Heterogeneous Catalytic Transfer Hydrogenation and Its Relation to Other Methods for Reduction of Organic Compounds

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I. Introduction

Reduction of organic compounds is important synthetically both in the laboratory and in industry. There are many methods of effecting reduction which may or may not lead to hydrogenation, but in this review only processes leading to the addition of hydrogen or replacement of a functional group by hydrogen will be considered. Further, this review will be concerned mostly with those processes that can be effected by heterogeneous catalysis using molecules other than molecular hydrogen as the source of hydrogen. Reduction of organic functional groups can be categorized into (i) addition of hydrogen to unsaturated groups as, for example, in the reduction of ketones to alcohols and (ii) addition of hydrogen across single bonds leading to cleavage of functional groups (hydrogenolysis). Removal of oxygen as a reductive process, as in the deoxygenation of oxiranes to alkenes, will not be discussed.

Of all the methods available for addition of hydrogen to organic compounds, heterogeneous catalytic transfer reactions have been relatively underutilized. This lack of popularity can be traced to the relatively meager success of much of the earlier research which suggested that the technique was of only limited scope and could provide only modest yields of products. The early pioneering work by Braude[1] was largely ignored because of poor yields and long reaction times, but the situation has changed considerably following the appearance[4] of a stimulating review and the introduction of greater catalyst loadings and different hydrogen donors.[2] Another reason for the underutilization of transfer reduction has been the very successful exploitation of molecular hydrogen and hydrides for reduction of organic compounds.

In comparison with catalytic reduction using molecular hydrogen, transfer reduction using hydrogen donors has real and potential advantages. Molecular hydrogen, a gas of low molecular weight and therefore high diffusibility, is easily ignited and presents considerable hazards, particularly on the large scale; the use of hydrogen donors obviates these difficulties in that no gas

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Anna Wilby (nee Superson) gained an M.Sc. from Warsaw Technical University in 1973 and spent the following 4 years as a research assistant. She emigrated to Britain following her marriage to a British Chemical Engineer, Tom, and then took a Ph.D. degree at Liverpool University in 1981 after carrying out research into methods of reduction in organic chemistry. From 1980 to 1983, she worked as a Senior Demonstrator in the Department of Organic Chemistry at Liverpool University and then expanded her interests by giving birth to a baby daughter, Sophia. Apart from her family, current interests include catalytic transfer hydrogenation and enzyme inhibitors.

Ian Entistle graduated in Chemistry from the University of Leeds in 1958. After carrying out postgraduate studies there in the Textile Chemistry Department and working for a brief period in the tobacco industry, he joined the Medical Research Council to study tobacco-smoke hydrocarbons. In 1967, he received his Ph.D. for this work from the University of Exeter, and joined Shell Research Limited where he is currently working as a Principal Scientist. His interests are pesticide design and synthesis, reduction chemistry, and general synthetic methods. He manages a group of pesticide synthesis chemists.

containment is necessary, no pressure vessels are needed, and simple stirring of solutions is usually all that is required. Potentially, transfer methods could afford enhanced selectivity in reduction. With a catalyst and molecular hydrogen, changes of catalyst, solvent, and temperature are possible variations in reaction conditions but, with hydrogen donors, a new dimension is opened up because the choice of hydrogen donor can affect the reaction through its competitive adsorption onto the catalyst surface. Thus, rate and specificity of reduction are amenable to control through choice of hydrogen donor. Most transfer hydrogenation mechanisms are poorly understood and there are a few direct comparisons of products of reaction following the use of molecular hydrogen or a hydrogen donor. Research in these areas is needed not only to unravel details of mechanism, but also to provide a proper appraisal of the advantages or disadvantages of the two methods.

In terms of electronegativity, hydrogen occupies a central position in the periodic table. With Pauling's definition of electronegativity,[3] hydrogen, having a value of 2.1, lies between fluoride (4.0) and many metals which typically have values of about 0.9–1.5. Therefore, in reactions involving its transfer, hydrogen may appear as a proton, atom, or hydride depending on reagents and conditions. On dissolving gaseous HCl in water, hydrogen is transferred as a proton to water; the reaction of lithium tetrahydroaluminate to a carbonyl group effectively involves the addition of hydride to the carbon of the carbonyl; many catalytic hydrogenations with molecular hydrogen actually involve atomic hydrogen dispersed in and over the catalyst. In many reductions with hydrogen donors, it may not be easy to decide just how hydrogen is transferred. For example, formic acid may be regarded as providing a proton and a hydride or two hydrogen atoms. However, for suitable hydrogen-donor properties, it seems clear that compounds containing hydrogen bonded to elements or groups with similar electronegativity to that of hydrogen itself provide the best hydrogen donors. In this respect, formic acid and formates, phosphinic acid and phosphinates, phosphorous acid and phosphites, hydrazine, hydrides of boron, aluminum, silicon, and tin, alcohols, amines, and hydrocarbons are all hydrogen donors in catalytic transfer reduction. An added advantage is gained when the products of the decomposing donor have large negative enthalpies of formation. Thus, CO_2 from formic acid and N_2 from hydrazine provide added driving force to the reactivity of these substances as hydrogen donors.

It is the purpose of this review to illustrate briefly the relationship of heterogeneous catalytic transfer reduction to other methods of addition of hydrogen in organic chemistry and then to survey the uses of catalytic transfer in relation to other routes to hydrogenation. The other methods for addition of hydrogen to organic

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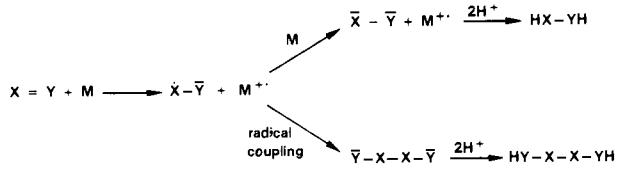

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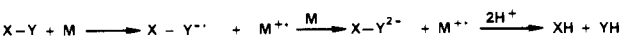

compounds include reductions with hydrides, hydrogen atoms, and protons (after initial addition of electrons). Heterogeneous catalytic transfer hydrogenation has been reviewed adequately up to 1972[4a] and recently very briefly,[4b] and, rather than cover the same work again, this present review is concerned mostly with important advances that have occurred since, although some early publications which are either important or were not reported in the previous review, are included here.

II. Other Methods of Addition of Hydrogen

In the following brief summary, allusions are made to extensive reviews from which many leading references can be obtained. Accounts of reduction methods have appeared.[5]

A. Addition of Electrons Followed by Protons (Electron Transfer)

This type of hydrogenation can be achieved either through electron transfer from a suitable substrate such as a metal or a metallic salt or through electrolysis by anodic reduction.

Reduction of organic functional groups by metals,[6] their salts,[7] or binary systems of metals and salts[8] can be effected in aqueous and nonaqueous solvents and may be represented by the general Schemes I or II in which M represents a metal or metallic salt in a suitable oxidation state, and X=Y, X—Y represent doubly and singly bonded organic species. The solvent can provide the necessary protons or these may be added during workup of the reaction. Common proton donors include water, acids, alkalis, alcohols, amines, and liquid ammonia and the most frequently used metals are Li, Na (or Na/Hg), K, Mg, Ca, Zn (or Zn/Cu or Zn/Hg), Al (or Al/Hg), Sn, Fe, and Ni. Metals with two or more valence states may have salts suitable for donation of electrons. Metal salts in which the anion provides the electrons have been used. Thus, reduction of quinones to hydroquinones by metabisulfite occurs by initial electron transfer from the metabisulfite anion to the quinone. Similarly, ammonium hydrosulfite reduces nitro groups to amine.

Metals and their salts have provided some of the oldest reducing agents. For example, aromatic nitro groups can be reduced in acidic solution to amine with Zn, Fe, or Sn[9] and, in alkaline solution, to hydroxylamines,[10] azo-,[11] azoxy-,[12] and hydrazo compounds.[13] Ketones can be reduced to pinacols (Mg/Hg)[14] or hydrocarbons (Zn/Hg; Clemmensen reduction)[15] and esters to alcohols (Na/C_2H_5OH; Bouvealt–Blanc reaction).[16] Alkyl chlorides, bromides, and iodides, but not usually fluorides can be dehalogenated to alkane by use of Mg (Grignard reaction),[17] Zn, or Na (Wurtz reaction).[18] Alkynes can be reduced to *cis*-alkenes with a Zn/Cu[19] couple, or to *trans*-alkenes with sodium in ethanol.[20] Aromatic hydrocarbons can be partly or fully hydrogenated through the use of Na, Ca, or K.

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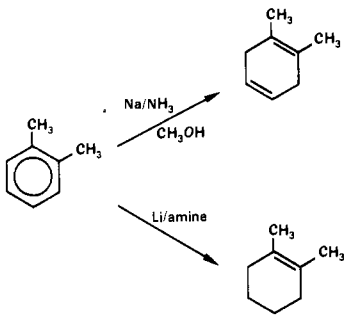

More recently, the use of dissolving metals in liquid ammonia or other amines (Birch reduction)[21-27] has become widespread because of the range of reductions that can be achieved. The original application of sodium in liquid ammonia has been extended to other alkali metals, such as lithium, in low molecular weight amines.[28] Although alkynes, aromatics, heteroaromatics, ethers, ketones, esters, acids, and amides can all be reduced, selectivity can be exercised through choice of factors such as the type of metal used, the ratio of alkali metal to substrate, solvent, and choice of proton donor. For example, Scheme III illustrates one type of selectivity that can be attained.

The reverse of this type of electron transfer (transfer of an electron from an organic compound to a metal cation) is the basis of much of photography.

A major disadvantage of the use of metals and their salts, particularly on a large scale, lies in their cost. Because of the stoichiometric, and often inefficient, nature of the reactions, relatively large quantities of metals or their salts are required to provide the electrons needed for reduction. Further, the separation of products from large amounts of aqueous solutions of metal salts may be laborious and inefficient. These disadvantages can be circumvented through the use of electrochemical systems, whereby electrons can be added to organic substrates directly from inert electrodes or a reducing agent can be regenerated in solution continuously.[29-31] This last approach effectively provides a catalytic use of metals or their salts. However, wider acceptance of electrolysis as a means of effecting reduction has undoubtedly been held back by its relatively slow nature (controlled by the need for large surface areas of electrodes), the need for special solvent systems with supporting electrolytes, and the need for the preliminary experiments which are required to ascertain the correct voltages for ensuring that only the required reduction takes place. Nevertheless, electrolysis may be a charge-transfer-catalyst system when the electrode material is not consumed. This aspect of electrocatalysis has been excellently discussed.[32,33] For a heterogeneous reaction, the catalytic rate (v) is given by the expression, $v = C(kT/h) \exp(-\Delta G^{\circ *}/RT)$ in which k, h, R, T, and $\Delta G^{\circ *}$ have the usual significance and C is the concentration. For electrocatalysis, $v = C(kT/h) \exp(-\Delta G^{\circ *}/RT) \exp(-\alpha F \Delta\phi/RT)$ in which α is the transfer coefficient and $\Delta\phi$ is the potential difference across the phase boundary

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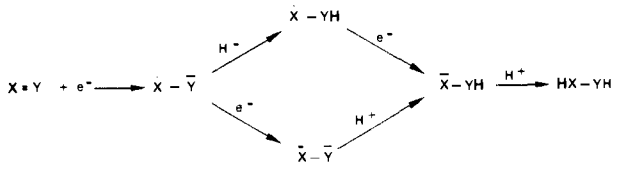

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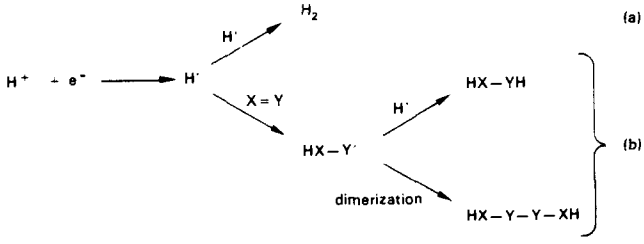


between the electrode and the bulk of the electrolytic solution. Comparison of the two expressions shows that both are temperature dependent (a heterogeneous reaction can be speeded up by increase of temperature), but the second, the electrocatalytic expression, is dependent also on interelectrode potentials. Thus, an electrocatalytic reaction can be increased in rate simply by increasing the interelectrode potentials and without a change in temperature. That this is an important difference is exemplified by the enormous amount of research now being put into electrochemical storage cells and electrocatalytic energy sources (e.g., electrochemical "combustion" of hydrocarbons).[34]

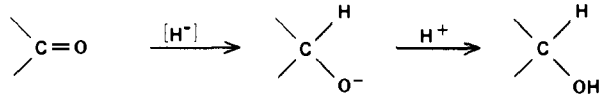
The direct transfer of an electron to an organic substrate is frequently most successful with electrode materials that give high hydrogen overvoltages. Thus, metals such as lead, mercury, and cadmium exhibit quite large hydrogen overvoltages and electrolysis at these electrodes can be described as one in which the organic substrate is adsorbed onto the electrode, receives an electron, and is then protonated (Scheme IV). Other metals such as Pt, Pd, and Ni have low hydrogen overvoltages and transfer electrons to adsorbed protons to generate hydrogen atoms (Scheme V). These hydrogen atoms may combine to generate hydrogen gas or may add to a coadsorbed organic substrate. Where these electrodes with low hydrogen overvoltages are composed of metals that adsorb organic molecules strongly, hydrogenation as in Scheme Vb occurs efficiently and the reactions resemble catalytic hydrogenation but, if protons are adsorbed more strongly than the organic substrate, then wasteful generation of hydrogen gas occurs (Scheme Va). Some aspects of these mechanisms of reduction are relevant to the later discussions on catalytic transfer hydrogenation. Protonation of an organic substrate may precede addition of electrons.

