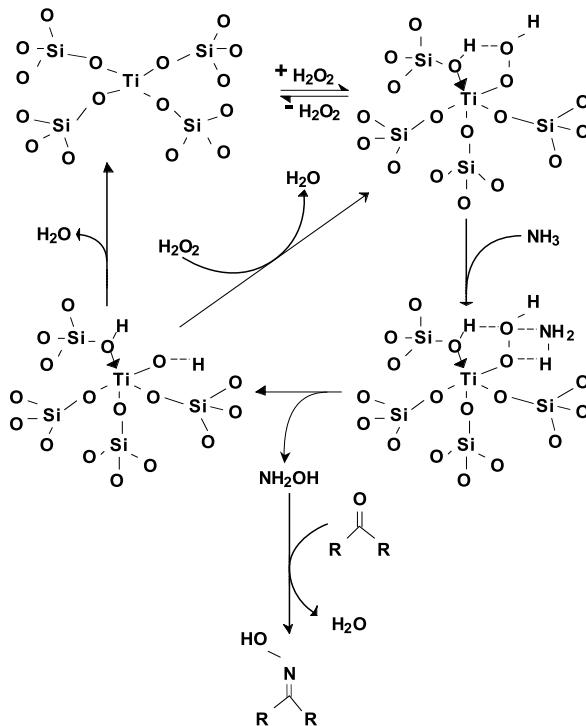
FIGURE 6.8 Mechanism of rate enhancement from methanol in alkene epoxidation.^{37,38}

FIGURE 6.9 Proposed mechanism for epoxidation of allyl alcohols.¹⁶

In the absence of alcohol solvents, hydrogen peroxide is thought to coordinate with Ti by displacing an Si–O bond as shown in Fig. 6.11. This sets the stage for ammonia interaction to form hydroxylamine and subsequent ammoximation of ketones to oximes.^{20,56,57}

Hydroxylation of benzene appears to proceed through an electrophilic aromatic substitution since electronwithdrawing substituents cannot be hydroxylated with TS-1 and H_2O_2 .³⁶ A possible rationale for this mechanism comes

FIGURE 6.10 Mechanism of alcohol oxidation.^{47,49}

FIGURE 6.11 Mechanism for ammoximation of ketones.²⁰

from the suggestion that the Ti(IV) is isolated in the hydrophobic environment of the silicalite and acts like a Lewis acid. When H_2O_2 coordinates with the Ti, its electron density is lowered, rendering it susceptible to nucleophilic attack.³¹ One might imagine that coordinated amines would attack similarly.

On the other hand, because of their inertness, alkanes probably oxidize by a radical mechanism⁵² shown in Fig. 6.12. If this is so, then it is uncertain how methanol would increase the rate of this reaction. Perhaps by complexing to Ti as in Fig. 6.8, it facilitates homolytic cleavage of the peroxy species or transfer of the OH radical to the alkyl radical.

6.1.4. OTHER METAL-FRAMEWORK OXIDATION CATALYSTS

The discovery that Ti(IV) incorporated into the framework of zeolites produces an outstanding oxidation catalyst stimulated the incorporation of other

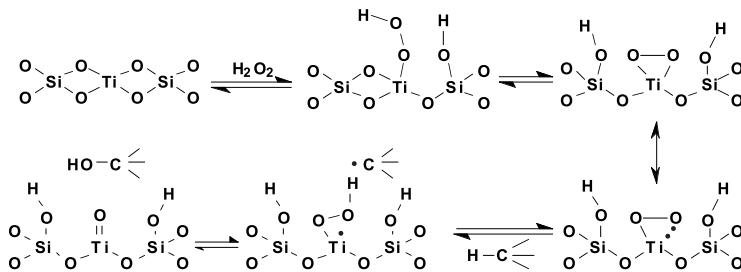


FIGURE 6.12 Suggested radical mechanism for oxidation of alkanes.^{33,36,55}

metals into zeolites. One of the most popular is vanadium.^{54,58–63} Other metals studied are Sn,^{63–65} Cr,^{63,66,67} Mo,⁶⁸ Fe,⁶⁵ Ga,⁶⁵ In,⁶⁵ and Zr.⁶⁹ None of these, however, exhibit the stability, recyclability, or catalytic activity of TS-1.³¹

6.2. OXIDATIONS WITH O₂, O₃, AND OTHER REAGENTS

Effective catalysts for heterogeneous oxidations using O₂ are mainly Pt and Pd with some activity by Ir⁷⁰ and Ru.⁷¹ Much work has gone into alcohol oxidations that are dehydrogenations to ketones or aldehydes. Also, oxygen may be inserted at allylic positions of alkenes and these may be dehydrogenated to ketones or aldehydes.⁷² In the case of aldehydes, additional oxidation may be accomplished to produce acids.^{72,73}

Of particular interest are oxidations of unsaturated alcohols, for example, oxidation of cinnamyl alcohol to cinnamaldehyde,^{74,75} and special promoters have been added to increase selectivity (Fig. 6.13).⁷⁵ Although the functions of these promoters are still not fully understood, some authors attribute their increased selectivity to physical blocking of reaction sites. This blocking reduces the size of the active site ensemble and suppresses the tendency for alcohols to strongly adsorb and dissociate on Pt.⁷⁵

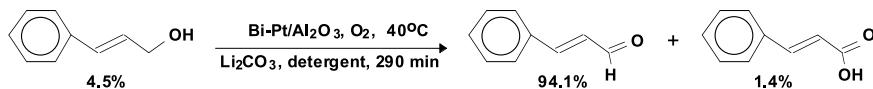


FIGURE 6.13 Bi promotion of Pt to increase selectivity of cinnamyl alcohol to cinnamaldehyde.⁷⁵

There are a few examples of O₂ oxidations catalyzed by zeolite-encapsulated complexes. Encapsulated CoPc was active in the oxidation of propene to aldehyde, whereas the free complex was inactive.⁷⁶ A triple catalytic system, Pd(OAc)₂, benzoquinone, and a metal macrocycle, was used to oxidize alkenes with molecular oxygen at room temperature.^{77,78} Zeolite-encapsulated FePc⁷⁹⁻⁸¹ and CoSalophen^{80,82} complexes were used as oxygen-activating catalysts.

Tertiary butylhydroperoxide (TBHP) is a popular oxidizing agent used with certain catalysts. Because of its size, TBHP is most effective with catalysts containing large pores; however, it can also be used with small-pore catalysts. Using first-row transition metals, Cr and V, impregnated into pillared clays, TBHP converts alcohols to ketones, epoxidizes alkenes, and oxidizes allylic and benzylic positions to ketones.⁸³⁻⁸⁷

Mn impregnated into MCM-41, a silicalite containing uniform mesopores of approximately 22 Å, catalyzes TBHP epoxidation of alkenes.⁸⁸ Over Mn-MCM-41, both *cis*- and *trans*-stilbene yield *trans*-stilbene oxide, which the authors conclude signals a radical mechanism.⁸⁸ In contrast, over Ti-MCM-41, *trans*-stilbene cannot be oxidized, only *cis*-stilbene is epoxidized to the *cis*-stilbene oxide, which suggest a radical-free mechanism.⁸⁹ Finally, emphasizing the shape selectivity possibilities, only *trans*-stilbene (not *cis*-stilbene) can be epoxidized over Mn-ZSM-5, a zeolite with relatively small pores of 5.1 x 5.4 Å (Fig. 6.14).⁸⁸

Because of current interests in ecology and the environment, a re-emerging body of work consists of the catalytic oxidation of wastewaters.⁹⁰ Since many of the water pollutants are unknown, special terminology has grown up with the field. For example, BOD (biochemical oxygen demand), COD (chemical oxygen demand), ODI (oxygen demand index), TIC (total inorganic carbon), TOC (total organic carbon), and TC (total carbon) are terms used to describe the presence of oxidizable materials under specific analytical conditions. Because it is difficult to completely oxidize phenol and because it is a relatively common water pollutant, phenol is frequently studied as a model compound.⁹⁰⁻⁹⁸

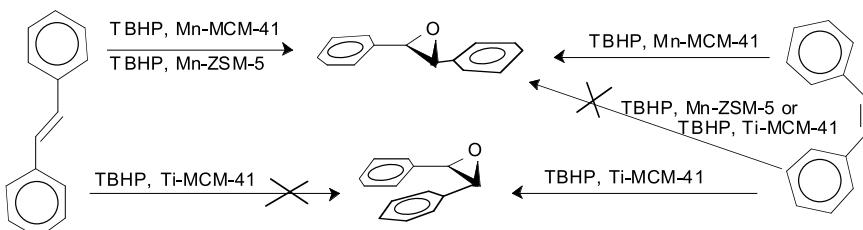


FIGURE 6.14 Epoxidations of stilbenes over Mn- and Ti-containing zeolites.^{88,89}

Various strategies have been devised to catalytically eliminate organic materials from wastewaters, such as a Pt-Ru/C bimetallic catalyst plus oxygen,⁹⁰ catalysts plus oxygen in supercritical water,^{99,100} catalysts plus hydrogen peroxide,¹⁰¹ catalysts plus oxygen plus ultrasound^{97,98} and catalysts plus ozone.^{97,102,103}

Ozone has been little studied in connection with heterogeneous catalysts, likely because it is such a strong oxidizing agent on its own.¹⁰³ However, ozone is an even better oxidizing agent when used with certain heterogeneous catalysts than without them. Some evidence suggests that two atoms of oxygen may be utilized when ozone is used in combination with certain heterogeneous catalysts.¹⁰³

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Immobilized Homogeneous Catalysts

- 7.1. Immobilization by Different Methods
- 7.2. Enantioselective Immobilized Catalysts
- 7.3. Surface Organometallic Chemistry

References

Catalysis can be characterized by the competition between homogeneous and heterogeneous systems. Heterogeneous catalysts are preferred for industrial processes because they can be easily separated and reused in a subsequent cycle. Homogeneous catalysts, however, have identical catalytic sites and usually have high selectivity. Consequently, heterogenizing homogeneous catalysts by immobilization is a trend toward the development of chemically homogeneous but physically heterogeneous catalysts.

7.1. IMMOBILIZATION BY DIFFERENT METHODS

7.1.1. ATTACHMENT TO POLYMER SUPPORTS

Poly(styrene–divinylbenzene) copolymers can be used as catalyst supports. Attachment of catalytic groups to the polymer supports can be achieved by

well-known organic and organometallic synthesis routes. For example, metal-containing polymers can be prepared by ligand exchange of metal complexes with poly(styrene–divinylbenzene) containing phosphine groups (Scheme 7.1).

The functionalized polymers have catalytic properties similar to those of their soluble analogues.¹ A solution-like character is characteristic of polymer gels. As polymers become more highly cross-linked, they lose the solution-like character and their properties approach of those of inorganic solids.