Addition of protons followed by hydride ions is an interesting alternative reduction method. This so-called "ionic reduction" with trifluoroacetic acid (proton donor) and triethylsilane (hydride donor) has been used extensively to reduce thiophenes to perhydrothiophenes[35] and in the conversion of ketones and aldehydes into ethers.[36]

B. Addition of Hydride Ion (Hydride Transfer)

A typical hydride reduction is exemplified by Scheme

SCHEME VI



VI showing the overall reduction of a carbonyl group to alcohol. The hydride ion may be derived from an obvious "hydride reagent" like lithium tetrahydroaluminate or from a not-so-obvious hydride donor such as an alcohol or amine.

The more obvious hydride reagents are derived from elements in groups 11, 12, and 13 of the periodic table,[311] particularly those in the first and second rows. In this region of the periodic table, the elements are less electronegative than hydrogen and cleavage of any bonds from them to hydrogen tends to lead to reactions in which H^- is transferred to a substrate molecule. Two elements, boron and aluminum, form the most readily available and most stable hydrides. Aluminum hydride (AlH_3 or $[AlH_3]_x$) and boron hydride (BH_3 or B_2H_6) can be prepared most easily from the readily available lithium tetrahydroaluminate and sodium tetrahydroborate respectively. Hence much of the more recent chemistry of hydride transfer is associated with these last two compounds or derivatives of them,[37] although there has been increasing recent interest in the group 14 silanes and stannanes as reducing agents.[38-40] Lithium tetrahydroaluminate is a powerful hydride donor and therefore relatively unselective in that most unsaturated groups are reduced by its action. Sodium tetrahydroborate is much less powerful a reducing agent and therefore more selective.

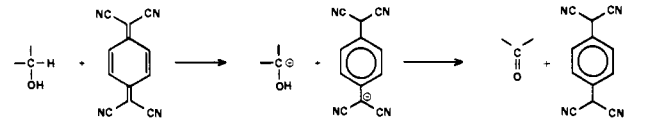
The usefulness of these hydride reagents has been increased even further by the observations that replacement of one or more hydrogen atoms in AlH_4^- or BH_4^- by alkoxy,[41] alkyl,[42] cyano,[43] or sulfide[44] can enhance or decrease their activity. For example, replacement of three hydrogen atoms in AlH_4^- by alkoxy groups (OR) to give $AlH(OR)_3^-$ yields a much less active hydride donor than AlH_4^- itself. Conversely, $BH(OR)_3^-$ is more reactive than BH_4^-. Some of these modified hydride donors are remarkably inert to protons. Thus, sodium trihydrocyanoborate, $NaBH_3CN$ is stable in aqueous solutions of pH 3.

The range in reactivities of these complex hydrides allows considerable selectivity in the variety of unsaturated functional groups that can be reduced.[45] However, cleavage of single bonds by these reagents is not usually easy, but can be achieved in certain cases. Whereas, alcohols themselves are stable to C–O bond cleavage by hydride donors, their *p*-toluenesulfonates can be cleaved by lithium tetrahydroaluminate to give the corresponding alkane.[46] Similarly, it is possible to replace halogens, particularly iodides, by hydrogen. For example, iodides can be reduced to the corresponding alkane through the use of tri-*n*-butylstannane.[38]

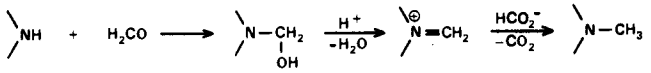
Of relevance to the technique of catalytic transfer reduction is the use of hydride donors with noble metal catalysts to effect hydrogenation. The mechanism of some of these reactions is obscure and will be discussed later, but the reactions have practical value. Sodium tetrahydroborate with palladium on carbon in toluene can be used to reduce polyunsaturated fatty acid esters to monoenoates.[47] More obvious in mechanism is the oxidative addition of triethylsilane to *trans*-RhCl-

SCHEME VII

SCHEME VIII



SCHEME IX



(CO)(Et_2PPh) to give a catalytic reductive procedure for the conversion of acyl chlorides into aldehydes.[39]

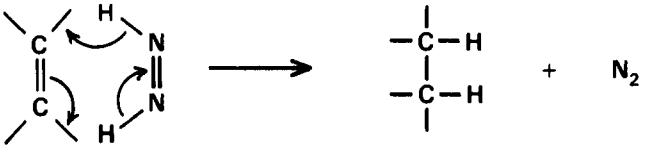
There are some well-known organic reactions which appear to proceed via transfer of hydrogen as hydride species, although the reagents themselves are not immediately obvious hydride donors. Through the use of aluminum alcoholates an equilibrium can be set up with ketones (Scheme VII), and if reaction conditions are properly arranged, the equilibrium can be shifted to the right or left and provides either an oxidation or reduction, depending on which species is regarded as the substrate and which the reagent (Meerwein–Pondorff–Verley reduction[48]/Oppenauer oxidation[49]). Similarly, alcohols will donate an α-hydrogen atom (as hydride) to good hydrogen acceptors such as tetracyanoquinodimethane (Scheme VIII).[50-52] Formic acid and formates are recognized as hydride donors in such reactions as the methylation of amines using formaldehyde/ammonium formate (Scheme IX; Leuckart reaction).[53] Phosphinic acid (hypophosphorous acid) has been used to reduce aromatic diazo compounds to the corresponding arene via a hydride-donor mechanism in which the phosphinic acid is oxidized to phosphorous acid[54] and to replace nuclear halogen by hydrogen in activated aromatic compounds.[55] As will be shown later, all of these hydride donors also provide good sources of hydrogen for catalytic transfer hydrogenation and can provide useful leads in the search for other or better hydrogen donors.

C. Addition of Hydrogen Atoms

Atomic hydrogen is a powerful reducing agent, but readily dimerizes to inactive molecular hydrogen. There are several ways for creating conditions under which atomic hydrogen can be generated or whereby hydrogen atoms can be transferred from a donor molecule (HD) to an acceptor substrate (A). Many of these hydrogen-atom-transfer reactions proceed via radical mechanisms (Scheme X), as for example, with the high-temperature disproportionation of 1,2-dihydronaphthalene to naphthalene and 1,2,3,4-tetrahydronaphthalene[56] and the reductive hydrogenolysis of carbon–halogen bonds using trialkyl- or arylsilanes and stannanes.[40,57] In some hydrogen-transfer reactions, two hydrogen atoms appear to be transferred simultaneously via a nonpolar transition state. Reduction of alkenes (Scheme XI), alkynes, and azo compounds by diimide proceeds through a six-membered transition state to yield, initially, products of cis addition of hydrogen. Diimide

SCHEME X

SCHEME XI



does not reduce unsymmetrical (polar) unsaturated bonds (–N=O, >C=O, –C≡N) and does not effect hydrogenolysis of single bonds. The high-temperature (380–570 °C) reduction of nitroarenes to anilines by hydrogen transfer from paraffins has been surmised to proceed via a diimide-like reduction.[58] Reduction of quinoline to 1,2-dihydroquinoline through the use of Hantzsch esters was reported some years ago[59] and these esters have since been investigated sporadically as hydrogen donors.[60a-e]

The above transfers of hydrogen atoms to suitable organic substrates have some relevance to catalytic transfer hydrogenation but the closest apparent similarity to the latter techniques lies in catalytic hydrogenation, a widely used reaction.[307,308] As will be shown later, although there are similarities between heterogeneous catalytic hydrogenation using molecular hydrogen as the hydrogen source, and heterogeneous catalytic transfer hydrogenation using hydrogen-donor molecules as the source of hydrogen, there are sufficient differences to merit the separation of the two methods in any consideration of their uses and their mechanisms of reaction. The relationship between heterogeneous catalytic transfer reduction to homogeneous catalytic transfer reduction will only be touched upon when considering mechanisms of reaction because the homogeneous method has a very widespread literature which has been reviewed extensively, if not explicitly.[61-63] A major advantage of the heterogeneous catalyst systems over the homogeneous ones lies in the ease with which the catalyst can be separated after reaction has ceased. Usually, the separation of the heterogeneous catalyst from a reaction mixture is a simple matter of filtration, but recovery of homogeneous catalysts is much more time consuming. Discovery and modification of homogeneous catalytic activity depends mostly on the skill of the chemist in devising new molecular species and the heterogeneous catalysts are necessarily more restricted in the scope they offer for molecular modification of the catalyst structure. Despite this reduced scope, heterogeneous catalysts suitable for effecting reduction with molecular hydrogen have been the subject of intensive investigation for many years and have been reviewed.[64] By changes in temperature, pressure, solvent, catalyst support, catalytic metal, and catalyst modifiers, a wide range of unsaturated groups can be hydrogenated and single bonds hydrogenolyzed. In many ways, heterogeneous catalytic hydrogenation forms a useful complement to reduction through the use of hydride or electron donors (sections IIA and IIB). For example, in a molecule containing both an alkene and ketone function, catalytic hydrogenation can be arranged to reduce only the alkene or, alternatively, hydride transfer (as by the use of sodium tetrahydroborate) can effect reduction of the ketone to alcohol

without affecting the alkene. The most widely used and active metals in both heterogeneous and homogeneous hydrogenation catalysts have been Pd, Pt, Rh, and Ni, and to a lesser extent, other transition metals such as Re, Ir, Cu, etc.[65,66] As will be discussed in the section on heterogeneous catalytic transfer reduction, the most useful reactions discovered to date have centered on the use of Pd, with lesser use of Pt and Rh, and the other transition metals scarcely at all. It is worth noting that, in most work on heterogeneous catalytic hydrogen-transfer reduction, relatively low temperature (<100 °C) and atmospheric pressures have been employed which is remarkably at variance with working practices in heterogeneous catalytic hydrogenations using molecular hydrogen. It is quite possible that elevated temperatures and increased pressures could lead to the wider application of metals other than palladium for transfer reduction.

III. Catalytic Hydrogen-Transfer Reduction

As stated earlier, this review is concerned mainly with heterogeneous transfer reduction, but in the following sections a brief summary of relevant information on homogeneous transfer reduction is given to allow a proper comparison to be made between the two approaches and to highlight similarities and differences. Further, the understanding of mechanisms of reaction in homogeneous transfer systems is generally better understood than in the heterogeneous systems and, in certain instances, this knowledge of homogeneous systems appears to be applicable to an understanding of heterogeneous ones.

This part of the review is sub-divided into sections dealing with catalyst types, hydrogen-donor types, reaction conditions, solvents, mechanisms and finally, a list of functional groups that can be reduced successfully using heterogeneous transfer methods. This last section includes also some indication of the selectivity of the method and any advantage it might have over other methods of reduction.

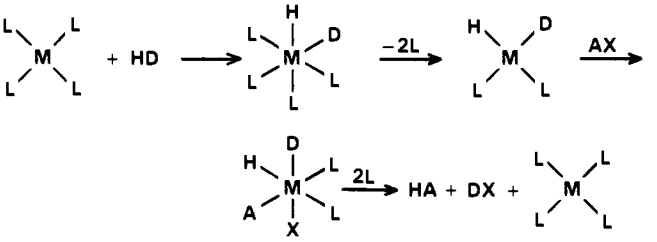
A. Catalyst Types

1. Homogeneous Catalysts

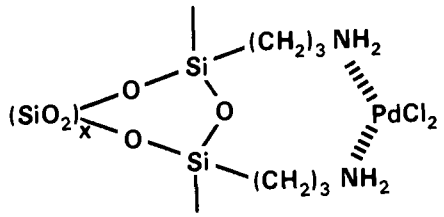
Most of the elements that have proved valuable in forming compounds suitable for catalytic homogeneous reductions form part of the second transition series in the periodic table. Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni, and Co have been used as catalysts for the transfer of hydrogen from molecular hydrogen or hydrogen donors to organic substrates. Generally, the most active catalysts are to be found in the salts and complexes of Rh, Ru, and Pd, although strenuous efforts have been made to find catalysts from among the less expensive metals and some success has been achieved in this direction, as for example, with the complex molybdenum compound, $MoH_4(DPE)_2$.[67]

The catalytic activity of the transition-metal salts and complexes is the result of a delicate balance of valence states and strengths of chemical bonds.[68] Too strong a bond between hydrogen donor and the transition metal results in stable compounds showing no catalytic activity. Similarly, there is no catalytic activity if reaction between hydrogen donor and the transition element cannot occur. Not only must the hydrogen source be accommodated by the transition metal, but also the organic substrate must be able to bond if transfer of hydrogen to the substrate is to occur. The products of catalytic transfer hydrogenation may themselves inhibit catalytic activity (self-inhibition); this phenomenon appears not to be unusual.[69] Thus, *catalytic* activity depends on a balance of energies with regard to the binding of the substrate to the metal and the desorbing of any resulting reduced substrate. The process can be represented as in Scheme XII, in which HD is a hydrogen donor (e.g., formic acid, in which D = CO_2H) and AX is a reducible organic substrate. Oxidative additions and eliminations lead to the formation of a reduced species HA and regeneration of the catalyst, ML_4. The activity of the catalyst depends on the existence of free coordination sites on the central metal or on the possibility of producing a vacant site by loss of a ligand. Therefore, the coordination number of the metal complex should be less than the maximum possible, or for saturated complexes, the ligand–metal bond strength should be such that dissociation is possible or that ligand displacement by solvent, hydrogen donor, or substrate hydrogen acceptor can occur. Kinetic measurements of rates of various hydrogen-transfer reactions indicate that their mechanisms depend on the nature of the catalyst and the coordinative powers of the hydrogen donor, the hydrogen acceptor, and the solvent. Some types of compounds bond strongly to the central metal atom and effectively deactivate it so that the catalyst is described as being poisoned. Thus, sulfur compounds, some phosphines,[70] CO, O_2, hydrogen halides,[71] and some solvents[72] act as general catalyst poisons. Sometimes the catalyst may induce polymerization of the substrate and become inactivated through being locked up in the resulting polymer.[73] Because of the wide choice of ligands, extensive modification of homogeneous catalysts is possible, but the final catalytic activity is a result of a delicate balance of factors and small changes of structure can lead to large changes in activity.

SCHEME XII



Operational temperatures for catalytic transfer hydrogenation using homogeneous catalysts are rarely low (for examples of reactions carried out at 20–80 °C, see ref 73–76), and usually require moderate to high temperatures in the region of 100–200 °C (see 69, 71, 77–84 as examples). Another problem associated with homogeneous catalysts has been the difficulty of their recovery from reaction products.[78–83] By attaching homogeneous catalysts to a solid, often polymer, support "insoluble homogeneous" (hybrid) catalysts have been prepared and used for hydrogenation with molecular hydrogen.[85–92] As an example, $PdCl_2$ has been attached to silica through amino group ligands (structure 1) and



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was active in the reduction of unsaturated to saturated esters.[93] Unfortunately, many of these catalysts appear to be unstable and lose the complexed metal to the reaction medium (i.e., the catalyst is dissolved from its support) or the complex salt is reduced to the metallic state.

Finally, mention should be made of a significant advantage of homogeneous catalysts. By making chiral catalysts through the use of chiral ligands, stereoselectivity can be attained, sometimes to a high degree.[62,94] For catalytic transfer hydrogenation, the highest optical yield attained appears to be about 20%.[77,80,95]

The salient features of mechanisms of homogeneous catalytic transfer hydrogenation discussed above have been elucidated by many carefully devised experiments with catalysts, substrates, and hydrogen donors of known structure. These mechanistic features are useful for discussion of heterogeneous catalytic transfer hydrogenation in which, because of the heterogeneous nature of the catalyst, experimental results are much more difficult to achieve and interpret. Accordingly, comparisons of results of homogeneous and heterogeneous catalytic transfer reductions and a knowledge of the mechanisms of the homogeneous methods allow some inferences to be drawn regarding the mechanisms of heterogeneous transfer reductions. Table I gives leading references to a variety of homogeneous catalysts that have been used for transfer reduction.

TABLE I. References to Homogeneous Catalysts Used in Transfer Hydrogenation

catalyst	ref
$RuCl_2(PPh_3)_3$	71, 72, 79, 81, 84, 85, 95–97, 100–103, 105, 106, 109, 110, 112, 116, 118, 120, 122
$RuH_2(PPh_3)_4$	75, 79, 81, 97, 100, 102, 105, 106, 109, 110, 113, 297
$RuH_2(CO)(PPh_3)_3$	106, 110
$RuH(CO)Cl(PPh_3)_3$	297
$RuH(CF_3CO_2)(CO)(PPh_3)_2$	73
$RuCl_2(PR_3)_3$ [R, chiral]	80, 81, 95
$RuCl_2(PPh_3)_4$	297
$RuCl_3$	72, 104, 109, 111, 121, 297
$RhCl(PPh_3)_3$	72, 74, 82, 84, 97, 103, 106, 109, 110, 115, 120, 297
$RhCl(CO)(PPh_3)_2$	110, 115, 122, 297
$RhCl(CO)_2(PPh_3)$	297
$RhX(PR_3)_3$ (X = diene, halogens; PR_3 = various phosphines]	69, 98, 99
$RhCl_3 \cdot 3H_2O$	72, 104, 106, 121, 297
$RhH(PPh_3)_4$	72, 97, 102, 106, 109, 110, 115, 122
$RhH(CO)(PPh_3)_3$	297
$IrHCl_2(Me_2SO)_3$	74, 96
$IrHCl_2(CO)(PPh_3)_2$	297
$IrH_2Cl(PPh_3)_3$	297
$IrHCl_2(PPh_3)_3$	297
$IrH_3(PPh_3)_2$	117
$IrH_5(PPh_3)_3$	297
$IrX(CO)(PPh_3)_2$ [X = Cl, Br, I]	297
$IrH(CO)(PPh_3)_3$	297
$IrH(CO)_2(PPh_3)_2$	297
$IrCl(C_6H_{12})PPh_3$	99
Ir(Phen)(COD)Cl	74, 96
$IrH[P(OPh)_3]_4$	297
$Os(CF_3CO_2)(CO)(PPh_3)_2$	73
$OsHCl(PPh_3)_3$	122
$OsH(CO)Cl(PPh_3)_3$	297
$PdCl_2(PPh_3)_2$	102, 103, 110, 115
$Pd(OAc)_2$	104
$PdCl_2$	72, 93, 102, 104–109
$(NH_4)_2PdCl_4$	102, 104–106, 109
$MoH_4(DPE)_2$	67
$PtCl_2(PPh_3)_2$	103, 110, 115
$PtCl_2/SnCl_2$	108, 297
K_2PtCl_4	104
$PtCl_2(SnCl_2)(PPh_3)_2$	115
cis-$PtCl_2(PEt_3)_2$	297
$FeCl_2(PPh_3)_2$	109, 110, 115, 119
$CoCl_2(PPh_3)_2$	109, 110, 115
$NiCl_2(PBu\text{-}n_3)_2$	109, 110, 115
$ReCl_5$	109
$CoH[P(OPh)_3]_3$	110

2. Heterogeneous Catalysts

Naming of homogeneous catalysts is usually a matter of routine chemical nomenclature, but no such simplicity exists for heterogeneous catalysts. IUPAC symbols and terminology for use in heterogeneous catalysis have been published.[123]

The most active catalysts for heterogeneous transfer reduction are based on palladium metal. Catalysts may be pure bulk metal, finely divided, dispersed on various carriers, as with palladium on carbon, $Pd/CaCO_3$, $Pd/BaSO_4$, and Pd/asbestos or be of a porous or skeletal type. Less versatile catalysts are derived from Ni, Rh, Ru, Pt, Ir, Os, and Co, again as finely divided metals, as metals supported on carbon (charcoal) or as skeletal metals like Raney Ni.[124] In a study of relative catalytic activity for the transfer hydrogenation of 2-methylbuta-1,3-diene using 2-methylhydroquinone as the hydrogen donor, decreasing activity was observed in the order Pd > Rh > Ni > Pt. Alloys of many metals have been examined for catalytic activity toward hydrogenation, dehydrogenation, and hydrogenolysis in industrial processes, but with a few exceptions such as Pd–Ru and Ni–Cu, these alloys have created only modest interest. However, the synergistic effects of mixed catalysts have been emphasized, and it was shown that the catalysts need only be mixed physically and not alloyed.[125] It was proposed that this synergism was due to the different activities of each of two mixed catalysts to intermediates produced during catalytic hydrogenation, and not the effect of one catalyst on the other. From this point of view, synergistic effects of simple mixed catalysts in catalytic transfer hydrogenation could repay further study.

Sometimes, pure finely divided (black) metals prove to be more active than supported ones. For instance, in the hydrogenation of methyl linoleate using indoline as the hydrogen donor, catalytic activity was found to fall in the order, Pd black > Pd/C > Pd/asbestos > Pt black > Raney Ni > Pt/asbestos.[47] A similar order of activity was found in the hydrogenolysis of benzyloxycarbonyl and benzyl protecting groups of peptides using cyclohexadiene as hydrogen donor, i.e., Pd black > 10% Pd/C > 5% Pd/C > 10% $Pd/BaSO_4$ > 5% $Pd/BaSO_4$.[126] In other circumstances, this order of activity

is reversed. For example, the finely divided metals Ru, Rh, Pd, and Pt were inactive for the dehydrogenation of benzhydrol,[103,127] but all of these metals when supported on charcoal effected its dehydrogenation. It was found that commercially available catalysts supported on charcoal contained small quantities of chloride ions which were responsible for their good activity; heterogeneous catalysts prepared by hydrogenation of chloride-free metal oxides were inactive. Similar results have been observed in the transfer reduction of cycloheptene, using indoline as hydrogen donor.[70] This synergistic effect of traces of chloride ions contrasts sharply with the observation that the normally vigorous transfer reduction of 1,3-dinitrobenzene to 1,3-diaminobenzene using formic acid as hydrogen-donor with Pd/C catalyst is stopped almost instantaneously by addition of chloride ion (as HCl for example).[128]

Some of the variations observed in catalytic activity of metals in free finely divided form (blacks) or finely divided and supported are due to different methods of preparation and aging. Metals that are produced in a finely divided form tend to agglomerate and lose their catalytic activity. This agglomeration may even be accelerated by the action of the substrate or even through polymerization of the substrate onto the catalyst.[129] Precipitation of metals onto a supporting surface is often advantageous, both because it leads to a more uniform size of particles or clusters of atoms than can usually be obtained with unsupported metals, and also it leads to a large area of active surface for a given weight of metal (higher specific surface density). As illustrated above for chloride ions, even small quantities of some compounds can alter substantially the properties of a catalyst and can have a promoting (enhancing) or poisoning effect. These alterations in the activity of a catalyst surface are generally caused either through simple physical blocking of some adsorption sites or through changes in the orbital energies of electrons in surface atoms. A large range of analytical and kinetic techniques has been used to investigate the nature of catalysts and their surfaces. These techniques include measurements of surface area, particle size, pore structure, and the application of various forms of spectroscopy.[130-132] Whatever the reasons for changes in activity of a catalyst, careful control in the preparation of a heterogeneous catalyst is of great importance if catalysts with reproducible activity are to be prepared.[124,133] This stringent requirement for exact reproducibility in the preparation of heterogeneous catalysts is not a problem for homogeneous catalysts which are prepared as discrete molecular species.