Homogeneous nickel catalysts has been used in the oligomerization of olefins. These complexes were heterogenized by anchoring to cross-linked polystyrene resins through a carbon atom of the ligand. The heterogenization caused, however, a drastic change of the process as ethylene polymerization instead of oligomerization was observed.^{2,3} A Rh-based, polymer-supported hydroformylation catalyst was prepared and the activity and stability of this catalyst compares favorably with that of other heterogeneous hydroformylation catalysts.⁴

Organonickel(II) complexes were anchored by covalent bonds to polymers⁵ and onto the periphery of highly branched macromolecules called dendrimers.⁶ Autoxidation of thiols was catalyzed by thermoelastic polyurethane resin containing a Co(II)–phthalocyanine⁷ (Pc) and by Co(II)–phthalocyaninetetrasulfonate bound to cationic latexes.⁸ Polyaniline-supported cobalt salen (CoSalen) was used for the synthesis of the pyrrolidine-containing α -hydroxyamide core structure.⁹ The antimycotic agent terbinafine was synthesized from allyl acetate and an amine with the aid of a polystyrene-supported Pd(PPh_3)₄ catalyst, but the turnover rate of the reused catalyst dropped dramatically.¹⁰ Fe(III)– and Mn(III)–porphyrin complexes bound to the surface imidazole and pyridine groups on solid supports (polystyrene and modified silica) were efficient catalysts for the epoxidation of cyclooctene by PhIO.¹¹

Polymer-supported catalysts often have lower activities than the soluble catalysts because of the intraparticle diffusion resistance. In this case the immobilization of the complexes on colloidal polymers can increase the catalytic activity. Catalysts bound to polymer latexes were used in oxidation reactions, such as the Cu-catalyzed oxidation of ascorbic acid,¹² the Co-catalyzed oxidation of tetralin,¹³ and the CoPc-catalyzed oxidation of butylphenol¹⁴ and thiols.^{15,16} Mn(III)–porphyrin bound to colloidal anion exchange resin was



SCHMENE 7.1

used for the epoxidation of styrene.¹⁷ Co(II)Salen-disulfonate was also bound to a similar resin and used for the oxidation of phenols.¹⁸ Mo(VI)-grafted carboxylated resins were used as epoxidation catalysts.¹⁹ Polymers, functionalized by bipyridyl and acetylacetone, were used as ligands for the preparation of Fe(III) and Co(II) complexes, which showed high activity and selectivity in the oxidation of cyclohexane.²⁰

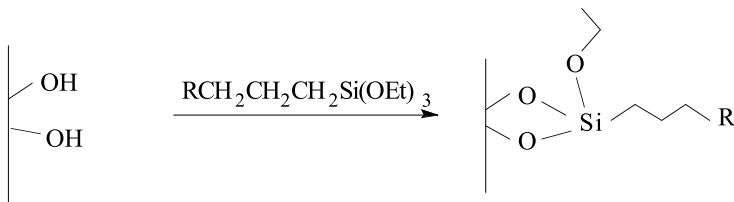
7.1.2. CATALYSTS ANCHORED TO INORGANIC SOLIDS BY COVALENT BONDS

It has been accepted that inorganic solids, unlike polymers, prevent the intermolecular aggregations of the active surface species because of their rigid structures. Therefore, the attachment of metal complexes to an inorganic solid support by covalent bonds is one of the simplest routes to produce physically heterogeneous catalysts with active sites identical to those of homogeneous systems.²¹ It is achieved, however, only rarely. In many cases, the supported catalysts have different chemical structures, because if the bond is too strong, the anchoring process often induces modification of the coordination sphere and the oxidation state of the metal. Too-weak bonds, however, usually lead to leaching of the metal. In most cases the structural change causes severe reduction of the catalyst activity. Therefore, at present, the heterogenization is a way of preparing new catalysts with controlled structure rather than a simple way to physical heterogenization.³ The catalysts contains organic and inorganic materials and are often referred to as *hybrid catalysts*.

Zeolites and clays are special inorganic solids, because they have well-defined structures and pores with molecular dimensions, which can solvate the adsorbed molecules and provide solvent-like environments. Catalysis occurs within these pores; that is, they are transitions between solutions and typical solids. It is well known that homogeneous organometallic complexes are bad catalysts for the hydrogenation of aromatic hydrocarbons. It was found, however, that Rh and Ni complexes covalently bonded to zeolites containing supermicropores can hydrogenate aromatics with high efficiency under very mild conditions.²² The influence of the zeolite was explained as a cooperative effect owing to an increase of the concentration of reactants inside the pores.

Silica is the most commonly used solid support. Treatment with complexes bearing alkoxy- or chlorosilane functional groups is a common way to generate supported complexes on silica or any inorganic oxide containing surface silanol (Si-OH) groups (Scheme 7.2).^{23,24}

The reaction of preformed cyanoalkylsilane with silica gel followed by hydrolysis leads to the formation of chemisorbed carboxylic acid groups that are capable of strongly binding metal ions including Cu(II), Mn(II), Ni(II),



SCHEME 7.2

and Co(II).²⁵ A silica-supported Co(II) catalyst was used for the oxidation of alkylaromatics and the epoxidation of alkenes.²⁶

Metalloporphyrinosilicas as a new class of hybrid organic–inorganic materials were prepared by polymerization of 3-*tert*-butyl-5-vinylsalicylaldehyde with styrene and divinylbenzene and used as selective biomimetic oxidation catalyst.²⁷ Synthesis and structural characterization of rare-earth bis(dimethylsilyl)amides and their surface organometallic chemistry on mesoporous silicate MCM-41 have been reported.²⁸

The external surface of zeolites is also considered to feature mainly silanol groups. Cl- and aminopropylsiloxanes have been attached with strong covalent bonds to zeolite Y, and the grafted groups can be functionalized by further reaction to generate imino and benzamido groups.²⁹ Rh complexes heterogenized to ultrastable Y zeolite (USY zeolite) by the Si(OEt)₃ sticky end were used for regiospecific hydrosililation of styrene.³⁰ The supported catalyst presents enhanced stability and increased selectivity and is a real alternative to classical homogeneous hydrosililation catalysts. Heterogenized Rh complexes are also useful in hydroboration reactions.³¹ Organonickel(II) complexes were anchored by covalent bonds to silica.³²

Silica-supported metal (e.g., Pd/SiO₂) catalysts also have surface silanol groups that can react with the alkoxy silane groups of the complexes. These combination catalysts consist of a tethered complex on a supported metal. A Rh complex was tethered to the surface of a Pd/SiO₂ catalyst, and the tethered catalyst was more active for the hydrogenation of aromatic compounds than the free complex or the supported catalyst separately.³³ It is possible that the H₂ is activated on the supported metal and the hydrogen atoms migrate to the silica, where they react with the reactant molecules coordinated by the tethered complex.

Molybdenum allyl complexes react with surface OH groups to produce catalysts active for olefin metathesis.^{34,35} Using silica as a support for the heterogenization of Ti and Zr complexes for the polymerization of ethylene did not give clear results.³⁶ In these cases, HY zeolite appeared to be a more suitable support. The comparable productivity of the zeolite-supported catalyst with

respect to the system in solution is a consequence of the better stability of the active species. Rh phosphonate carbonylation catalysts were supported on carbon, silica, or alumina and carbon was found to be the most suitable support.³⁷

Catalytic transfer hydrogenolysis, both in liquid and in vapor phases, is a widely used reaction in organic chemistry.³⁸ Especially the hydrogen transfer between ketones and secondary alcohols has been studied in detail. Alkoxides of aluminum, zirconium, and lanthanides were used as homogeneous catalysts in this reaction. Oxides as Al_2O_3 , chlorinated alumina, and Zr_2O were also used as heterogeneous catalysts, but large amounts of these solids were necessary.³⁹⁻⁴¹ In the vapor phase, the MgO is an excellent catalyst in spite of its deactivation.⁴² The deactivation of MgO may be prevented by treatment with carbon tetrachloride.^{43,44} The first heterogenization of the homogeneous hydrogen transfer catalysts by anchoring them to a solid oxide surface via covalent bonds was made by Inada and associates.⁴⁵ A synthesis that can produce isolated surface alkoxyzirconium complexes has been reported.⁴⁶ The $\equiv\text{SiOZr}(\text{OiPr})_3$ surface complexes synthesized by this method were efficient catalysts for the Meerwein-Ponndorf-Verley reduction of ketones and the Oppenauer oxidation of alcohols.

7.1.3. ENCAPSULATED CATALYSTS

Supporting homogeneous catalysts on solid materials by covalent bonds is an obvious method but has often led to unsatisfactory results. Metal macrocycles encapsulated in zeolites also combine successfully the advantages of the homogeneous and the heterogeneous catalysts and they are free from the previously mentioned problems, because in these catalysts the metal macrocycles are trapped in the zeolite cages topologically rather than chemically. If the cages are large enough, the metal complexes should be free to move about within the confines of the cavities but prevented from leaching by small pore openings. The term *ship-in-a-bottle complex*⁴⁷ is widely used for these encapsulated catalysts. The name *zeozyme* (zeolite-based enzyme)^{48,49} is also used because these catalysts are structural models of enzymes. These complexes may retain their solution-like activity, and the zeolite is also expected to impart shape selectivity to the catalyst. The zeolite should also provide a stabilizing effect by blocking bimolecular deactivation pathways (*site isolation effect*).

Metal macrocycles encapsulated in zeolites can be synthesized in different ways.⁵⁰⁻⁵³ The *flexible ligand*⁵¹ or *intrazeolite complexation*⁵³ method involves the diffusion of a ligand into the pores of a metal-exchanged zeolite, where upon complexation with the metal ion, it becomes too large to exit. This

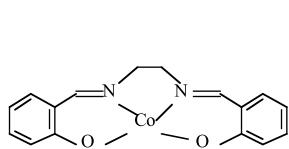
approach is suitable for the preparation of encapsulated metal-Salen complexes. The *template synthesis*⁵¹ or *intrazeolite synthesis*⁵³ method involves the diffusion of ligand precursors into the zeolite pores where they assemble around an intrazeolite metal ion that acts as a template. The basis of the *zeolite synthesis method*⁵¹ is building the bottle around the ship by crystallization of the zeolite around a *metal complex* which serves as a *template for zeolite synthesis*.⁵³ This affords the advantage of encapsulating a well-defined intrazeolite complex without contamination from free ligand as well as uncomplexed metal ions. The high degree of metal complexation is very important for high selectivity because the unchelated metal ions can catalyze side reactions. The method is restricted to metal complexes, e.g. metallophthalocyanines, that are stable under the relatively harsh conditions of the zeolite synthesis.

The first *ship-in-a-bottle* type of catalyst was synthesized by Romanovsky, and Zakharov and colleagues in 1977.^{54,55} Encapsulation of different metal phthalocyanines and the reactivity of these catalysts were studied by this^{56–63} and other research groups.^{64–68}

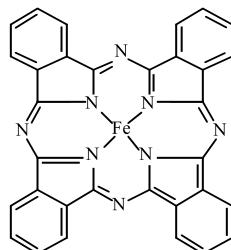
The major types of complexes under intense investigation are the tetradentate Schiff base, for example, CoSalen, and phthalocyanine, for example, iron phthalocyanine complexes (Fig. 7.1).⁶⁹

The physicochemical properties of Schiff-base complexes encapsulated in zeolite⁷⁰ and the surface chemistry of zeolite-encapsulated CoSalen and $[Fe(bpy)_3]^{2+}$ catalysts were studied and published.⁷¹

CoSalen Y carries oxygen as a cargo.⁷² The catalytic properties of the zeolite-encapsulated metal complexes depend mainly on the complexed metal atoms, which are used usually as oxidation catalysts but other applications are also beginning to emerge. The zeolite-encapsulated catalysts can be regarded as biomimetic oxidation catalysts.⁷³ In liquid-phase oxidation reactions catalyzed



Cobalt salen (CoSalen)



Iron phthalocyanine (FePc)

FIGURE 7.1

by *ship-in-a-bottle* catalysts, usually monooxygen donor reagents (peroxides or iodosylbenzene) are used as oxidants.