The major factors that need to be considered in the preparation of a heterogeneous catalyst are (a) the type of metal salt to be reduced to metal, (b) the kind of reducing agent used, (c) procedures adopted for washing the prepared catalyst, and (d) the purity and physical form of any supporting material. For example, formation of finely divided nickel from its alloy with aluminum (Raney Ni) in the usual way[134] gave a catalyst which, in its activity towards hydrogenation, was different from a nickel catalyst prepared by reduction of a soluble nickel salt with $NaBH_4$.[135,136] Contrariwise, two series of the finely-divided metals (blacks) Ru, Ir, and Os, obtained from suitable soluble salts by reduction, in one case with sodium formate and in the other with sodium tetrahydroborate, exhibited no differences in activity toward transfer reduction of 4-*tert*-butylcyclohexanone using 2-propanol as hydrogen donor.[137]

The formation of the catalytic metal as crystallites and particles of optimal size and shape for maximum activity depends on the speed of stirring during reduction of the metal salt, and on the temperature. Since metal atoms on a surface or in crystallites or particles tend to migrate and cluster, particularly at elevated temperatures, the temperature regime applied during preparation of the catalyst is important; variations in temperature during catalyst preparation between one batch and another can lead to large changes in activity. The most active sites in crystallites are located at edges and corners where interatomic coordination is smaller than in the bulk of the metal or on a plane surface.[138,139] With alloys, the actual composition of the alloy at the metal surface may change from that in the bulk of the metal through thermal effects.[143] The commercial production of batches of catalysts with uniform activity is a major problem for heterogeneous catalysis generally, and not just for catalytic hydrogen-transfer reduction.

While homogeneous catalysts can be deactivated by catalyst poisons, this effect seems to be more severe with the heterogeneous catalysts, particularly where these are formed from metals deposited on active carbon (charcoal) as a support. The finely divided form of the catalyst is ideal for adsorption of gases and the activity of a heterogeneous catalyst can be reduced or completely inhibited by traces of S, P, N, Hg, and other elements or their compounds.[70,139,144,145] Even oxygenated compounds may inhibit catalysis. For example, benzaldehyde is known to inhibit the disproportionation of cyclohexene over palladium.[146] Of course, not all S, P, and N compounds inhibit catalytic activity and, although sulfur-containing substrates are usually avoided in catalytic reduction, some sulfur-containing compounds can be reduced by catalytic transfer methods. The state of oxidation of an element is frequently of importance in determining whether or not it imparts a poisoning character to a substrate. Divalent sulfur is a notorious catalyst poison[147] but, for sulfoxides and sulfones (tetra- and hexavalent, respectively), little if any poisoning is observed. On the hard and soft acid/base principle[148] (or class a and b elements),[149] the transition metals which provide the most active catalysts are "soft" acids and their characteristic poisons are "soft" bases (e.g., divalent sulfur). Once the surface of a heterogeneous catalyst is covered with these strongly bound poisons, the substrate-acceptor and hydrogen-donor molecules cannot react. It is frequently impossible to reactivate a heterogeneous catalyst by simple means. This poisoning effect may be induced even by the products of reduction (self-inhibition). For example, in the catalytic transfer reduction of the 1-phenyltetrazolyl ether of 4-cyanophenol, using a Pd/C catalyst and hydrazine as hydrogen donor, the formation of the product (cyanobenzene) led to the reaction rate decreasing as the percentage of product increased.[150] Although a high yield of cyanobenzene was achieved ultimately, it was necessary to use a very extended reaction time compared with the times normally expected for this process under similar reaction conditions.

Solvents are not normally regarded as "poisons" in

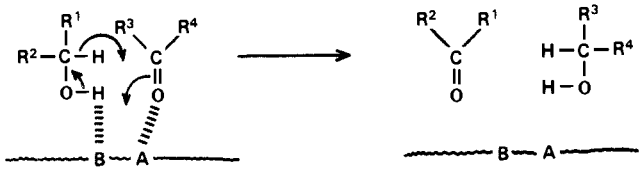
heterogeneous catalysis and yet they may bind strongly to the surface of a metal and inhibit its catalytic activity.[70,126] It is perhaps fortunate that most typical organic solvents are either relatively nonpolar or contain electronegative, relatively "hard" elements like oxygen. However, in considering possible solvent systems for heterogeneous catalytic transfer reduction, it is important to realize that the solvent may compete so effectively for sites on the catalyst surface that the substrate and hydrogen-donor molecules cannot reach the catalytic sites. On the other hand, solvent may promote catalytic activity by displacing other strongly bound species. Thus, water is known to poison H/D exchange between C_6H_6 and D_2O over Pt;[151] in the catalytic transfer hydrogenolysis of 1-phenyltetrazolyl ethers of phenols,[150] neat formic acid was relatively ineffective even at 110 °C, but a two-phase benzene/water/formic acid system was highly active at 80 °C. Unlike the more usual poisons, which often form actual chemical bonds between themselves and the metal catalyst, solvents mostly bind reversibly to the catalyst. In this dynamic situation, there are finite chances for substrate and hydrogen-donor molecules to reach the catalyst surface. An increase in temperature weakens this dynamic coordination of solvent molecules and increases the thermal content of substrate and hydrogen donor, so that for any one solvent, raising the temperature of the system removes some of the inhibiting effect of the solvent on the activity of the catalyst.[152] For example, it has been observed that, under otherwise identical reaction conditions, the catalytic transfer reduction of dinitroarenes to diaminoarenes using Fe(III) hydroxide and hydrazine was completely changed by change of solvent. In methanol or ethanol, reaction proceeded smoothly, but did not do so in mixtures of ethanol/ethylene glycol (1:1 v/v) or ethanol/ethylene dichloride. 1,3-Dinitrobenzene was reduced with Raney Ni and hydrazine to 3-nitroaniline in ethanol, but to 1,3-diaminobenzene in ethanol/dichloroethane. Similarly, catalytic hydrogen-transfer reduction of 1-phenyltetrazolyl ethers of phenols to give arenes was found to be strongly solvent dependent.[150]

Intentional poisoning of catalysts can be used to advantage where selectivity is required. In the transfer reduction of fatty acids containing alkyne groups, the high activity of the catalysts used led to the formation of fully saturated fatty acids as well as *trans*-alkenyl products instead of the desired *cis* products.[106] Similarly, in the reduction of simple alkynes using Pd/C and ammonium formate or sodium phosphinate as hydrogen donor, *cis*-alkenes were formed, but overreduction to alkane also occurred.[129,145] Modification of commercial Pd/C catalysts by precipitation of lead or mercury metals onto them afforded catalysts which were selective for the reduction of alkynes to *cis*-alkenes without the formation of significant quantities of *trans*-alkenes or alkanes.[145] It was observed that the molar ratio of Pb or Hg to Pd in these catalysts were critical. With too small a ratio of Pb or Hg to Pd, the selective properties of the catalyst were no different from that of Pd alone, but the rate of transfer reduction was reduced. With too high a ratio, the catalyst was selective, but the reaction rate became inordinately slow. With an optimum ratio, both selectivity and reaction rate were very good. The selective poisoning effect found for these Pd/Hg catalysts mirrors similar earlier results on the gas-phase hydrogenation of acetylene.[153]

Several comparisons of the effectiveness of homogeneous and heterogeneous catalysts toward transfer reduction have been published, but have not shown that either type of catalyst has better all round properties than the other in terms of general reactivity. Up to the present, heterogeneous catalysts have not proved to have any value in reductive asymmetric synthesis.[154] The dehydrogenation of benzhydrol to benzophenone has been compared for Ru/C, Pd/C, Pt/C, and the soluble salts, $RuCl_2(PPh_3)_3$, $PdCl_2(PPh_3)_3$, $PtCl_2(PPh_3)_3$.[127] The activity of the soluble catalysts was slightly better than that of the heterogeneous catalysts, as judged by the time and temperature required for an adequate reaction rate. Dehydrogenation with the soluble catalysts required a 4-h reaction time at 186 °C, but the heterogeneous catalyst required 24 h at 210 °C. The heterogeneous Pd/C catalyst was inactive for transfer reduction of 1-phenylbut-1-en-3-one, but the homogeneous catalysts, $RuCl_2(PPh_3)_3$ and $RhH_2(PPh_3)_3$, effected its reduction to the saturated ketone, 1-phenylbutan-3-one, at 140 °C in the presence of poly(vinyl alcohol).[97,100] At 140 °C, both $RuH_2(PPh_3)_4$ and $RhH(PPh_3)_4$ transferred hydrogen from limonene or cholesterol to unsaturated fatty acid esters, but the heterogeneous catalysts, Pd/C, Pd/asbestos, Pd black, and Pt/asbestos were all inactive.[102] Although Pd/C is active in this reduction when cyclohexene is used as the hydrogen donor, selectivity is low.[106] A comparison of the activities of Rh/C and Ir/C with those of phosphine complexes of these metals in the transfer reduction of ketones with 2-propanol or in the dehydrogenation of cyclohexane showed that the heterogeneous and homogeneous Rh catalysts had similar activity, but the Ir/C catalyst was less active than its homogeneous counterpart.[99] Reductions of nitro compounds with indoline as hydrogen donor and a variety of soluble and heterogeneous catalysts gave the following results (percentage yields of amine are given in parentheses): $RuCl_3$(88), $RhCl_3$(82), $PdBr_2$(50), Pd black(50), $PdCl_2$(20), and Pd/C(20).[109] Phosphine complexes of Ru and Rh have been found to be more selective than corresponding heterogeneous catalyst for the transfer hydrogenation of unsaturated cyclic ketones and oxiranes.[103] With respect to liquid-phase transfer hydrogenations, heterogeneous catalysts have a number of advantages over many soluble homogeneous catalysts. Generally, heterogeneous catalysts seem to need lower reaction temperatures, can be used in aqueous media, have no need of nitrogenous or oxygen-free atmospheres, can utilize simpler hydrogen-donor types (see later), and are easily separated from the reaction products. Often, a heterogeneous catalyst can be reused several times for the same type of reaction before its activity is noticeably diminished.

Heterogeneous transition-metal catalysts have been used in vapor-phase-transfer reductions, but these have been effected also by a variety of metallic oxides. Detailed studies of the vapor-phase-transfer hydrogenation of ketones using alcohols as hydrogen donors have revealed their intrinsic mechanistic similarity to the Meerwein–Pondorff–Verley reaction when MgO,[155,156] MgO/SiO_2,[157] Al_2O_3,[158,159] Al_2O_3/Na,[160,161] lanthanide oxides,[162] indium,[163] and hydroxyapatite[164] were used as catalysts. These catalysts appear to have two active centers, one basic and one acidic (Scheme XIII). The

SCHEME XIII



alcohol (hydrogen-donor) is adsorbed on the basic site (B) and the ketone on an adjacent acidic site (A) and hydrogen is transferred as hydride. All types of unsaturated ketones are reduced to the corresponding unsaturated alcohols in this reaction.

There have been many industrially oriented studies of concurrent hydrogenation/dehydrogenation reactions in the vapor phase. For example, transfer of hydrogen from cyclohexane to thiophene was found to proceed using Co–Mo/Al_2O_3 catalyst with Cr, Ti, V, Zn, and Zr as promoters, although the reaction led also to the undesired desulfurization of the thiophene.[165]

Table II lists references to the various types of heterogeneous catalyst that have been used for transfer hydrogenation. The table is not exhaustive, but provides leading references to much of the available literature.

3. Controlled Changes from Homogeneous to Heterogeneous Catalysts

In an unusual series of experiments, the catalytic activity of various systems has been compared in both homogeneous and heterogeneous modes.[193] For the system, $H_2PtCl_6 + xSnCl_2$, as the proportion of $SnCl_2$ decreased ($0 \leq x \leq 6$), the system changed from being homogeneous to heterogeneous. In the homogeneous mode ($x = 6$), no catalytic hydrogenation (with H_2) could be achieved, but in the heterogeneous mode ($x = 0$), cyclohexene was reduced to cyclohexane. In contrast, the same system in the homogeneous mode effected hydrogenation of styrene to ethylbenzene but, as x decreased from 6 to 0.9, the rate of hydrogenation fell; as x decreased further ($0.9 \geq x \geq 0$), the rate of hydrogenation rose again. Similar interesting variations in reduction rates were observed for $RhCl_3 + xSnCl_2$, $NiCl_2/NaBH_4$/dimethylformamide, $CoCl_2 \cdot 6H_2O/NaBH_4$/dimethylacetamide. Dehydrogenation was investigated in the systems, $RhCl_3$, H_2IrCl_6, and Li_2IrCl_6. Repetition of those experiments for catalytic transfer hydrogenation would be highly desirable.

4. Organic Catalysts

Under this heading would come normally most enzyme systems, a vast area clearly outside the scope of this review. There have been attempts to mimic enzyme systems, with simple model compounds and, in just a few of these cases, as for example with Hantzsh esters, hydrogen-transfer reduction has been the reaction attempted. 1,5-Dihydro-5-deazaflavins have been used to catalyze the transfer of hydrogen from formic acid to benzaldehyde causing it to be reduced to benzyl alcohol.[194] This "NADH-like" reaction has been compared to the enzymic formate- and 5-deazaflavin-dependent NADP reduction in methane-producing bacteria. Similar reductions of aldehydes by NADH analogues previously have only been reported as proceeding stoichiometrically;[60] arenediazonium salts have been reduced to arenes[60d] and allylic acetates to alkenes[60e] with model NAD(P)H compounds.

TABLE II. References to the Commoner Heterogeneous Catalysts Used in Transfer Hydrogenation

catalyst	ref
Pd/C	2, 47, 70, 72, 79, 97, 100, 102, 103, 106, 109, 126, 127, 129, 145, 154, 166, 170, 172, 176, 178–186, 188
Pd (black)	47, 72, 103, 109, 126, 127, 137, 167–169, 173, 174, 189, 190, 191
Pd/asbestos	47, 70, 72, 102, 187
$Pd/BaSO_4$	126
$Pd/CaCO_3$	152
Pd/Pb/C; Pd/Hg/C	145
Ni(Raney)	47, 102, 127, 137, 145, 175, 177, 182, 189–191
Pt/C	103, 127, 128, 182
Pt (black)	47, 102, 103, 137, 189, 190
Rh/C	99, 103, 127, 128, 145, 179, 182, 183
Rh (black)	103, 127, 137, 189–191
Ru (black)	103, 127, 137, 189, 190
Ru/C	103, 127, 145
Ir (black)	137
Ir/C	99
Pd/Ru	291
Ni/Cu	214
Os (black)	137
Co (black)	137
Fe (black?)	137, 152, 171
MgO/SiO_2	157
MgO	155, 156
Al_2O_3	158, 160, 161
lanthanide oxides	162
In	163
$Co/Mo/Al_2O_3$	165

The use of quinones as stoichiometric dehydrogenating agents is a well-known reaction which appears to proceed through ionic charge-transfer[195] or hydride-transfer[82] mechanisms. By incorporating quinones into a polymer system, it has proved possible to use them catalytically. Polynaphthoquinone is reduced to polynaphthohydroquinone by H_2S at 30–100 °C. In the absence of air, S is deposited but, in the presence of air, H_2O is formed by transfer of hydrogen from H_2S *via* the polynaphthoquinone/polynaphthohydroquinone system.[196] At higher temperatures (300–330 °C), catalytic hydrogen transfer could be effected from ethylbenzene to nitrobenzene with the production of styrene and aniline. Similarly, *n*-propylbenzene, cumene, and cyclohexanol have been used as hydrogen donors.

Reduction of organic compounds following electronic excitation (photochemistry) is not considered here, but photolytic catalytic hydrogen transfer is dealt with briefly. Conversion of solar light energy into chemical energy is, of course, the basis of photosynthesis and considerable research effort has gone into systems that might mimic the natural ones. In recent work, photoexcited corrole was found to catalyze the reduction of benzaldehyde to benzyl alcohol through electron (hydrogen) transfer.[197] The electronically excited corrole was able to remove an electron from benzenethiol and, on returning to the electronic ground state, to transfer the electron to benzaldehyde. Presumably, protonation completed the series of reactions. Other reducible substrates which have been investigated in such photoreductive systems include dyes and azobenzene,[198] quinones,[199] riboflavins,[200] NAD,[201] and nitrobenzene.[202]

SCHEME XIV

$$R_2CHOH \longrightarrow R_2CO + H_2 \quad (a)$$

$$2R_2CHOH \longrightarrow R_2CHOCHR_2 + H_2O \quad (b)$$

$$3R_2CHOH \longrightarrow (R_2CH_2)_2 + R_2CO + 2H_2O \quad (c)$$

$$2R_2CHOH \longrightarrow R_2CH_2 + R_2CO + H_2O \quad (d)$$

$$\left.\begin{matrix} R_2CHOH \\ + \\ R_2'CHOH \end{matrix}\right\} \longrightarrow R_2CH_2 + R'_2CO + H_2O \quad (e)$$

B. Hydrogen Donors

1. Homogeneous Catalysis

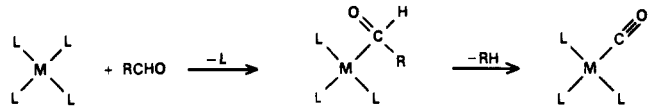
Although homo- and heterogeneous catalysts can utilize common types of compounds as hydrogen donors, it is more often the case that different types of compounds are favored in the two systems. The more active hydrogen donors for homogeneous catalysis appear to be principally alcohols, hydroaromatics, cyclic ethers, and occasionally formic and ascorbic acids whereas, for heterogeneous catalysis, the more widely used donors tend to be hydrazine, formic acid and formates, phosphinic acid and phosphinates, indoline, and cyclohexene. There is no clear division between the two types, but some of the hydrogen donors which are active for heterogeneous catalysts are water-soluble inorganic salts and cannot be used with many homogeneous catalysts. More recently, trialkylsilanes and trialkylstannanes have proved to be good hydrogen donors in both homo- and heterogeneous catalysis.[40] Whereas tri-*n*-butylstannane reduced α,β-unsaturated aldehydes in methanol under fairly drastic conditions,[203] in the presence of $Pd(PPh_3)_4$ and a promotor, the reduction can be achieved in 10 min at room temperature.[40]

Of the alcohols, secondary ones have proved to be the best hydrogen donors and it is the hydrogen on the carbon attached to the hydroxyl (α-hydrogen) which is transferred in the first reductive step. Tertiary alcohols having no α-hydrogen atoms are not hydrogen donors and under the influence of catalysts, tend to condense to form ethers or to eliminate water to form alkenes.[71] Primary alcohols may or may not be good hydrogen donors and form a special case which is discussed more fully below.

Secondary alcohols in the presence of a homogeneous catalyst, but in the absence of a hydrogen acceptor may react in one of five principal modes viz., by dehydrogenation, dehydration, reductive coupling, disproportionation, and hydrogenolysis (equations a–d, respectively); where a second type of alcohol is involved, a reaction (e) similar to (d) may occur.[103,127] In the presence of a suitable hydrogen acceptor, reaction (a) usually occurs with the hydrogen being transferred to the acceptor, but not of course as the molecular hydrogen of reaction (a), and the secondary alcohol is transformed into a ketone.

An α-hydrogen of a primary alcohol is less likely than that of a secondary alcohol to react as a hydride species, because of the smaller electron-releasing inductive effect of one alkyl group as against two. Nevertheless, ethanol

SCHEME XV

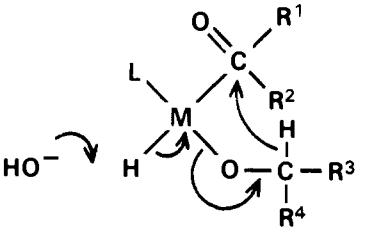


and 1-propanol have been used successfully for the transfer reduction of carboboranes,[204] aldehydes,[110] alkynes,[117] dienes,[121] and alkenes.[115] Benzyl alcohol is active in the reduction of double bonds in unsaturated ketones,[71,84] acids and esters,[77,95] and cycloalkenes,[115] and in the reduction of aldehydes to alcohols.[75,110] Even so, primary alcohols may not be rewarding as hydrogen donors because aldehydes, the products of their dehydrogenation, act as catalyst poisons. Also, aldehydes when complexed to some homogeneous catalyst systems are decarbonylated so that CO becomes a ligand which may inactivate the catalyst (Scheme XV).[67,119,121,205] In some catalyst systems in which ethanol or benzyl alcohol have been used successfully as hydrogen donors, attempts to detect such carbonyl complexes were unsuccessful.[115] There are reports of the resistance of aldehydes to decarbonylation[110] and, in contrast, others in which the aldehydes are decarbonylated to give a new active catalyst as a result of incorporation of the CO as a ligand.[206]

Diols, some primary and some secondary, have been used as hydrogen donors even though they yielded aldehydes by dehydrogenation. Ethane-1,2-diol, cyclohexane-1,2-diol, hexane-1,6-diol, and butane-2,3-diol have been utilized in the catalytic transfer reduction of alkenes to alkanes[100,105,106,116,140] and of ketones to alcohols.[207] Similarly, polyols such as furanoses, pyranoses, and poly(vinyl alcohol) have been employed to reduce unsaturated ketones to saturated ketones,[76,78,81,97,187,208,209] and α,β-unsaturated acids to saturated acids.[95] In the absence of a hydrogen-acceptor substrate, sugars undergo mutual oxidation/reduction to give, in place of two aldehyde groups, an alcohol and a lactone.[97,209] The best hydrogen donors among the sugars have been found to be glucoses or glucosides having an arrangement of three *cis*-hydroxyl groups which provide the best coordination to the catalytic metal.[76,182,208]

Despite the use of a variety of alcohols, 2-propanol remains the most popular donor, because of its simplicity, cheapness, availability, and the ease of removal of both it and its dehydrogenation product, acetone, from reaction systems. The mechanism of hydrogen transfer from 2-propanol to a ketone substrate using the catalyst, $RhCl(PPh_3)_3$, has been very extensively investigated so that most details of the mechanism are clear.[210] A synergist for this reaction is potassium hydroxide which is believed to be effective by removing a proton from the reacting complex during part of the catalytic cycle. Certainly, many other homogeneous catalyst systems using an alcohol as the hydrogen donor appear to need base (KOH) for their activity.[74,98,99,211–213] Scheme XVI indicates how this synergistic activity may arise by promoting the transfer of a hydride ion from an alkoxy radical onto an adjoining coordinated ketone. Despite this careful work, the full mechanistic details of general catalytic transfer reduction are not understood completely. Kinetic studies to compare the transfer reduction of cycloalkenes and aldehydes with $RuH_2(PPh_3)_4$ as catalyst and 2-propanol as hydrogen

SCHEME XVI



donor revealed a large kinetic isotope effect in the reduction of alkenes[113] (transfer of hydrogen being the rate-limiting step) and no isotope effect with aldehydes.[110] This result does not invalidate the overall view of this type of hydrogen transfer, since it probably reflects only the different timing of certain steps of the whole reaction of cycloalkenes as compared with aldehydes.

Of other kinds of hydrogen-donor that have been used, some mention should be made of cyclic ethers like dioxane[69,82] and dihydrofuran[110] and of aldehydes[120] and formic acid.[104,116,120] Hydroaromatic compounds, which may be concomitantly dehydrogenated to aromatic compounds, have been used widely as hydrogen donors. For example, most functional groups can be reduced by using tetrahydroquinoline, piperidine, pyrrolidine, and indoline (ref 72, 105, 107, 109, 114, 128, 140, 141) and the hydrocarbons, indan and tetralin have served to reduce aldehydes to alcohols (ref 75, 110, 142). Aromatization is not necessarily the driving force of these reactions because, although indoline is dehydrogenated to indole in these reactions,[140,141] piperidine does not yield pyridine.[141] The effects of these hydrogen donors are not uniform so that successful use of one donor in one situation does not imply its success in another. Aldehydes can be reduced to alcohols in high yields using $RuH_2(PPh_3)_4$ at 140 °C with 2,5-dihydrofuran or 2-propanol as hydrogen-donor,[110] but the same donors with $RhCl_3$ at 120 °C were ineffective in reducing nitrobenzene to aniline.[72]

Some leading references to the use of the above hydrogen donors in catalytic transfer reduction are given in Table III.