The first room temperature oxidation using encapsulated catalysts was reported by Herron and colleagues.⁷⁴ They oxidized alkanes by iodosylbenzene, catalyzed by iron–phthalocyanine encapsulated in zeolite. In a competitive experiment, cyclohexane was preferentially oxidized over cyclododecane. The oxidation of octane favored the 2 position, which is the result of the orientation effects in the zeolite. Although the activity of intrazeolite FePc was greater than that of the free complex, it was still rather poor. The reason is that the iodosylbenzene leads to zeolite pore blockage. Parton and associates reported that FePc in zeolite and *t*-butyl hydroperoxide were used for the oxidation of alkanes⁷⁵ and cycloalkanes.⁷⁶ The resistance of the encaged complex against oxidative destruction exceeds by far those of free iron–phthalocyanine. The peroxides, however, can bleach the catalysts unless added slowly. The oxidation of *cis*-pinane by *t*-butyl hydroperoxide was catalyzed by zeolite-encapsulated FePc and CoPc catalysts.⁷⁷ FePc and CoPc were used for the epoxidation of cyclohexene with H₂O₂.^{78,79} Ascorbic acid was oxidized by zeolite-encapsulated Cu(II) complexes.⁸⁰ Thiols were oxidized by zeolite-encapsulated phthalocyanines.⁸¹

Electron-withdrawing substituents increase the catalytic activity of the FePc complexes because the central metal ion becomes easier to reduce via inductive effects. Whereas all the Cu ions in nonchlorinated CuPc are in the divalent state, 25% of the Cu ions in CuCl₁₄Pc are in the monovalent state.⁸² At the same time, replacing the abstractable hydrogens by electron-withdrawing halogen atoms reduces the possibility of oxidative degradation.⁸³ The perfluorinated phthalocyanine complexes of Fe⁸⁴ as well as Co and Cu⁸⁵ showed enhanced catalytic activity and oxidative stability when they were encapsulated. The Cu(II)–Cu(I) redox process was well defined, likely as a consequence of the site isolation. The intrazeolite FeF₁₆Pc complex was active for the oxidation of cyclohexane but was easily deactivated with excess peroxide. It was found, however, that F₁₆Pc complexes of Ru(II) encapsulated in zeolite were active in the room temperature oxidation of alkanes using *t*-butyl hydroperoxide as oxygen donor^{86–88} and the catalyst show no sign of deactivation, in contrast to the iron analogues.

Encapsulated Cu–chlorophthalocyanines oxidize hexane at C-1 using O₂ and at C-2 using H₂O₂ as oxidants. The dimeric structure of copper acetate is intact when it is incorporated into the zeolite. This is a regioselective aromatic hydroxylation catalyst, which mimics the specificity of the monooxygenase enzyme tyrosinase.^{82,89} Zeolite NaY catalysts made with a tetranuclear Cu(II) complex were synthesized and characterized.⁹⁰

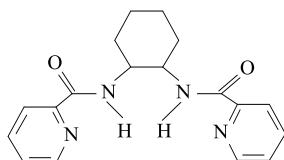
Chelation of zeolite Mn²⁺ by N-containing ligands gives rise to good heterogeneous liquid-phase oxidation catalysts. Mn(II)Salen Y catalyzes the selective

oxidation of olefins with PhIO to epoxides.⁹¹ High selectivity was observed but the low solubility of the oxidant in the reaction medium did not allow high rates. FeSalen and MnSalen were used for the oxidation of cycloalkenes with H₂O₂.⁹² Also, the more soluble H₂O₂ was used with encapsulated Mn(II)-bipyridyl complexes. These complexes can catalyze the oxidation of cyclohexene to adipic acid using 30% aqueous H₂O₂ as the oxidant at room temperature.^{93,94} The optimized catalyst preparation method allowed the preparation of one *cis*-[Mn(bpy)₂]²⁺ complex per supercage. The reaction proceeds via epoxidation followed by ring opening to 1,2-diol and subsequent oxidative cleavage. These catalysts are active, selective, and stable epoxidation catalysts for the epoxidation of alkenes with diluted H₂O₂ as oxidant.⁹⁵ The only deactivation is found to be adsorption of the very polar side products. The encapsulation of [Ru(II)(bpy)₃]²⁺ in the zeolite cage prevents the formation of dinuclear complexes; the free coordination sites are taken up by the lattice oxygen atoms. The [Mn(bpy)₂]²⁺ complexes can also retain their mononuclearity only when they are encapsulated in zeolites.⁹³ Metal-salen complexes encapsulated in zeolite Y were used for the hydroxylation of phenol.⁹⁶ Oxidizing properties of zeolite-encapsulated Ru-bipyridyl complexes⁹⁷ and the emission of zeolite-occluded manganese-di-imine complexes were also studied.⁹⁸

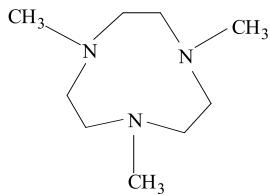
A new class of oxidation catalysts is prepared by complexation of metal-Y zeolites with tetradentate *N,N'*-bis(2-pyridinecarboxamide) derivatives (Scheme 7.3).

Iron *N,N'*-bis(2-pyridinecarboxamide) complexes encaged in zeolite Y were used for the partial oxidation of alkanes.⁹⁹ Epoxidation with manganese *N,N'*-bis(2-pyridinecarboxamide) complexes encapsulated in zeolite Y was also reported.¹⁰⁰

The vanadium(IV) complex of salen in zeolite was found to be an effective catalyst for the room temperature epoxidation of cyclohexene using *t*-butyl hydroperoxide as oxidant.⁸⁸ Well-characterized vanadyl bis-bipyridine complexes encapsulated in Y zeolite were used as oxidation catalysts.¹⁰¹ Ligation of manganese ions in zeolites with 1,4,7-triazacyclononanes gives rise to a binuclear complex stabilized by the zeolites but allows oxidation with excellent selectivity (Scheme 7.4).



SCHEME 7.3

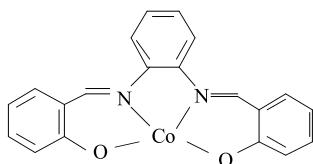


SCHEME 7.4

By complexation of MnNaY with 1,4,7-trimethyltriazacyclononane, a new heterogeneous catalyst was obtained for olefin epoxidation with H₂O₂.¹⁰² Excellent epoxide selectivities were obtained, with limited epoxide solvolysis. The oxygenation appears to go through a radical intermediate. The manganese trizacyclononane epoxidation catalyst was also heterogenized via surface glycidylation.¹⁰³

Dioxygen is a cheap and ideal source of oxygen but it is very difficult to activate and there are relatively few examples of O₂ oxidations catalyzed by zeolite-encapsulated complexes. Encapsulated CoPc is active for the oxidation of propene to aldehyde, whereas the free complex is inactive.¹⁰⁴ A triple catalytic system, Pd(OAc)₂, benzoquinone, and a metal macrocycle, was used to oxidize alkenes with molecular oxygen at room temperature.¹⁰⁵ Zeolite-encapsulated FePc^{106–108} and CoSalophen (Scheme 7.5)^{107,109} complexes were used as oxygen-activating catalysts. With the use of a Ru complex instead of Pd(OAc)₂ in the triple catalytic system, primary alcohols can be oxidized selectively to aldehydes.¹¹⁰

For the preparation of CoSalophen Y the Co–Y was impregnated by salicylaldehyde, and 1,2-phenylenediamine in methanol was added slowly to the mixture.¹⁰⁷ This was a successful encapsulation of a salen-type complex with larger diamine than the ethylenediamine, a successful preparation of an encaged metal–salen complex by the intrazeolite ligand synthesis method, and a successful intrazeolite synthesis using two different precursor molecules.



CoSalophen

SCHEME 7.5

The encapsulated complexes were used in hydrogenation reactions, too. A mixture of cyclohexene and 1-hexene are hydrogenated in nearly equal amounts by the free PdSalen complex, whereas the zeolite-encapsulated PdSalen hydrogenated only the 1-hexene in the same mixture.¹¹¹ Zeolite-encapsulated PdSalen was more selective for the hydrogenation of cyclooctadiene to cyclooctene than Pd on carbon.¹¹² RuSalen Y is much more active for the hydrogenation of alkenes than RhSalen Y or PdSalen Y. The hydrogenation of 1-alkenes is strongly preferred. This selectivity is not exclusively due to shape selectivity but is governed by the preferred hydrogenation of 1-alkenes over the salen complex.¹¹³ The catalytic hydrogenation of toluene to methylcyclohexane occurred in the presence of FePc encapsulated in zeolite.¹¹⁴ Benzene was unreactive under the same conditions. FePc in zeolite was also unreactive toward butadiene hydrogenation.¹¹⁵ Hydrogenation of the carbonyl group was performed over PtSalen complexes occluded in zeolites. The hydrogenation of methylpyruvate occurred at a conversion of up to 70%, whereas bulkier pyruvates showed less or no conversion.¹¹⁶ NiSalen encapsulated in zeolite was reported to be a highly efficient alkene hydrogenation catalyst.¹¹⁷

7.1.4. CATALYSTS ANCHORED BY ION EXCHANGE

Catalysis of supported metal ions is an area of interest. There are a number of advantages in depositing catalytically active metal ions on a support. The ion exchange method of catalyst immobilization is simple and the attractiveness of this method is further increased by providing stable inorganic ion exchangers of known structures as supports.

Zirconium phosphate materials are being developed as replacements for ion exchange resin catalysts. Pd-bipyridyl complexes intercalated in these materials catalyze the oxidative carbonylation of aniline but the catalyst slowly loses Pd.¹¹⁸ On the contrary, Rh³⁺ ions intercalated in zirconium phosphate are stable catalysts for the oxidation of CO.^{119,120} Rh³⁺ ions or their complexes with N-donor ligands are also stable and effective catalysts for the conversion of aniline to carbamates.¹²¹ Pd and its complexes are versatile catalysts for a wide range of chemical reactions. Zirconium molybdate, an inorganic ion exchanger, was used as a support on which Pd(II) was immobilized by the ion exchange method.¹²² The catalytic activity was studied via H₂O₂ decomposition. Aerobic epoxidation of alkenes, including terpenes, was performed under mild conditions in the presence of isobutyraldehyde as a reductant and zeolites containing Co(II), Cu(II), Ni(II), or Fe(III) ions.¹²³ CrY zeolite is found to convert cyclohexene selectively to cyclohexen-1-one by oxidation with molecular oxygen.¹²⁴ The low-temperature combustion of chlorobenzene over CuY, PdY and HPdY were studied.¹²⁵

It is well known that Rh(I) complexes can catalyze the carbonylation of methanol. A heterogenized catalyst was prepared by ion exchange of zeolite X or Y with Rh cations.¹²⁶ The same catalytic cycle takes place in zeolites and in solution because the activation energy is nearly the same. The specific activity in zeolites, however, is less by an order of magnitude, suggesting that the Rh sites in the zeolite are not uniformly accessible. The oxidation of camphene was performed over zeolites exchanged with different metals (Mn, Co, Cu, Ni, and Zn).¹²⁷ Cu-loaded zeolites have attracted considerable attention because of their unique properties applied in catalytic redox reactions.^{128–130} Four different Cu sites with defined coordinations have been found.¹³¹ It was found that the zeolitic media affects strongly the catalytic activity of the Cd²⁺ ion sites in Cd zeolites used to catalyze the hydration of acetylene.¹³²

The liquid-phase autoxidation of cyclohexane is carried out in the presence of dissolved cobalt salts. A lot of heterogeneous catalysts were developed for this process but most catalysts lacked stability. The incorporation of cobalt ions in the framework of aluminophosphate and aluminosilicate structures opens perspectives for heterogenization of this process. CoAPO (cobalt aluminophosphate) molecular sieves were found to be active heterogeneous catalysts of this oxidation.¹³³ Site isolation was critical to get active catalysts.¹³⁴

In the classic homogeneous Wacker oxidation process, the alkene is oxidized to aldehyde by Pd²⁺, the Pd⁰ is reoxidized by Cu²⁺, and the resulted Cu⁺ is oxidized by molecular oxygen. To overcome the disadvantages of the homogeneous process, various types of alternative systems have been developed. Pd/CuY zeolite has been shown to be active for the Wacker-type oxidation and the mechanism was found to parallel that of the homogeneous system.¹³⁵ On Pd-doped V₂O₅ catalyst, Pd²⁺ complexes are the catalytic centers, whereas the redox groups are provided by the V₂O₅ surface.¹³⁶ Zeolite Y containing Pd²⁺ and Cu²⁺ is also an effective bifunctional catalyst, in which Pd²⁺ can oxidize the ethylene and Cu²⁺ can reoxidize the reduced Pd.¹³⁷ Heteropoly compounds containing Mo have been found to enable the reoxidation of reduced Pd.^{138–141} It was found that the oxidation of ethylene to acetaldehyde in the heteropolyanion system is much faster than in the classic system. Pd salts of heteropolyanions supported on silica were used as catalysts in the gas-phase Wacker oxidation of 1-butene.¹⁴² In such catalysts the Pd reaction center (Pd²⁺) and the redox component heteropolyanions (HPA) are combined in one complex. The reoxidation of the reduced HPA by dioxygen is the rate-determining step. The Pd²⁺–Mn²⁺–heteropolyanion system was also used as a heterogeneous Wacker catalyst.¹⁴³ Interaction of the heteropolyanion with Cu(II) was studied in the oxidation of cyclohexene.¹⁴⁴ Pd-exchanged zeolite Y was used as catalyst for the palladium-catalyzed aerobic oxidation of 1-octene to 2-octanone in a triple catalytic cycle involving the Pd(II)/Pd(0)–*p*-benzoquinone/hydroquinone–metal macrocycle^{ox}–metal macrocycle redox system.¹⁴⁵ Polymer-supported

Pd(II) Wacker-type catalysts were also studied.¹⁴⁶ Selective oxidation of benzene to phenol by molecular oxygen in the presence of Pd and heteropolyacids have been published.¹⁴⁷

7.1.5. CATALYSIS BY LAYERED MATERIALS

Intercalation into layered materials is also a promising method for the heterogenization of macrocycles. The swelling silicates generally referred to as *smectites* (e.g., montmorillonite, hectorite) can be described as layers containing two sheets of silica with an interlayer containing octahedral aluminum. Substitution of the tetrahedral silica with tetrahedral alumina results in a negative charge on the clay. The charge-balancing cations are mainly Na^+ or Ca^{2+} . These cations can be replaced by simple ion exchange with almost any desired cation, including transition-metal ions or cationic complexes. Layered silicate clays can be pillared by the intercalation of inorganic polymeric cations. Pillared clays can provide large-pore two-dimensional networks. Butenonitriles were hydrogenated selectively to butyronitrile on palladium-exchanged titanium-pillared montmorillonite.¹⁴⁸

The intercalated catalysts can often be regarded as biomimetic oxidation catalysts. The intercalation of cationic metal complexes in the interlamellar space of clays often leads to increased catalytic activity and selectivity, due to the limited orientations by which the molecules are forced to accommodate themselves between sheets. The clays have electrostatic fields in their interlayer; therefore, the intercalated metal complexes are more positively charged. Such complexes may show different behavior. For example, cationic Rh complexes catalyze the regioselective hydrogenation of carbonyl groups, whereas neutral complexes are not active.¹⁴⁹ *Cis*-Alkenes are hydrogenated preferentially on bipyridyl-Pd(II) acetate intercalated in montmorillonite.¹⁵⁰ The same catalyst was also used for the reduction of nitrobenzene.¹⁵¹

Cationic Rh-triphenylphosphine complexes can be incorporated in hectorite and montmorillonite.^{152–154} The complexes were active for the hydrogenation of alkenes and alkynes. A small amount of metal complex is desorbed from the intercalated catalyst during the reaction. The Rh_2^{4+} intercalated in hectorite was active, whereas without phosphine ligands it was inactive in homogeneous circumstances.¹⁵² A heterogenized Rh(I)-triphenylphosphine complex was prepared by ion exchange of bentonite with Wilkinson complex, $[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{RhCl}$, and it was found that the active species were situated on the external surface of the catalyst.¹⁵⁵

The positively charged phosphonium ligand was intercalated in the hectorite and was used to catalyze olefin hydroformylation.¹⁵⁶ Cu(II)-exchanged clays were tested as catalysts in the cyclopropanation reaction of styrene with

ethyl diazoacetate.¹⁵⁷ K10 montmorillonite exchanged with Cr(III) was used as a catalyst in Diels-Alder reactions.¹⁵⁸

The catalytic application of clays is related closely to their swelling properties. Appropriate swelling enables the reactant to enter the interlamellar region. The ion exchange is usually performed in aquatic media because the swelling of clays in organic solvents, and thus the expansion of the interlayer space, is limited and it makes it difficult for a bulky metal complex to penetrate between the layers. Nonaqueous intercalation of montmorillonite with a water-sensitive multinuclear manganese complex was achieved, however, with the use of nitromethane as solvent.¹⁵⁹ The complex cation is intercalated parallel to the sheets.

When organic cations (e.g., cationic tensides) are employed, clay organo-complexes are formed, which can be used in organic solvents. A Pd-hexadecylammonium montmorillonite catalyst was prepared by the reduction of $\text{Pd}(\text{OAc})_2$ by ethanol in the interlamellar space. At small ethanol concentrations in toluene, selective interlamellar sorption of ethanol was established; consequently, the reduction also occurred only in the interlamellar space.¹⁶⁰ The catalyst was used for the hydrogenation of alkenes.¹⁶¹

The structure of the layered double hydroxides is the reverse of that of the clays. They are anionic materials in which the sheets are intercalated with anions instead of cations. These ions can be exchanged with several different anions. The cationic nature of the layers lends itself to pillaring by large Keggin anions.

Anionic complexes can easily be prepared by the sulfonation of the aromatic rings in the complexes. Sulfonated cobalt phthalocyanine intercalated in a layered double hydroxide host was a stable catalyst for the oxidation of thiols^{162,163} and phenol derivatives.¹⁶⁴ It was concluded that the complex has been intercalated with the plane of the phthalocyanine ring perpendicular to the sheet of the host (*edge-on* orientation) (Fig. 7.2).

The catalyst effectiveness decreased upon increasing the concentration of the intercalated complexes via aggregation of the closely associated complexes.¹⁶⁴ Sulfides were also oxidized by heterogeneous Co(II) complexes.¹⁶⁵ Catalytic oxidation of thiols was mediated by Mo complex intercalated in a layered double hydroxide.¹⁶⁶

7.1.6. CATALYTIC MEMBRANES

Faujasites are highly hydrophilic materials. In the transformation of apolar compounds such as hydrocarbons, all other molecules have higher polarity, so the rate of transformation is seriously decreased because the more polar products adsorb preferentially on the zeolite. This was a serious problem in the oxidation

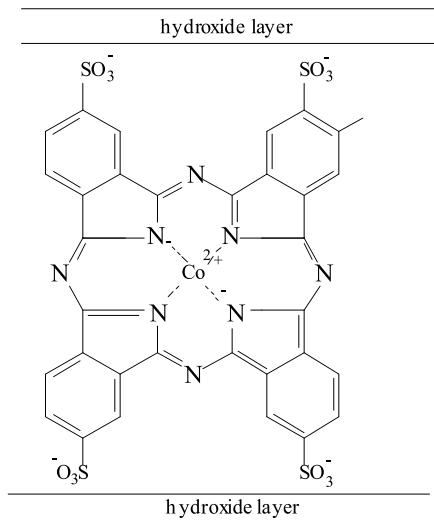


FIGURE 7.2

of alkanes using FePcY catalysts. FePc was also immobilized on activated carbon.¹⁶⁷ In this case, the deactivation by sorption was strongly suppressed but, in contrast to zeolites, the complexes are not protected and deactivation occurred by oxidative destruction of the complex.¹⁶⁸ This problem can be solved by embedding the zeolite-encapsulated catalyst in a hydrophobic poly-dimethylsiloxane (PDMS) membrane. It is a cheap and easy-to-prepare polymer and additionally it is one of the most hydrophobic polymers. This membrane preferentially sorbs the apolar compounds and acts as a reservoir for apolar molecules. Furthermore, the flexible siloxane chains provide fast mass transfer through the membrane.

Moreover, the membrane could be mounted as an interface between the apolar substrate and the polar oxidant in a membrane reactor, avoiding the use of any solvent. Dilution of the reagents by solvent and competition between solvent and reagents on the active sites can thus be avoided. In the countercurrent membrane reactor, the substrate and the oxidant are circulated at each side of the membrane and alkanes can be oxidized with peroxides without solvents. Of course, the system carries all of the other advantages of membrane reactors: continuous operation and easy separation.

The PDMS-membrane-occluded FePcY was the first room temperature catalytic membrane and the first solid catalyst dispersed in dense organic polymer.¹⁶⁹ The catalytic system mimics the cytochrome P-450 enzyme and can oxidize alkanes at room temperature with rates comparable to those of the

enzyme.^{170,171} It was found that the reaction in the membrane was not controlled by diffusion. FePc without a zeolite mantle was also incorporated into the membrane. Autoxidation occurred, especially in the presence of good swelling agents. These results confirm that the zeolite plays an important role in the protection of the active sites. $[\text{Mn}(\text{bpy})_2]^{2+}\text{-Y}$ was also incorporated into PDMS polymer matrix and was used for the epoxidation of alkenes.^{94,172}

The FePcY-PDMS supramolecular catalyst resembles the architecture of natural enzymes. In this system the PDMS membrane takes over the role of the phospholipid double layer; likewise, the zeolite imitates the protein and the FePc complex the Fe-protoporphyrin. Zeolite-encaged Cu-histidine complexes were also studied as mimics of natural Cu-enzyme complexes.¹⁷³

7.2. ENANTIOSELECTIVE IMMOBILIZED CATALYSTS

The production of enantiomerically pure products is of great importance in chemical industry. The most desirable way to obtain these products is by chiral catalysis. Homogeneous complexes can often be used as chiral catalysts; however, because of their difficult regenerability, the development of heterogeneous chiral catalysts by immobilization of these complexes is difficult but highly desired.