TABLE III. References to Hydrogen Donors Used in Homogeneous Catalytic Transfer Hydrogenation

hydrogen donor	ref
cyclohexene	72, 75, 109
indan	142
tetralin	75, 110, 290
indoline	72, 104, 106, 107, 109, 114, 140, 141
tetrahydroquinoline	107, 114, 140, 141
dihydrofuran	75, 110
dioxan	69, 82
ethanol	115, 117, 121, 204
propan-2-ol	67, 73, 74, 75, 98, 99, 105, 110, 113, 115, 122, 205, 210–213, 290–293
pentan-2-ol	118, 294
2-methoxyethanol	295
benzyl alcohol	71, 75, 84, 95, 115
tetrahydrofurfurol	295
steroids	102
1,2-ethanediol	116, 207
2,3-butanediol	106, 140
1,2-cyclohexanediol	105, 106, 140
polyvinyl alcohol	79
ascorbic acid	210
sugars	76, 78, 81, 95, 97, 105, 106, 208, 209
phenols	119
formic acid	296, 297

TABLE IV. References to the Commoner Hydrogen Donors Used in Heterogeneous Catalytic Transfer Hydrogenation

hydrogen donor	ref
cyclohexene	47, 70, 167, 170, 173, 181, 184, 185, 186, 189, 226, 285, 288
cyclohexadiene	126, 281
limonene	70, 154
ethanol	177
propan-2-ol	137, 175, 177
benzyl alcohol	166
benzhydrol	127
hydroquinone	289
sugars	182
indoline	47, 70
N-benzylaniline	178
formic acid	47, 70, 128, 214, 281
formates	128, 129, 180, 225
phosphinic acid	128, 184
sodium phosphinate	128, 145, 170, 192
sodium tetrahydroborate	47
hydrazine	152, 171, 174, 192

2. *Heterogeneous Catalysis*

Some of the best hydrogen donors for heterogeneous catalytic transfer hydrogenation comprise of simple molecules such as cyclohexene, 1,4-cyclohexadiene, hydrazine, formic acid and formates, phosphinic acid and phosphinates, phosphorous acid and phosphites, and sodium tetrahydroborate (see Table IV). Generally, these donors are used with noble-metal catalysts (either finely divided or supported on carriers), but sometimes with other metals such as copper and nickel, often for use at higher temperatures. With the noble metals, particularly Pd, Pt, and Rh these hydrogen donors give up hydrogen to the substrate under mild conditions with reaction temperatures rarely exceeding 100 °C. After giving up their hydrogen, the other reaction products from the hydrogen donors are frequently easily removable from the reaction system. Thus, formic acid exhibits two modes of decomposition[214] and may give CO_2 or CO as its non-hydrogen containing side products, depending on the catalyst used. Similarly, hydrazine decomposes to give either nitrogen or ammonia together with hydrogen, but phosphinic acid (hypophosphorous acid) is normally oxidized to phosphorous acid by water in giving up its hydrogen, rather than undergoing decomposition. The mode of reaction of formic acid or hydrazine depends markedly on conditions of temperature, pressure, and type of catalyst. For example, in the gas phase over a copper catalyst, formic acid decomposes through the formate anion whereas, with nickel, it decomposes via an anhydride.[214,215] The different modes of decomposition of hydrazine are revealed by the types of functional groups that can be reduced with this hydrogen donor.[216] The decomposition of hydrazine over metals such as Pd tends to yield mostly hydrogen and nitrogen and can lead to hydrogenolysis of C–O bonds[174,192] or reduction of nitro groups[152,171] whereas its decomposition with oxidizing agents tends to produce diimide initially. The decomposition of hydrazine via diimide is characterized by the fact that diimide adds hydrogen to symmetrical (nonpolar) double bonds like those found in alkynes and alkenes, but not polar bonds like carbonyl.[216] The mode of decomposition of tetrahydroborates with catalysts is obscure. Although nitro compounds are not reduced directly by sodium tetra-

hydroborate via hydride transfer, in the presence of a noble-metal catalyst, reduction to amine occurs.[72]

In general, hydroaromatic compounds, terpenes, ethers, dienes, and alcohols are not so good as hydrogen donors with heterogenous as they are with homogeneous catalysts. Although these donors have been used in heterogeneous reactions, rather higher temperatures are needed for hydrogen transfer than those required when using homogeneous catalysts. Terpenes and dienes have been used as hydrogen donors for the hydrogenation of aldehydes, ketones, and alkenes.[154] In comparative studies, reduction of the alkene group in unsaturated fatty acids using a Pd/C catalyst was found to be less efficient than with homogeneous catalysts when using various hydrogen donors in the order, indoline > formic acid > cyclohexene > sodium tetrahydroborate > tetrahydroquinoline > 2,5-dihydrofuran.[47] A similar sequence of activity was found for the reduction of cycloalkenes over Pd/C.[70] In this last case, the order of activity for hydrogen donation was found to be indoline > formic acid > tetrahydroquinoline > piperidine > pyrrolidine > cyclohexene > *N*-methylpyrrolidine > di-*n*-propylamine > *d,l*-limonene > 1,2-dihydronaphthalene. The hydrogen donors, tetralin, 2-propanol, and dioxane, usually very effective in homogeneous catalytic reduction, were not active in this heterogeneous system. Interestingly, this same study revealed that the Pd/C catalyst was more effective with these donors in the hydrogenation of cyclohexene than were the homogeneous catalysts examined. Although 2-propanol was inactive in this system, it has been used successfully in other systems. Ketones[137,175] and aromatic hydrocarbons and alkenes[175] have been reduced with 2-propanol.

Although the dehydrogenation of benzhydrol[127] and of sugars[182] with heterogeneous catalysts has been investigated, these substances were not considered as hydrogen-donors, in contrast to similar experiments carried out with homogeneous catalysts.[67,80,81,95,105,106]

It should be remembered that hydrogen transfer from a hydrogen donor to an organic substrate (hydrogen acceptor) through the intermediacy of a heterogeneous catalyst is infrequently stoichiometric in donor and acceptor, unlike the reactions involving homogeneous catalysts. Many of the hydrogen donors can be decomposed by heterogeneous catalysts without there being any acceptors present. The equilibrium Scheme XVII existing in a closed system over a noble-metal catalyst has been known for many years[217,218] as has the decomposition of hydrazine.[216] These dehydrogena-

SCHEME XVII

$$HCO_2H \rightleftharpoons H_2 + CO_2$$

tions are more favored thermodynamically when hydrogen is transferred to an acceptor instead of being evolved as molecular hydrogen.[170] However, the simple adsorption and decomposition of hydrogen donors on active sites of a heterogeneous catalyst must be balanced against the competition for those sites from solvent, from putative acceptors and from reaction products. Further, different, but contiguous, sites may be necessary for donor and acceptor.[145] Enhancement of any one of these competitive binding forces to the active sites on the catalyst can lead to evolution of hydrogen without reduction of substrate if the hydrogen donor binds so successfully as to prevent adsorption of substrate. Contrariwise cessation of hydrogen production may occur through the substrate or solvent binding more successfully than the donor (poisoning of catalyst) and through autoretardation of reduction caused by oversuccessful binding of reduction products to the catalyst. All of these phenomena are well-known in catalytic transfer reduction and help to explain the sometimes apparently contradictory order of effectiveness of a series of hydrogen donors with any one catalyst or substrate system in comparison with another system or with homogeneous catalysis. For these reasons, and others relating to the catalyst itself, much of heterogeneous catalytic transfer hydrogenation, particularly in the liquid phase, is not well understood, except in very simple systems. Therefore, attempts at mechanistic interpretations of observed reactions are necessarily somewhat tentative (see later section). The discrepancies between homogeneous and heterogeneous catalysis and the discrepancies within heterogeneous catalysis alone should serve to deflate the oversimplistic view that heterogeneous catalytic transfer hydrogenation is simply a question of generating molecular hydrogen which can then be used with the catalyst as if molecular hydrogen had been used in the first place as the source of hydrogen.

C. Influence of Temperature on Catalytic Hydrogen-Transfer Reduction

1. Homogeneous Systems

In homogeneous systems at equilibrium or under steady-state conditions, normal solution kinetics can be applied and energies of activation and enthalpies have been determined experimentally for several systems.[71,82,110,114,115,141] Table V lists some representative results for a variety of reactions. In a practical sense, increase in temperature will lead usually to a faster overall rate of reaction, i.e., faster reduction, but for equilibria, the change in position of equilibrium with increasing temperature is not easy to predict. In many reductions, a linear increase in rate of reduction with increase in temperature has been observed.[71,82,84,114,115] Often, where comparative reactions can be studied, the transfer of hydrogen from a donor to an acceptor with a homogeneous catalyst requires a higher temperature than with heterogeneous catalysts using the same metal. However, increase in temperature has attendant difficulties in that unwanted reactions may be encouraged, as with overreduction and isomerization.[102,105,106] Where these side-reactions are unimportant, increase in temperature of reaction can afford higher yields of product for a given time of reaction. At 160 °C, reduction of cyclooctadiene with $FeCl_2(PPh_3)_2$ as catalyst and phenols as hydrogen donors was only 16% complete in the same time that a temperature of 270 °C gave a 99% yield.[119] α,β-Unsaturated ketones have been reduced optimally at 140 °C using $RuH_2(PP_3)_4$ as a catalyst and 1,6-hexanediol as the hydrogen donor. Different hydrogen donors may require different optimum temperatures. For example, in one series of reductions of α,β-unsaturated ketones with $RuCl_2(PPh_3)_3$ as catalyst,[120] formic acid was active as a hydrogen donor at 100 °C, formanilide at 180 °C, and various aldehydes

TABLE V. Thermodynamic Quantities Calculated from Variation of Reaction Rate with Temperature

reaction type	solvent	hydrogen donor	catalyst	E_A, kcal/mol	ΔH_A, kcal/mol	ΔS_A, eu	ref
hydrogenolysis							
Ph–Cl	CH_3OH	indoline	$PdCl_2$	14.5			141
Ph–Br				14.4			
Ph–I				13.5			
reduction of –CHO to $-CH_2OH$							
n-$C_5H_{11}CHO$	PhBr	benzyl alcohol	$RuH_2(PPh_3)_4$	10.3	9.6	−41.8	110
n-$C_5H_{11}CHO$	n-C_6H_{14}	benzyl alcohol	$RuH_2(PPh_3)_4$	17.2	16.6	−17.0	
n-$C_5H_{11}CHO$	PhBr	propan-2-ol	$RuH_2(PPh_3)_4$	11.0	10.3	−42.5	
n-$C_5H_{11}CHO$	$PhCH_3$	propan-2-ol	$RuH_2(PPh_3)_4$	31.4	30.7	20	
reduction of alkene							
PhCH=CHCOPh	DMF	1-phenylethanol	$RuCl_2(PPh_3)_3$	25.4	24.3	−7.55	71
PhCH=CHCOPh	DMF	polyvinyl alcohol	$RuH_2(PPh_3)_4$	14.0			79
c-C_7H_{12}	$PhCH_3$	indoline	$RhCl(PPh_3)_3$	33.2	32.0	10.2	114
c-C_7H_{12}	$PhCH_3$	propan-2-ol	$RhH(PPh_3)_4$	21.4	20.7	−10.8	115
c-C_5H_6	$PhCH_3$	dioxane	$RhCl(PPh_3)_3$	21.6			82

at 200–285 °C. Similarly, variation in the hydrogen acceptor will afford various optimum temperatures for any one hydrogen donor. For example, with indoline as donor and $PdCl_2$ as catalyst,[141] chlorobenzene could be hydrogenolyzed at 70 °C but bromo- or iodobenzene required a temperature of 100 °C.

As mentioned above, the effect of temperature on equilibria is unpredictable without experimental data. At higher temperatures, the rate of the reverse reduction in equilibrium Scheme XVIII was increased as well as the rate of the forward reaction and the product yield was dependent on temperature. Although the yield of products from these reactions (Scheme XVIII) were attained more rapidly with increase in temperature, the actual yield did not vary in a simple manner.[142]

SCHEME XVIII

$$R^1R^2C{=}O + R^3R^4CHOH \overset{\text{catalyst}}{\rightleftharpoons} R^1R^2CHOH + R^3R^4C{=}O$$

By their nature, homogeneous systems are amenable to the kind of kinetic analysis applied to reactions in solution, and the results of these investigations are explicable in terms of solution kinetics. The starting materials (catalyst, hydrogen donor, hydrogen acceptor, and solvent) are all compounds in standard states in solution. This situation contrasts markedly with heterogeneous systems in the liquid or gas phase, where generally the nature of the all-important catalyst surface is poorly defined, varying in activity from area to area and reaction occurs by transfer of reactants and products between solid and liquid or gas phases. Nevertheless, a heterogeneous catalyst increases the rate (k_1) for a forward reaction *and for the reverse reaction* (k_{-1}) because of the equilibrium constant ($K = k_1/k_{-1} = \exp(-\Delta G°/RT)$; a heterogeneous catalyst does not change the Gibbs free energy of a reaction. However, reaction conditions for the forward reaction are often different from the reverse reaction, and lead to an overall acceleration in the forward reaction. This is especially true of catalytic hydrogen transfer, where the products of reaction are removed rapidly from the catalyst. For example, when formic acid is used as a hydrogen donor, CO_2 is released usually to atmosphere and is not available for the back reaction. Similarly, adsorption of the products of a catalytic transfer reduction must be removed from the catalyst surface or the reaction becomes self-inhibiting. Again, this removal alters the conditions for the reverse reaction and upsets the equilibrium process.