7.2.1. CHIRAL COMPLEXES ANCHORED BY COVALENT BONDS

The insoluble polymer-supported Rh complexes were the first immobilized chiral catalysts.^{174,175} In most cases, however, the immobilization of chiral complexes caused severe reduction of the catalytic activity. Only a few investigations of possible causes have been made. The pore size of the insoluble support and the solvent may play important roles. Polymer-bound chiral Mn(III)Salen complexes were also used for asymmetric epoxidation of unfunctionalized olefins.^{176,177}

A chiral diphosphine ligand was bound to silica via carbamate links and was used for enantioselective hydrogenation.¹⁷⁸ The activity of the neutral catalyst decreased when the loading was increased. It clearly indicates the formation of catalytically inactive chlorine-bridged dimers. At the same time, the cationic diphosphine-Rh catalysts had no tendency to interact with each other (*site isolation*).¹⁷⁹ New cross-linked chiral transition-metal-complexing polymers were used for the chemo- and enantioselective epoxidation of olefins.¹⁸⁰

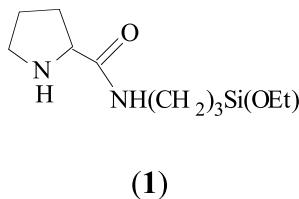


FIGURE 7.3

Zeolite-anchored complexes may exhibit a greater activity and selectivity in chiral catalysis. This has been demonstrated by Corma and colleagues.^{181–184} They prepared a chiral ligand from L-proline (1 in Fig. 7.3).

Rh and Ni complexes of this ligand were anchored to the silanol groups of silica and a USY zeolite. The catalysts were used in the hydrogenation of N-acyldehydrophenylalanine derivatives (Scheme 7.6).

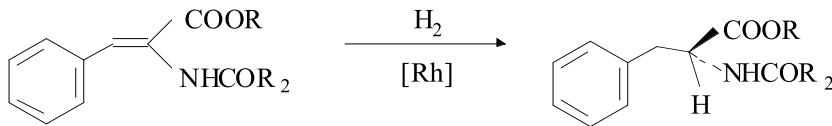
On silica, the rate was lower than in the case of the free complex. The zeolite, however, shows a cooperative effect on the rate and on enantioselectivity of the reaction. The positive effect on the rate can be related to the strong capacity of the zeolite to adsorb H₂. These zeolite-anchored complexes can also be recycled without loss of activity.

Chiral dioxomolybdenum complexes were synthesized from (2*S*,4*R*)-4-hydroxyproline and connected to the surface of USY zeolite by covalent bonding (2 in Fig. 7.4).

The catalyst was used for the epoxidation of allylic alcohols at room temperature using *t*-butyl hydroperoxide as the oxidant. The activity of the heterogenized catalyst is comparable with that of the free complex, yielding products with excellent yields and selectivity and moderate enantioselectivity.¹⁸⁵

7.2.2. ENCAPSULATED CHIRAL COMPLEXES

It was a major improvement when Jacobsen and associates subsequently Katsumuki and colleagues discovered the chiral Mn(III) complexes for the enantiose-



SCHEME 7.6

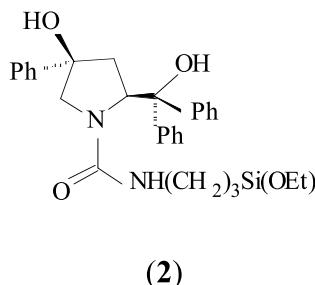


FIGURE 7.4

lective epoxidation of alkenes with high enantioselectivity.^{186–194} The catalysts have emerged as the most enantioselective epoxidation catalysts uncovered to date. The homogeneous catalyst derived from chiral 1,2-cyclohexanediamine has been prepared on a large scale.¹⁹⁵ Industrial application, however, seem to be difficult because of the limited stability of the catalyst.^{196,197} Encapsulation of the Jacobsen catalyst into the zeolite cages seems to be a way to develop more stable epoxidation catalysts. The synthesis of zeolite-encapsulated metal-Schiff base complexes was the first step in this direction.¹⁹⁸

Zeolite Y consists of almost spherical 1.3-nm supercages interconnected through 0.74-nm apertures. Molecular modeling predicts that the *N,N'*-bis(salicylidene)-1,2-cyclohexanediaminato manganese(III) complexes (approximately 1.3 nm) fit inside the supercages, whereas the Jacobsen catalyst, having four *tert*-butyl groups, needs larger cavities. Nevertheless, the similar tetra-*tert*-butyl-6-Salophen was encapsulated in Zeolite Y.¹⁹⁰

In the Jacobsen catalyst, the presence of the four *tert*-butyl groups disfavors all side-on olefin approaches with the exception of the approach from the diimine bridge (3 in Fig. 7.5).^{190,199}

Without the *tert*-butyl groups, the enantiomeric excess of the free complex is much lower. One can imagine, however, that in the case of the encapsulated catalysts the zeolite cage, instead of bulky groups, can also provide the steric constraints. Corma and co-workers synthesized the (*R,R*)-*N,N'*-bis(salicylidene)-1,2-cyclohexanediaminato manganese(III)⁺ complex (4 in Fig. 7.5) in zeolite Y by the condensation of (*R,R*)-1,2-cyclohexanediamine and salicylaldehyde around Mn(II) ions resident in the supercages and a final oxidation step.²⁰⁰ The complex was encapsulated successfully inside the supercages but the MnSalen Y resulted in lower enantiomeric excesses in every case than the corresponding homogeneous complex.

Ogunwumi and Bein synthesized the (*R,R*)-*N,N'*-bis(3-*tert*-butyl-5-methylsalicylidene)-1,2-cyclohexanediaminato Mn(III) chloride (5 in Fig. 7.6) (with

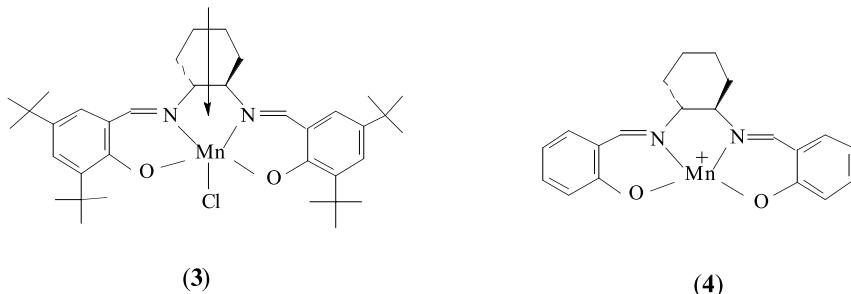


FIGURE 7.5

dimensions of approximately 1.5 nm) and the same complex without alkyl groups (6) encapsulated in zeolite EMT.^{201,202} This zeolite is a hexagonal form of the faujasite structure, and the hypercages of EMT are accessible through three 12-ring windows.

The encapsulated complex with bulky alkyl groups was more active than the complex without alkyl groups. The catalytic activity increases on the addition of axial ligands as pyridine N-oxide, and the highest enantiomeric excess, 88%, was also achieved in the presence of the pyridine N-oxide.

7.2.3. ION-EXCHANGED CHIRAL CATALYSTS

Modification of clays with metal complexes containing chiral ligands can be used for the preparation of catalysts for asymmetric reactions. Since the modified clays have limited interlayer space, the interaction between chiral ligands and substrates can be enforced and this may enhance the selectivity.^{203,204}

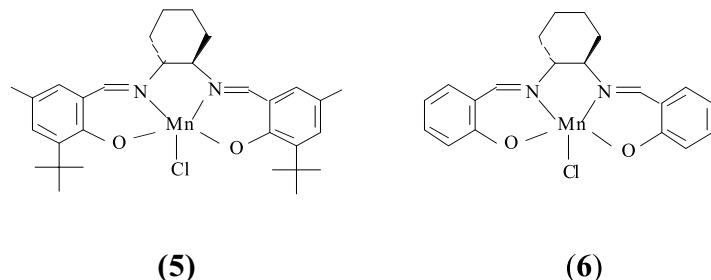


FIGURE 7.6

Prochiral organic acids were hydrogenated on clay-supported Rh–chiral phosphine complexes.^{205,206} Hectorite-supported chiral Rh(I)–phosphine complexes were used for the asymmetric hydrogenation of α,β -unsaturated carboxylic acids.²⁰⁷ It was found that the interaction between the α -ester group of itaconates and phenyl groups of phosphine can play an important role in the determination of the configuration of products.

BINAP complexes (7 in Fig. 7.7) are among the most efficient chiral catalysts for enantioselective hydrogenations, hydrosilylations, etc. Heterogenization of this complex is highly desired because of the high price of the complex.

Ru(II)BINAP was sulfonated and immobilized by the supported-aqueous-phase technique.^{208–210} Immobilization of Ru(II)BINAP by ion exchange of the sulfonated complex on anionic minerals was also reported.²¹¹ The complex is only present at the outer surface and is not intercalated within the interlamellar space of the clay.

7.2.4. CHIRAL MEMBRANES

Immobilization of chiral complexes in PDMS membranes offers a method for the generation of new chiral catalytic membranes. The heterogenization of the Jacobsen catalyst is difficult because the catalyst loses its enantioselectivity during immobilization on silica or carbon surfaces whereas the encapsulation in zeolites needs large cages. However, the occlusion of this complex in a PDMS matrix was successful.²¹² The complex is held sterically within the PDMS chains. The Jacobsen catalyst occluded in the membrane has activity and selectivity for the epoxidation of alkenes similar to that of the homogeneous one, but the immobilized catalyst is recyclable and stable.

Ru(II)BINAP was also incorporated into a PDMS matrix.²¹² The heterogenization of chiral complexes in polymers is an interesting perspective. To minimize complex leaching, reagents should be chosen that cannot dissolve the

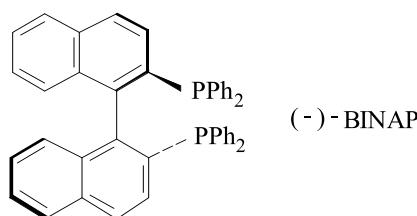


FIGURE 7.7

complex, or the complex should be linked via a functional group to the polymer by ionic, coordinative, or covalent bonds.

7.3. SURFACE ORGANOMETALLIC CHEMISTRY

Surface organometallic chemistry deals with the reactivity of organometallic complexes with surfaces to create well-defined surface-anchored complexes.^{213–217} Immobilization of homogeneous metal complexes by anchoring the molecules to solid surfaces via covalent bonds is also a reaction between an organometallic compound and a surface. In that case, however, the goal is only to bond the complex to the support; one hopes that the active site in the complex remains unchanged and the surface reaction does not create new surface sites. It means that the nature of the anchoring process is nonessential whereas in the surface organometallic chemistry, the surface reaction is the basic event.

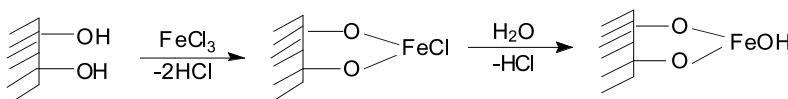
Since the rules controlling organometallic reactions in solution and on surfaces have been shown to be similar, the same synthetic strategies can be used to obtain grafted transition metal complexes with a predetermined coordination sphere. Of course, differences also occur, mostly due to the presence of the surface as the *far-largest ligand*. Accordingly, the first objective of surface organometallic chemistry is the study of the mechanisms of the surface reactions. The second objective is a practical one: how we can prepare well-defined surface sites using surface reactions.^{218–224}

7.3.1. REACTIONS WITH OXIDE SURFACES

In principle, different surface sites can serve as anchoring sites but the surface OH groups are the most common anchoring groups on the oxide surfaces.²²⁵ These OH groups can take part in different reactions. For example, inorganic salts can react with the surface OH groups (Scheme 7.7).²²⁶

The reaction between the surface OH groups and SnCl_4 leads to similar surface species (8 in Fig. 7.8).²²⁷

Silica is known to have covalent Si–O bonds in which silicon always assumes a tetracoordinated structure. The OH groups on the silica surface are believed to occur in different forms (9–11 in Fig. 7.9).



SCHEME 7.7

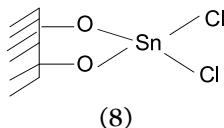


FIGURE 7.8

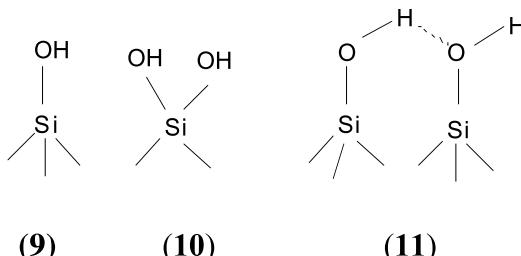
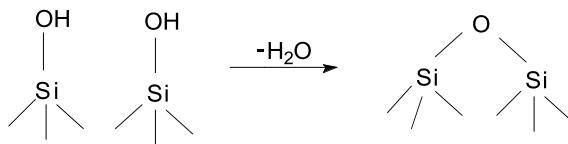


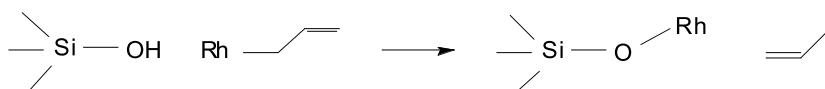
FIGURE 7.9

The number of leaving alkyl groups seems to depend on the degree of hydroxylation of silica. When the silica is heated, water is driven off and the surface concentration of OH groups decreases. At 450°C siloxane bonds are also formed (Scheme 7.8).

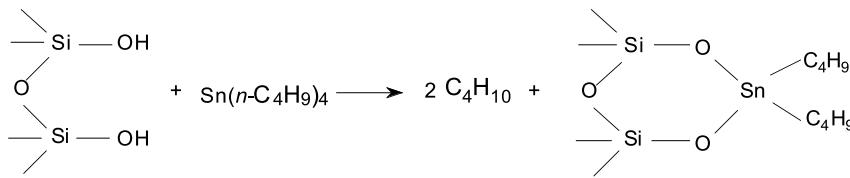
Metal alkyl reagents react with the acidic OH groups of silica, probably by the electrophilic cleavage of the metal–carbon bond. For example, the electrophilic cleavage of the metal–carbon bond occurs when organometallic reagents react with the electrophilic OH groups of the silica surface (Scheme 7.9).^{228–230}



SCHEME 7.8



SCHEME 7.9



SCHEME 7.10

Tetrabutyltin reacts a similar way with the OH groups. On partially dehydroxylated silica (treated at 200°C) the reaction shown in Scheme 7.10 takes place.²²²

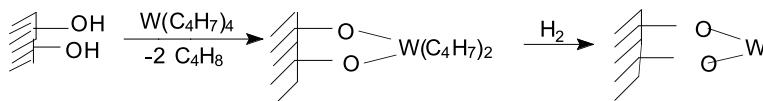
Anchored organometallic complexes of tungsten were prepared by the interaction of $W(C_4H_7)_4$ with surface OH groups, and the resulting surface species play a role as precursors for the synthesis of different surface tungsten compounds (Scheme 7.11).²³¹

Metal alkyls of main-group elements (e.g., Mg, Li, Al, Zn, Ga) are known to react with hydroxyl groups of silica with the liberation of the corresponding alkane. The studies were mainly devoted to the quantitative determination of the concentration of surface hydroxyl groups.^{232–235} The reaction of methylolithium with surface OH groups has been used widely for the determination of the OH groups. Methylmagnesium,²³⁶ trimethylaluminum,²³⁷ ethylolithium,²³⁸ and dimethylzinc²³⁹ were also used for the determination of active surface hydrogens. During these studies, little attention was paid to the nature of the organometallic fragments. In surface organometallic chemistry, however, the structural determination of the grafted organometallic entities is the primary aim.

The reaction of alkylolithium with surface OH groups produces reactive lithiated surface. For example, neopentylolithium reacts with the surface silanol groups of silica (Scheme 7.12).²⁴⁰

$CoCl_2$ was bound to the silica surface using the previous reaction and acetylacetone ($AcAcH$) (Scheme 7.13).^{241,242}

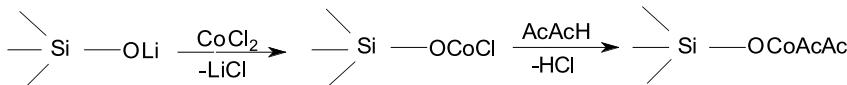
Catalysts with Sn–alumina interaction were prepared by the reaction of the lithiated alumina surface and $SnCl_4$ (Scheme 7.14).²⁴³



SCHEME 7.11



SCHEME 7.12

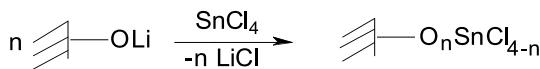


SCHEME 7.13

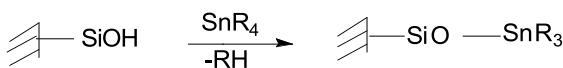
The reaction of tetraalkyltin complexes with oxide surfaces was studied^{244,245} but no description at the molecular level has been reported. The low-temperature reactivity of tetraalkyltin (SnR_4 , where R=Me, Et, i-Pr, Bu) complexes toward the surface of silica was studied in detail.²⁴⁶ At room temperature, the complex is physisorbed. Above 100°C, the adsorbed molecules react with the OH groups and the evolution of alkanes is observed (Scheme 7.15).

Spectroscopic data show that Sn remains tetracoordinated on the surface and one H atom of the terminal methyl is bonded to a surface OH group by hydrogen bonding (12 in Fig. 7.10).

The same surface species is obtained at ambient temperature by the reaction of Bu_3SnH and the silanol groups, suggesting that the Sn–H bond is more reactive in this case than the Sn–C bond. The surface reaction depends upon the degree of dehydroxylation of the surface of silica. On silica dehydroxylated at 500°C the reaction leads to one well-defined surface complex. On the other hand, on silica dehydroxylated at 200°C, the evolution of alkane is continuous. The difference in the latter case is related to the presence of neighboring OH groups, because the number of the surface vicinal OH groups capable of



SCHEME 7.14



SCHEME 7.15

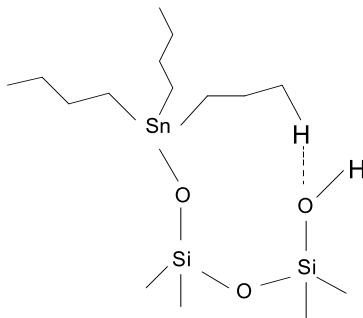


FIGURE 7.10

reacting with one Sn center is higher in the case of SiO_2 (200) than in the case of SiO_2 (500). The reaction between tetrabutyltin and silica or silica-supported rhodium was studied by Mössbauer spectroscopy.²⁴⁷

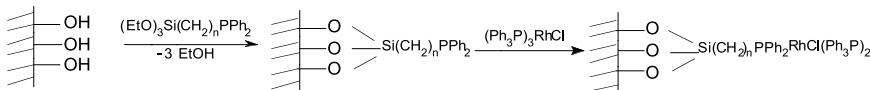
Alumina is known to have more ionic character and its surface has a more complex structure than that of silica. Reaction of Bu_3SnH with the surface of partially dehydroxylated aluminas was followed and it was found that the extreme sensitivity of tin chemical shifts to the molecular environment constitutes a method whereby surface organometallic complexes of tin can be used as molecular probes for determining surface structures of oxides.²⁴⁸

Bifunctional ligands containing alkoxy groups can be used for anchoring metal complexes to surface OH groups through a longer alkyl chain (Scheme 7.16).^{249–251}

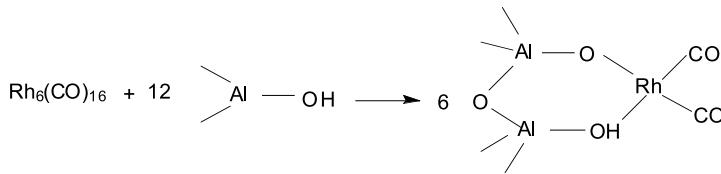
The insertion of the flexible chain between the anchoring site and the silica surface gives the PPh_2 ligands a high degree of freedom, thereby permitting their easy coordination to the metal center and the ability to react as a free phosphine in solution.

Redox reactions belong to the common surface reactions. A typical redox process is the reaction of $\text{Rh}_6(\text{CO})_{16}$ with OH groups on the surface of alumina. The reaction leads to the oxidation of the Rh(0) to Rh(I) with evolution of H_2 (Scheme 7.17).²⁵²

The activation of C–H bonds of alkanes is one of the challenges of catalytic research. Sublimation of tetraneopentyl zirconium (ZrNp_4) onto the surface of



SCHEME 7.16



SCHEME 7.17

a silica partially dehydroxylated at 500°C results in the electrophilic cleavage of one $\text{Zr}-\text{C}$ bond by a surface proton with the formation of the $\equiv\text{Si}-\text{O}-\text{Zr}(\text{Np})_3$ -grafted species (Scheme 7.18).^{253–256}

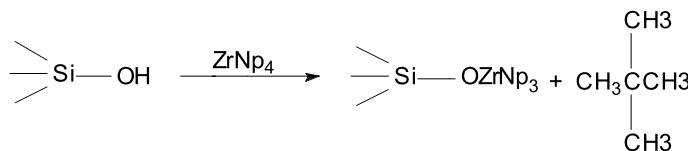
Reaction of this well-characterized species with dry hydrogen at 150°C leads to the formation of zirconium hydride and the evolution of alkanes.²⁵⁷ Hafnium and titanium monohydride can be obtained in the same way.²⁵⁸

Zirconium, titanium, and hafnium hydrides can activate the C–H bonds of several alkanes at low temperatures (even at room temperature) because they are very electrophilic and reactive. Moreover, the surface complex is immobilized by the strong metal–silica bonds, and this immobilization can prevent the coupling reactions leading to the deactivation of the complex.