2. Heterogeneous Systems

The discussion in section III C1 on the influence of temperature on homogeneous systems has dealt in part with heterogeneous systems also. A major difference between the two types of catalyst, apart from the phase differences, lies in the difficulty of ensuring that heterogeneous catalysts can be prepared reproducibly not only in one laboratory, but also in other laboratories. It is straightforward to describe the synthesis of a homogeneous (solution) catalyst and there are ample techniques available to verify that the catalyst is what it is supposed to be, and that it is pure. For example, a whole battery of techniques (elemental analysis, spectroscopy, analytical chromatographic methods) can be utilized to determine the purity of a solution catalyst. Such is not the case with heterogeneous catalysts for which the method of preparation may be all-important in determining activity and which have a propensity for changing their catalytic properties, through use or simply over a period of time in storage. Even pure metals deposited as thin films in ultra-high-vacuum conditions do not necessarily lead to reproducible catalysts because of the various degrees of migration of atoms and formation of crystallites.[138,139,214] It is also open to question as to just what relevance such prepared films have to the everyday catalysts used routinely in chemical reactions. These latter catalysts certainly have surfaces with a very different topography from that of a deposited film. A similar argument regarding relevance to everyday catalysts can be proposed for single crystal studies. The argument concerning relevance is not used to denigrate studies of films and single crystals, since these can give fundamental information concerning adsorption sites on catalysts and kinetics of reaction[219] but, rather, is used to emphasize the difficulties involved in mechanistic studies on the ill-defined catalysts routinely used for carrying out chemical syntheses.[124,133] Since the nature of the catalyst is not defined properly, results from mechanistic studies of heterogeneous catalytic transfer reduction are often not applicable to another catalyst. For instance, the dispersion of Pd on charcoal gives a very different catalyst from Pd dispersed on barium sulfate; even the activity of Pd on charcoal itself as a catalyst depends on its mode of preparation and the nature of the support[218,220,221] and

may vary widely from batch to batch. Heterogeneous catalysts can be examined by a variety of physical and spectroscopic techniques but, unlike the techniques available for determining the structures and purity of soluble catalysts, these techniques yield less precise information on purity or uniformity of structure.[222-224]

For the above reasons, mechanistic studies on heterogeneous catalytic liquid-phase-transfer hydrogenation are sparse compared with similar studies on heterogeneous gas-phase or homogeneous (soluble) catalysts, but some general points emerge. Increase in temperature leads to increased rates of reduction for most systems. The hydrogen donors used in heterogeneous systems often give volatile products (e.g., CO_2 from formic acid or N_2 from hydrazine) and removal of these volatiles from the reaction systems precludes a state of equilibrium being reached. For other donors (e.g., indoline, perhydroaromatics, terpenes) the position of equilibrium is shifted so far in favor of the products of reaction (aromatic compounds) that, for all practical purposes, increase in temperature, simply leads to increased rate of reduction. However, other factors may determine optimal conditions and, because of the possibility that overreduction, isomerization, or decomposition of substrate may occur as side-reactions at elevated temperatures, e.g., air oxidation of aniline after reduction of nitroarenes or of quinols from quinones, the optimum reaction temperature may simply be that which gives the best yield of desired product in reasonable time. Reduction of sensitive compounds such as peptides[126,167-170,173,174,225] must be carried out under as mild conditions and/or as quickly as possible to minimize side-reactions. An illustration of the effect of temperature can be observed in the reduction of aromatic dinitro compounds using hydrazine and Raney Ni in ethanol as solvent. At 25–30 °C, no reduction was observed, but reaction was fast at 78 °C. The importance of solvent and temperature of reaction is nicely illustrated by this transfer reduction. Although in ethanol, no reaction was observed at 25–30 °C, in a mixture of ethanol and methylene chloride, reduction occurred at 28 °C; raising the temperature to 78 °C caused a lot of side-reactions to occur, with the formation of tarry products.[152]

For some hydrogen donors, increase in reaction temperature increases the rate of decomposition of the donor without an equivalent increase in the rate of reduction of hydrogen acceptor.[226] An activation energy of 11.2 kcal mol^{-1} and an enthalpy of 10.6 kcal mol^{-1} have been calculated for the reduction of cycloheptene using indoline as the hydrogen donor and a Pd/C catalyst.[70] These values are significantly lower than the Arrhenius energy and enthalpy for the reduction of cycloheptene[114] using indoline and the soluble catalyst, $RhCl(PPh_3)_3$ (see Table V). These lower values provide some quantitative support for the qualitative impression that, for comparable transfer reductions, heterogeneous catalysts require lower temperatures to exert their activity than do homogeneous catalysts.

D. Influence of Solvent on Catalytic Transfer Reduction

1. Homogeneous Systems

A correct choice of solvent is an important factor governing the activity of a soluble catalyst in transfer reduction. Most soluble catalysts are either coordinated to ligands or coordinated with solvent. Often, a ligand (L) can be displaced by a suitable solvent (S in Scheme XIX) from a metal complex, $M^{m+}X^{m-}L_n$ (m = 1, 2, 3...; n = 0, 1, 2...), to form new complexes, $M^{m+}X^{m-}L_{n-x}S_x$ (m = 1, 2, 3...; n = 0, 1, 2...; $n - x$ = 0, 1, 2...). These

SCHEME XIX

$$M^{m+}X^{m-}L_n + S \rightleftharpoons M^{m+}X^{m-}L_{n-1}S + L$$

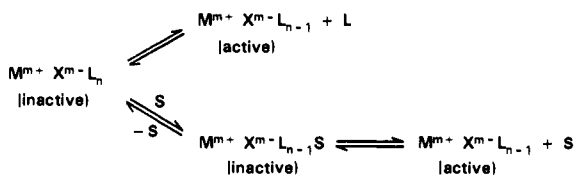
new complexes incorporating solvent molecules may be more or less active than the original complex, because binding by the solvent alters the electron density around the central metal atom and changes its ability to effect oxidative addition. Some metal catalysts, $M^{m+}X^{m-}L_n$, are active in solution only after dissociation of one or more ligands leaves the central metal atom with less than its maximum coordination number, thereby facilitating oxidative addition (Scheme XX).

SCHEME XX

$$M^{m+}X^{m-}L_n \rightleftharpoons M^{m+}X^{m-}L_{n-1} + L \rightleftharpoons M^{m+}X^{m-}L_{n-2} + 2L$$

If solvent molecules (S) displace the original ligands (L) and themselves do not dissociate from the central metal, then all catalytic activity is lost. Scheme XXI is a

SCHEME XXI



partial expression of these factors. Thus, the original soluble "catalyst", $M^{m+}X^{m-}L_n$, may be inactive because it is surrounded by its maximum number of ligands and cannot react by oxidative addition. On dissociation of a ligand from the complex to give $M^{m+}X^{m-}L_{n-1}$, this new species can react by oxidative addition and the compound is then catalytically active. If the dissociated ligand is replaced by a solvent molecule, S, to give $M^{m+}X^{m-}L_{n-1}S$, then this complex will be inactive also, like the original catalyst, unless it can dissociate by losing either a ligand or solvent molecule. The solvent molecule in the intermediate, $M^{m+}X^{m-}L_{n-1}S$, may affect the ability of the complex to dissociate, i.e., may make it harder or easier to lose another ligand molecule. This variation induced by solvent alters the ability of the metal to act catalytically. For example, transfer of hydrogen from carbinols to unsaturated ketones in the presence of catalysts, $RuCl_2[P(4\text{-}XC_6H_4)_3]_3$ (X = H, F, Cl, CH_3, OCH_3), is inhibited in CCl_4, $CHCl_3$, chlorobenzene and α-chloronaphthalene which slowly react with the original complex to give new Ru complexes that are inactive in hydrogen transfer.[71]

Besides these ligand-displacement mechanisms by the solvent, catalyst activity may be reduced or destroyed completely if the solvent coordinates to the catalyst better than the hydrogen donor or hydrogen acceptor can do. In the dehydrogenation of free anomeric sugars with $RuH_2(PPh_3)_4$ as catalyst and chalcone, PhCH=CHCOPh, as hydrogen acceptor, the selectivity of reaction and yield of reaction product (a lactone) fell as the solvent was changed in the order, anisole > diphenyl

ether > chlorobenzene > benzene ≫ diglyme >>> dioxane. The last two solvents competed successfully with the sugar molecules for coordination sites on the Ru and dehydrogenation became very slow.[97] As a second example, the dehalogenation of halobenzenes with $PdCl_2$ and indoline as hydrogen donor in a series of alcohols as solvents gave arenes in yields which decreased in the order, methanol > cyclohexanol > 2-propanol > ethanol > 1-propanol > 2-butanol > 1-butanol. Long-chain normal alcohols were unsuitable as solvents. With dimethylformamide and dimethylacetamide, reduction of Pd(II) to Pd(0) occurred and, with aromatic solvents (toluene, cumene), Friedel–Crafts reactions were observed.

Some indication of the importance of competitive binding of substrate and solvent can be found in the reduction of aromatic nitro compounds using $RhCl_3$ as catalyst and indoline as hydrogen donor.[72] In methanol, ethanol, *N*-methylformamide, ethyl acetate, benzene, dioxane, chlorobenzene, and toluene little variation in yield or reaction rate was observed, but reduction was significantly slower in *N*,*N*-dimethylacetamide, dimethyl sulfoxide, and benzonitrile. These results suggest that the nitro compounds and indoline could coordinate to the Rh better than many polar solvents could, but not so well as some of the most polar solvents. Similarly, aldehydes are known to bind strongly to $RuH_2(PPh_3)_4$ and their transfer reduction to alcohols, using indan, benzyl alcohol, 2-propanol, and 2,5-dihydrofuran as hydrogen donor, was largely unaffected by variation in the nature of the solvents.[110,142] Some initial rates ($\times 10^3$) found for these reductions in various solvents with indan are as follows: benzene (1.8), *p*-xylene (1.8), 1,2-dichlorobenzene (1.8), *n*-hexane (1.7), bromobenzene (1.4), anisole (1.4), chlorobenzene (1.4), diethyl ether (1.4), methyl benzoate (1.3), benzonitrile (1.1), dimethyl sulfoxide (1.1 $mol \cdot L^{-1} \cdot min^{-1}$). In sharp contrast, reduction of alkenes in a polar solvent like chlorobenzene is very slow and a considerable variation in these rates of reduction of alkenes are observed on variations of the type of solvent.[113,115] Comparative rates ($\times 10^4$) of reduction of alkenes have been found to be: toluene (4.0), benzene (4.0), anisole (3.6), *N*,*N*-dimethylacetamide (1.0), chlorobenzene (0.1), acetic acid (0.1), dimethyl sulfoxide, (0.0 $mol \cdot L^{-1} \cdot min^{-1}$).[113]

Finally, the solvent should not deactivate the catalyst by destroying it, as may happen with water. The effects of solvent on soluble catalyst activity are broadly understood, although quantitative predictions of variation in activity with change of solvent are less certain because of concomitant and uncertain competition from hydrogen donor and hydrogen acceptor. These explanations of variation in catalyst activity with solvent have been used as explanations for the variation in solvent effects found with heterogeneous catalysts, but as shown below, the heterogeneous systems are less readily amenable to comparable interpretation.

2. Heterogeneous Systems

As with the homogeneous catalyst systems, coordination of solvent to the catalyst in heterogeneous systems must be competitive with binding of hydrogen donors and hydrogen acceptors. If the coordinate link between solvent and catalyst is stronger than the binding of donor or acceptor, then transfer reduction is inhibited or stopped altogether. Several examples emphasize this solvent effect and serve as a reminder that, in seeking optimum conditions for any attempted transfer reduction, a trial of a range of solvents should be a prime consideration. Even water can prove to be a poison on metals such as Pt, especially at low temperature.[151] The deprotection of the amino acid derivative Z-Ala, by 10% Pd/C and cyclohexene as donor at 25 °C required only 45 min in acetic acid, but over 5 h in dimethylformamide. Other solvents such as ethanol, methanol, and *N*,*N*-dimethylacetamide gave rates of deprotection between these extremes and yet other solvents (hexamethylphosphoramide, trifluoromethanol, phenol, trifluoroacetic acid, tetrahydrofuran, dimethyl sulfoxide, 2-propanol) were impractical in that they caused deprotection to be very slow and incomplete.[126]

Cycloheptene can be reduced by Pd/C and indoline at 90 °C in toluene, anisole, ethanol, diethyl ether, and tetrahydrofuran, but not in acetic acid, dimethyl sulfoxide, pyridine, chlorobenzene, benzonitrile, or nitrobenzene.[66]

Using Raney Ni and hydrazine, 3,3′- or 4,4′-dinitrodiphenyl sulfone could be reduced to the corresponding diamine in refluxing ethanol (78 °C) in 16 h, but no reaction was observed at 30 °C, even after 50 h. In contrast, a change of solvent to ethylene glycol afforded a 98% yield of diamine at 30 °C after 50 h and methylene chloride gave an 84% yield at 30 °C after 20 h. Through the use of mixed solvents (ethanol/ethylene glycol, 1/1 or ethanol/methylene chloride, 1/1), 98% yields of diamine were obtained at 30 °C after only 10 and 8 h, respectively.[152]

Diphenylacetylene could be reduced very quickly with a Pd/C catalyst and sodium phosphinate as donor in aqueous tetrahydrofuran, acetone, ethyl acetate, or dioxane, but was not reduced in aqueous methanol.[145] Table VI gives references to work in which solvent has been observed to play an important role in heterogeneous catalytic transfer hydrogenation.