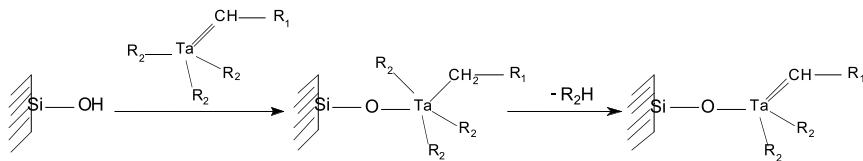
These surface hydrides are active catalysts for the hydrogenolysis of alkanes at moderate temperatures. Zirconium hydride can catalyze the hydrogenolysis of neopentane, isobutane, butane, and propane at 323 K but cannot catalyze the hydrogenolysis of ethane.²⁵⁹

Zirconium and hafnium hydrides can catalyze the olefin polymerization under olefin pressure and the polyolefin hydrogenolysis under hydrogen pressure.²⁶⁰ It is potentially interesting for plastic recovery and transformation into valuable products.

The $(\equiv\text{SiO}_3)_3\text{TiH}$ surface complex was active in the skeletal isomerization of alkanes at temperatures as low as 50°C and this remarkable activity is very promising because this catalyst has the possibility to isomerize light hydrocarbons under very mild conditions.²⁶¹



SCHEME 7.18



SCHEME 7.19

It was assumed that C–C bond cleavage passes through an elementary step of β -alkyl transfer. The mechanism of hydroisomerization passes also by a β -alkyl transfer step, but in this case the β -H elimination–olefin reinsertion occurs rapidly and a skeletal isomerization also occurs.

The chemistry of tantalum is different. The tantalum pentaalkyl complex does not exist, because it transforms easily into a carbene complex by α -elimination. This complex reacts also with silica, leading to a supported tantalum complex.^{262,263} Their reaction proceeds first by the addition of the silanol OH group across the tantalum–carbon double bond followed by elimination of an alkane (Scheme 7.19).

In a hydrogen atmosphere the complex reacts with hydrogen and can be transformed into tantalum(III) hydride (13 in Fig. 7.11).²⁶⁴

This catalyst can catalyze a new reaction, called *alkane metathesis*. By this reaction, alkanes are transformed into higher and lower alkanes.²⁶⁵ Silica-supported zirconium catalysts were also used for the mild oxidation of alkenes by H_2O_2 .²⁶⁶

A high metathesis activity was also observed when CH_3ReO_3 was chemisorbed on Nb_2O_5 . There appears to be a correlation between the catalytic activity and the Lewis acidity of the support.²⁶⁷ Catalytic activity of supported tungsten phenoxide in olefin metathesis was also studied.²⁶⁸

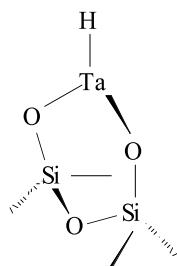


FIGURE 7.11

A new isomerization catalyst can be prepared by the modification of silica-supported nickel with tetrabutyltin. This catalyst is capable of the selective isomerization of 3-carene to 2-carene.²⁶⁹

Rhodium(I) complexes anchored by phosphine ligands usually have high selectivity but low stability.^{270–273} One of the possible way to tackle this problem is to bond the metal complexes by oxygen-containing anchoring ligands (14 in Fig. 7.12).^{274,275}

The reaction of silica-supported bis(allyl)Rh complexes with PMe_3 followed by hydrogen treatment leads to the synthesis of the surface $\text{SiO}-\text{RhH}_2(\text{PMe}_3)_4^+$ as the first example of a cationic organometallic complex attached to the silica surface by ion pairing. The counterion is presumed to be a siloxy group SiO^- on the silica surface.^{276,277}

The surface organometallic chemistry of metal carbonyl complexes supported on inorganic oxides and zeolites has been studied.^{278,279} Transition-metal ions linked by ionic bonds to a zeolite surface undergo *in situ* a reductive carbonylation to generate mononuclear monovalent carbonyl compounds inside the zeolite cages.^{280,281} By further treatment with CO and H_2O , the species are reduced until they form the so-called ship-in-a-bottle polynuclear metal carbonyl clusters.^{282–288} With conventional supports, such as silica or alumina, a similar surface chemistry is observed.²⁸⁹ The amount of surface water has a significant role in the reductive carbonylation of silica-supported RhCl_3 and IrCl_3 catalysts. In the presence of large amounts of water the process will eventually end with metal carbonyl clusters, whereas at low water contents the process stops at $[\text{Ir}(\text{CO})_3\text{Cl}]_n$ and $[\text{Rh}(\text{CO})_2\text{Cl}]_2$.²⁹⁰

7.3.2. REACTIONS WITH METAL SURFACES

The synthesis, characterization, and catalytic properties of materials obtained by the reaction of organometallic complexes of IIB, IVA, and VIA with metallic particles were studied extensively. Two types of materials may be obtained by

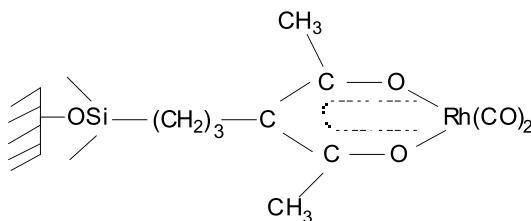


FIGURE 7.12



SCHEME 7.20

surface organometallic chemistry on metals: metal particles covered with organometallic fragments, and bimetallic particles.²⁹¹

The reaction of organometallics with metal surfaces is a very promising aspect of surface organometallic chemistry related to fine chemicals. The precise understanding of the reactions between organometallics and metal surfaces is essential to obtain highly selective catalysts by this route.^{292,293}

The catalysts prepared by the organometallic route can be divided into three groups:

1. Surface fragments are coordinated to the metal as in classic molecular catalysis.
2. Surface fragments are decomposed into atoms.
3. Surface fragments are fully hydrogenolyzed and the metal atoms are incorporated into the metallic lattice.

The reaction between tetrabutyltin and Rh/SiO₂ in the presence of hydrogen begins at room temperature. The hydrogenolysis of the butyl groups is not complete below 100°C and stable surface species with the general form of Rh_s[Sn(*n*-C₄H₉)_y]_x/SiO₂ are produced.²⁹⁴ The value of *y* depends on the amount of tetrabutyltin introduced. The *x* value depends on the *y* value and on the temperature and time of the reaction. At room temperature, usually two Sn–C bonds were hydrogenolyzed (Scheme 7.20)²⁹⁵

The surface species produced by this reaction are real surface organometallic fragments (15 in Fig. 7.13).

Above 100°C, the remaining Sn–C bonds of these surface organometallic fragments are hydrogenolyzed stepwise and the tin atoms can migrate into the particles, producing intermetallic compounds. This is a way to obtain well-defined bimetallic catalysts. The surface organometallic chemistry of tin^{296–299} and germanium^{300,301} were studied and the surface species were characterized.

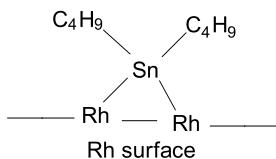


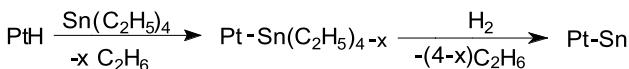
FIGURE 7.13

The reaction of Rh, Ni, and Ru with tetrabutyltin leads to bimetallic catalysts that exhibit high selectivities and activities in the hydrogenolysis of ethyl acetate to ethanol.^{302,303} The Rh was grafted to the surface by cationic exchange.³⁰⁴ The interaction between tetrabutyltin and Rh/SiO₂ was studied in detail and it was found that tetrabutyltin does not react significantly with the support but reacts slowly at 370 K in heptane solution with the oxidized Rh surface.^{305,306} The kinetics of the hydrogenolysis of tetrabutyltin on silica-and alumina-supported Rh catalysts was also studied.³⁰⁷ Analysis of the kinetic data of the hydrogenolysis of ethyl acetate led to the proposal of a reaction mechanism involving a single Rh atom.

The surface reaction of the chemisorbed hydrogen and tetraethyltin (a controlled surface reaction) was used to produce bimetallic surface species with direct Sn–Pt interaction, which were decomposed in a hydrogen atmosphere in a subsequent step (Scheme 7.21).³⁰⁸

This approach has been used to prepare Sn-Pt/Al₂O₃ catalysts with the exclusive formation of Pt–Sn and Sn–alumina interactions.^{309,310} Reactions catalyzed by metals were strongly influenced by the creation of bimetallic surface entities, whereas acid–catalyzed reactions were affected by the suppression of the acidity of the support by ionic forms of the second metal.^{311,312} Modification of the Ni/Al₂O₃ catalyst with lead was also performed by a controlled surface reaction between NiH and Pb(C₂H₅)₄.³¹³ When a lithiated Al₂O₃ surface was reacted with PdCl₂, the active ionic form of Pd was stabilized by reactive surface OH groups and this ionic form of Pd was stable even under hydrogenation conditions.³¹⁴

The organometallic route is a very useful procedure for the preparation of Pt–Sn materials. The complete reaction pathway during the hydrogenolysis of Sn(*n*-C₄H₉)₄ was studied in detail.³¹⁵ The hydrogenolysis is a stepwise process leading to alkyl fragments and tin adatoms. At 50°C the Sn(*n*-C₄H₉)₄ reacts selectively with the Pt surface. The reaction begins by the hydrogenolysis of one butyl group, but the surface species is not stable and reacts further. The stable situation is reached in which only one butyl group per Sn atom remains on the surface with the formula (Pt_{*s*})₃[Sn(*n*-C₄H₉)]. At 300°C, the complex hydrogenolyzed into adatoms, and at 500°C Sn migrates into the sublayers. At 100°C the Sn(*n*-C₄H₉)₄ reacts simultaneously with the Pt and silica surface, but the rate with silica alone is much lower than the rate with Pt/SiO₂.



SCHEME 7.21

7.3.3. SURFACE ORGANOMETALLIC CHEMISTRY AS A TOOL FOR TAILOR-MADE CATALYSTS

Reaction of organometallic complexes with the surfaces of oxides leads to surfaces that are covered by organometallic fragments.³¹⁶ The reaction of an organometallic complex with a surface may, in certain cases, lead to new catalytic materials that exhibit higher activities and/or selectivities than conventionally prepared catalysts. It can also lead to new catalytic materials with properties that are not found in classic heterogeneous or homogeneous catalysis such as the catalytic hydrogenolysis of alkanes at room temperature,³¹⁷ and it may also lead to molecular-like species with unusual oxidation states or coordination numbers, or with novel physical or chemical properties such as hydrophobic or hydrophilic surfaces, chiral surfaces, etc. An unanswered question is whether it is possible to graft organometallic compounds of unusual oxidation states and coordination numbers onto a surface, as this could lead to unexpected chemical properties.

The implications in catalysis can be very wide since it might be possible to change the organometallic fragment as in homogeneous catalysis. And a certain fragment grafted onto the surface of a metal particle may make a metal catalyst selective for a given reaction.

A bimetallic catalyst can be obtained by the reaction of tetrabutyltin with Rh/SiO₂ catalyst. The partial hydrogenolysis leads to the Rh_s[Sn(*n*-C₄H₉)₂]/SiO₂ surface organometallic complexes, which proved to be fully selective in the hydrogenation of unsaturated aldehydes into the corresponding unsaturated alcohols.³¹⁸

Citral offers three kinds of unsaturations, an aldehydic function, and a conjugated and an isolated C=C bond (Scheme 7.22).

Rh/SiO₂ does not exhibit any selectivity. The addition of tetrabutyltin can change its selectivity. It was found that the selectivity of the reaction can be governed by the surface coverage of the organometallic fragments. At low coverage, there is a complete hydrogenolysis leading to Sn atoms on the Rh surface. It seems reasonable to assume that this reaction occurs selectively on low coordination sites that are present at the corners or edges of the particles.

When the Sn/Rh ratio is about 0.2, the chemoselectivity for the hydrogenation of the conjugated C=C bond (citronellal) is 81%. At the same time, the activity is decreased. This can be explained by the selective poisoning of these low-coordination Rh sites by Sn adatoms. At higher coverage, the organometallic fragments are stable on the surface. If the coverage reaches a value close to unity, the catalyst becomes fully selective for the hydrogenation of the C=O bond.^{319,320} It was proposed that the -Sn(*n*-C₄H₉)-grafted fragments could influence the selectivity by both steric and electronic effects. The Sn atom in

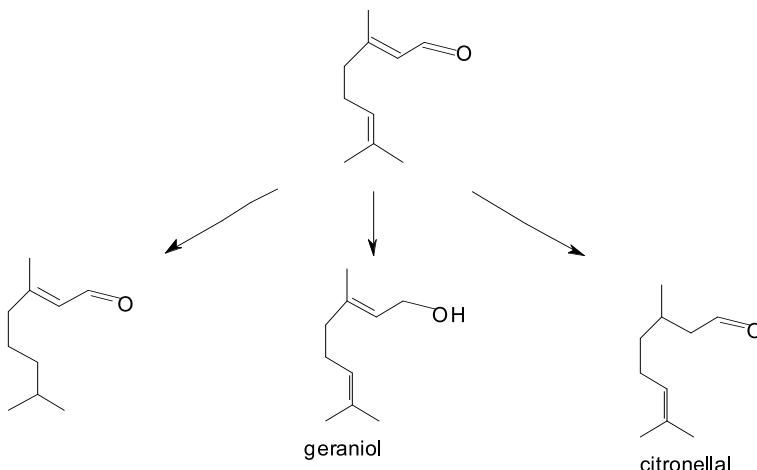
the grafted fragments is in an oxidized state and could activate the C=O bond. Ge has similar effects as Sn, whereas in the case of Pb, no butyl groups remain on the surface.³²¹

The Rh/SiO₂ is also unselective in the hydrogenation of acetophenone: the aromatic ring and the ketone group are simultaneously hydrogenated. The addition of Sn either as SnCl₂ impregnation or as Sn(CH₃)₄ vapor deposition promotes the rate of acetophenone hydrogenation when the surface composition is Sn_s/Rh_s = 0.66. It was assumed that the carbonyl oxygen interacts with the Sn atoms.³²²

As soon as the tetrabutyltin was introduced, the hydrogenation of the aromatic ring stopped. At low Sn/Rh_s values the tin atoms, present as adatoms, can be found on the places where the hydrogenolysis reaction of the organotin occurs. This could be the faces of the particles.³²³ In this situation, the hydrogenation of the aromatic rings does not occur because a flat adsorption of the ring is needed. Upon increasing the amount of the tin, both adatoms and alkyl-tin fragments are present on the surface.

In the isomerization of (+)-3-carene into (+)-2-carene or the dehydrogenation of 2-butanol into 2-butanone, the selectivity into the desired product is also increased by the introduction of small amounts of Sn, which will form adatoms poisoning unselective sites.³²⁴

The reaction of tin organometallic complexes with the external surface of zeolites can modify the adsorption properties.³²⁵



SCHEME 7.22

Chiral organotin compounds for heterogeneous bimetallic catalysis with chiral centers adjacent to the metals, for example, (*-*)-Ment₃SnH, were prepared by the coupling of menthylmagnesium chloride with tin halides.³²⁶ The reaction of chiral organotin compounds with partially dehydroxylated silica was studied. The amount of grafted tin and the nature of the grafted tin species depend on the type of the organotin compound and the temperature.³²⁷ The reactivity of chiral germanium derivatives toward Rh/SiO₂ was also studied. It was found that the surface species show low activity and weak enantiomeric excess for the asymmetric hydrogenation of keto compounds and alkene derivatives.³²⁸

7.3.4. SURFACE ORGANOMETALLIC CHEMISTRY FOR STUDY OF THE ELEMENTARY STEPS IN HETEROGENEOUS CATALYSIS

One of the difficulties in heterogeneous catalysis is that the surface is very complicated and the structure of the active sites is unknown at the atomic level. However, the disciplines of organometallic chemistry and heterogeneous catalysis are merging.³²⁹ Organometallic chemistry can serve as a guide for understanding heterogeneous catalysis.³³⁰ Since a surface organometallic fragment is a possible intermediate of surface catalysis, the chemistry of organometallic complexes may give information about poorly understood surface chemistry and about reaction paths or elementary steps that occur in heterogeneous catalysis.

During the catalytic cycle, surface intermediates include both the starting compounds and the surface metal atoms. This working site is a kind of supramolecule that has organometallic character, and, one hopes, the rules of the organometallic chemistry can be valid for this supramolecule. The synthesis of molecular models of these supramolecules makes it possible to study the elementary steps of the heterogeneous catalysis at a molecular level. Besides similarities there are, of course, also differences between the reactivity of a molecular species in solution and an immobilized species. For example, bimolecular pathways on surfaces are usually prohibited.

The reactions of the surface organometallic fragment bis(allyl)Rh(III) on silica with electrophiles and Lewis bases was studied in order to identify concepts of molecular chemistry that can be applied to the mechanism of heterogeneous catalysis. It was found that coordinated OH groups participate in the reactivity of monomeric surface organometallic fragments and that noncoordinated OH groups facilitate the migration of surface species. In this case the similarity of the supramolecular surface chemistry to molecular chemistry is limited.³³¹

Alkylidene complexes are generally considered to be reactive intermediates but the actual surface organometallic species have never been fully characterized. However, the synthesis of silica-supported tantalum(V) carbene complexes and their characterization have been reported.³³²

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APPENDIX

SOME BASIC ASSUMPTIONS ABOUT HETEROGENEOUS CATALYTIC HYDROGENATION

THE CATALYST

1. The catalyst surface is flat or nearly so (this assumption has been modified somewhat during the past 30 years to allow active surface sites also to be edge and corner atoms. In fact, based on analogy with homogeneous catalysts, some researchers favor corner sites and others favor edge sites. Interestingly, corner and edge sites severely reduce the possibility of steric interaction between the surface and the substrate, so the introduction of corner and edge sites lowers the importance of assumption 2. A metal particle size effect (approximately 3 nm) correlating with band gap broadening and catalytic activity recently reintroduced electronic considerations.

ADSORPTION STEREOCHEMISTRY

2. Preferred adsorption of the unsaturated bond of the substrate occurs at that face which presents the least steric interactions between the adsorbed substrate and the surface. Since some amazingly sterically hindered molecules can be hydrogenated, at least some active sites must look like corners or edges or some other protuberances.
3. The adsorbed substrate adopts that conformation which best balances the least strain within the adsorbed substrate and the fewest interactions

between the surface and the substrate. In this respect, the surface is treated as a very large substituent.

4. The strength of adsorption is inversely proportional to the level of congestion around the unsaturated bond; that is, tetrasubstituted alkenes adsorb least strongly, trisubstituted next, disubstituted next, and monosubstituted the most strongly. However, substituents containing oxygen or nitrogen seem to anchor substrates to the surface. This anchoring can stereodirect adsorption.
5. The rate of addition is also inversely proportional to the level of congestion. In some cases this depends on whether molecules are being hydrogenated individually or in competition. For example, in competition, 1,3-di-*tert*-butylbenzene hydrogenates faster than its 1,4-isomer; however, individually, the 1,4-isomer hydrogenates faster than the 1,3-isomer.
6. In competition, the less substituted alkenes displace more highly substituted alkenes (this can be virtually 100%, for example, 2,3-dimethylcyclohexene versus 1,2-dimethylcyclohexene.)

GLOBALITY OF MECHANISM

7. Addition, double bond migration, cis-trans isomerization, and exchange are all integral parts of the same mechanism and occur as allowed by structural features of the adsorbed substrate. Recent evidence suggests that exchange may occur with surface hydrogens or deuteriums, whereas addition occurs with subsurface hydrogens or deuteriums (see "Hydrogen")

DOUBLE BOND MIGRATION

8. Double bonds tend to migrate to more highly substituted positions within a substrate; that is, terminal alkenes isomerize to disubstituted or trisubstituted alkenes, disubstituted alkenes tend to migrate to trisubstituted, and trisubstituted to tetrasubstituted alkenes. Of course, migration can go both ways, and adsorbed surface species may not exhibit the same thermodynamic stability as their desorbed relatives. (The rate of migration is strongly catalyst dependent; for example, it frequently occurs rapidly on Pd and slowly on Pt.)
9. Double bond migration occurs either by the π -allyl mechanism (abstraction-addition) or by the Horiuti-Polanyi mechanism (addition-abstraction). Pd is thought to favor π -allyl and Pt Horiuti-Polanyi mechanisms.

CIS–TRANS ISOMERIZATION

10. Cis–trans isomerization occurs either by formation of a half-hydrogenated state (Horiuti-Polanyi mechanism) followed by rotation around the newly formed single bond and abstraction of an appropriate hydrogen onto the surface or by double bond migration (either Horiuti-Polanyi or π -allyl) from a cis (trans) position to an adjacent trans (cis) position (deuterium exchange studies favor the rotation mechanism).

HYDROGEN

11. Dihydrogen dissociates on the surface into hydrogen atoms that act independently. Mixtures of 50:50 $H_2:D_2$ produce equilibrated mixtures of $H_2:HD:D_2$. Portals for dissociation-recombination are edges and corners.
12. Hydrogen atoms are on the surface and compete with the substrate for active sites; however, emerging evidence suggests that both surface and subsurface hydrogens are involved in reactions.
13. Hydrogen atoms migrate rapidly over the surface compared with processes such as addition, double bond migration, and exchange. However, some evidence suggests that hydrogen atoms are immobile or at least move slowly on the surface. Recent evidence suggests that hydrogen moves more rapidly below the surface than on the surface.
14. Hydrogen atoms add to and leave from the substrate on that face of the substrate which is toward the surface (an exception is when solvent furnishes hydrogens to the top of an adsorbed molecule).

DEUTERIUM EXCHANGE

15. Deuterium exchange within an adsorbed unsaturated molecule occurs by multiple stepwise migrations of surface attachments in which deuterium or hydrogen from the equilibrated surface hydrogen-deuterium pool replaces hydrogen in each step. Some evidence suggests that this hydrogen-deuterium pool does not equilibrate as rapidly as some steps occur; for example, when rapid double bond migration occurs, as in the apopinenes, the surface (or maybe subsurface) hydrogen-deuterium pool enters the molecule only slowly.
16. Deuterium exchange within saturated products occurs by dissociative adsorption followed by multiple stepwise migrations as described in assumption 15 followed by the addition of deuterium and/or hydrogen from the equilibrated surface hydrogen-deuterium pool.

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