It is noted here that solvent effects are well documented when molecular hydrogen is used as the source of hydrogen in heterogeneous catalytic reduction. Not only does solvent affect rates of reduction, but it may also play an important part in determining the distribution of reduction products in those cases in which alternative reduction pathways exist. For example, hydrogenation of isoprene over a Pd/Nylon-66 catalyst gave only 2-methyl-2-butene in *n*-heptane as solvent but, in acetic acid, gave a mixture containing 2-methyl-2-butene (30%), 2-methyl-1-butene (30%), and 3-methyl-1-butane (16%).[90]

The rate of hydrogenation of alkynes over polymer-supported Pd has been found to decrease with change of solvent in the order: dimethylformamide > tetrahydrofuran > dimethyl sulfoxide > ethanol > acetone > nitromethane > acetic acid > chloroform.[89]

IV. Mechanisms of Heterogeneous Catalytic Transfer Reduction

Any discussion of mechanisms of heterogeneous catalytic transfer reduction immediately meets a severe limitation in the paucity of kinetic, thermodynamic, and stereochemical data. As if this lack of data were not

TABLE VI. References to Solvents Used in Heterogeneous Catalytic Transfer Hydrogenation

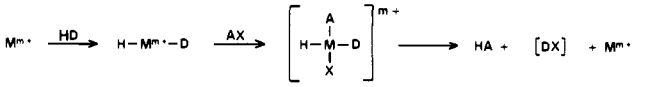
solvent	ref
cyclohexane	75
petroleum ether	145
cyclohexene[a]	176, 181, 187
benzene	175, 184, 226
toluene	70, 145
xylene	70, 180
methanol	47, 85, 126, 129, 167, 168, 174, 225, 281
ethanol	2, 126, 145, 152, 174, 184, 285
propan-2-ol[a]	137, 175
benzyl alcohol[a]	166
ethane-1,2-diol	152
methanol/acetic acid	225
ethanol/acetic acid	186
formic acid[a]	169, 172, 222
acetic acid	126
tetrahydrofuran	47, 70, 145, 179, 184
dioxane	47, 70, 145
acetone	145
ethyl acetate	145
dimethylformamide	126, 173, 225
dimethylsulfoxide	47, 70
methylene chloride	152
chlorobenzene	70

[a] Used as both solvent and hydrogen donor.

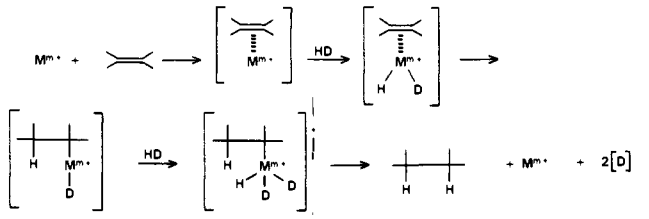
enough of an obstacle, one then has to face the difficulty of understanding the interlocking roles of binding of substrates at a catalyst surface and the topography of the surface.[227] In these circumstances it is often necessary to take the expedient path of examining the mechanistic details of reactions for which detailed information is available and then proceed to argue by analogy. It seems hardly necessary to stress that interpretation of mechanisms of reactions by comparing them with reactions that appear similar and for which some mechanistic knowledge is available is not a procedure guaranteed to provide wholly or even partly correct mechanistic deductions. However, to ignore this comparative reasoning is to ignore a fertile area that can provide hints, clues and indications to possible mechanisms, the outlines of which can be explored in greater detail by suitable experiments. Undoubtedly, the three major areas of catalytic chemistry that can provide mechanistic data which may not be too far removed from the reality of heterogeneous catalytic transfer reductions are those concerned with the homogeneous (soluble) catalysts, the hydrogenation or hydrogenolysis reactions of molecular hydrogen with heterogeneous catalysts, and hydrogen–deuterium exchange reactions over heterogeneous catalysts. Some of the salient features of homogeneous and heterogeneous catalysts will be adumbrated in the next few paragraphs. However, in these areas, there are immense amounts of information and the reader is directed to a few pertinent comprehensive reviews for leading references to more detailed aspects (ref 68, 92, 124, 130, 133, 138, 217, 218). Attention is directed mostly to metal catalysts and not their oxides since the latter are usually used in high-temperature gas-phase reactions and not those taking place in the liquid phase.

To a large extent, the catalytic activity of soluble, discrete molecular systems has been covered in sections IIIA–D concerned with the behavior of hydrogen donors, hydrogen acceptors, and solvents. Briefly, a catalytic metal center, M^{m+} (m = 0, 1, 2 ...), with or without ligands can add a hydrogen donor (HD) and a hydrogen

SCHEME XXII



SCHEME XXIII



acceptor (AX; reaction Scheme XXII). Elimination of HA and the elements of X,D from the complex, $HAXDM^{m+}$, give back the metal, M^{m+}, ready for the next catalytic cycle. This is a typical hydrogenolysis reaction which needs only slight modification in the mechanism to account for reduction of unsaturated systems such as alkenes (Scheme XXIII). Given a suitable combination of chemical bonding energies between the metal center and the donor, acceptor, and solvent, a catalytic cycle can be maintained through successive additions, followed by eliminations. These soluble, molecular, highly characterized systems are, in general, readily amenable to the usual methods of kinetic, thermodynamic, and stereochemical analysis.

Chemisorption onto heterogeneous catalysts ranges from the reversible type involving van der Waals (nonbonding) interaction to irreversible stable bond formation. Either of these extremes provide little or poor catalytic activity. With intermediate strength of chemisorption, interaction between the catalyst and substrate leads to alteration in their electronic and geometric structures. During adsorption onto a metal surface, metal–metal bonds are broken as shown by changes in electrical conductivity and ferromagnetic susceptibility.[228] The degree of metal–metal bond breaking varies with the nature of the adsorbate, i.e., varies with the degree of bonding interaction between metal and adsorbate. Cluster compounds show how a small assemblage of metal atoms can form normal chemical bonds to other elements or compounds grouped around the assemblage.[229] From cluster compounds to small crystallites of metals represents a very large increase in the number of metal atoms, but the crystallites have edges, corners, and defects, and, in those positions, relatively small assemblages of metal atoms occur having unsatisfied valences. The nature of the catalyst surface is very important in heterogeneous systems. Some reactions are relatively structure insensitive[230] but others are structure sensitive.[231] Indeed, as the molecular complexity of an adsorbate increases, it can be supposed that any catalyzed reaction will become more structure sensitive. This is undoubtedly one of the reasons why complex compounds often behave differently to catalysis compared with the simpler compounds commonly used to evaluate a reaction.

Early theoretical work on heterogeneous catalysis by metals tended to concentrate on the properties of the catalytic metal itself, without regard to the interactive effect of the adsorbate. This work revealed the importance of the degree of "d-band" filling with regard to catalysis.[138,232–234] Where only σ-bond interactions

with the adsorbate were involved, as with CH_4D_2 exchange, the reduction in activity as the d-band becomes filled is striking. However, experience with d-bonded interactions showed that back bonding from the metal into a π-antibonding orbital allowed metals to act catalytically, even though the d band was full or almost full. Later theoretical work has tended to use thermochemical arguments based on heats of formation or bond strengths to compare catalytic behavior of different metals or metal oxides.[228,235,236] Empirical correlations between catalytic activity and properties of metals or their salts are of widespread occurrence. More recently, molecular orbital calculations have been used to examine the mutual interaction of metals and adsorbates. Attempts to use perturbation methods have shown promise for the understanding of bonding between a metallic catalyst and organic substrates.[237-240] There is a vast literature on the application of ab initio molecular orbital methods to investigations of the binding of substrates (particularly simple molecules such as H_2, O_2, CO, N_2) to metal surfaces. Up to now, these ab initio methods have not been able to cope with the multiatom, multiconformational problems posed by even relatively small organic molecules.

These later ideas of the interaction between a catalyst and a substrate to give an activated adsorbate bring heterogeneous catalysis much closer to normal chemical experience of reactivity, and take it away from the older impression of "black magic" properties of catalysts. The interaction between a catalyst and a substrate is seen to be similar to the interaction between a homogeneous (soluble) catalyst and a substrate, but modified to take account of large assemblages of linked atoms or molecules, rather than isolated molecule/molecule encounters involved in homogeneous catalysis.

Heterogeneous catalysis of reduction by molecular hydrogen can be difficult to interpret mechanistically, because of difficulties in preparing and reproducing catalyst surfaces.[218,241] These difficulties have been listed succinctly.[222] It is clear that hydrogen can form ionic and covalent hydrides and can dissolve also in metals without there being any bond formation.[217,241] With some metals that form effective catalysts, hydrogen appears to form a relatively unstable hydride as, for example, with Pd and Ni. However, most hydrogenations are not regarded as proceeding through transfer of a hydride ion to the substrate. Deposited metal catalysts form crystallites in which the corner and edge atoms have more unsatisfied valences than do atoms on the faces of the crystallites. It seems that initial adsorption of molecular hydrogen takes place at these edges or corners to give bound "atomic" hydrogen or metal hydride and that these hydrogen atoms can migrate across the face or even into the bulk of the metal. The adsorption of a substrate (hydrogen acceptor) probably occurs under similar influences, but the actual mechanism of transfer of hydrogen to the substrate is not simple. In individual cases it is not generally clear whether the transfer occurs at a single atom site or from contiguous sites. For example, it has been proposed that hydrogenation of alkenes over various heterogeneous catalysts proceeds by transfer of hydrogen between adsorbed species.[242] The molecular hydrogen serves to maintain the catalytic cycle. This mechanism requires the adsorbed species (substrate and hydrogen) to be on contiguous sites. It follows that, if contiguous sites are necessary for reduction to occur, then alteration of the structure of the catalyst by doping it with an indifferent metal should result statistically in a reduction in numbers of contiguous atoms at various percentages of doping.[243] The activities of alloy catalysts have been widely examined and evidence has been found for the need for minimum numbers of contiguous atoms to effect catalysis. Unfortunately, these doping effects are not predictable, although reasoning by analogy can provide an indication of the effects to be expected. The cause of the unpredictability lies in the way in which the doping metal affects the catalytic metal. If the doping metal is truly indifferent in bonding, then its effect is simply that of a diluent, i.e., atoms of the catalyst metal at its surface are replaced by atoms of the doping (noncatalytic) metal. If there is a requirement for a minimum number of contiguous catalyst metal atoms to provide a catalytic site, then at some percentage of added diluent, this minimum number will not be reached and catalytic activity will disappear abruptly, i.e., too many "foreign" atoms surround each atom of the catalyst. On the other hand, the doping or foreign metal may alter the electronic band structure of the metal catalyst and so affect its ability to form bonds to hydrogen or the substrate.[145] This effect, whereby the electronic band structures of the catalyst and doping metal interact to give new band structures, is a continuous one and leads to a continuous change in catalytic activity, rather than the relatively abrupt changes found with a simple dilution effect. These effects have been observed in practice.[223] Experimental evidence has been found by spectroscopy for changes in electron band structure in some alloys, but not in others.[222]

The two effects on catalytic activity of alloyed metals discussed here (the need for a minimum number of contiguous atoms of catalyst metal and changes in its electron band structure), are only extremes of behavior which has been investigated through the use of other doping metals that change the electronic band structure and also interfere with the formation of the minimum number of contiguous atom sites.[243]

The disproportionation of cyclohexane over Pd to give cyclohexane and benzene has been studied kinetically and by specific activity measurements. It has been suggested from these results that increases in specific activity are associated with 4, 10–11, and about 20 contiguous Pd atoms.[244] H/D isotope exchange reactions between benzene, C_6H_6, and C_6D_6 at 0 °C over a variety of metals has shown that their exchange activities are related linearly to their percentage d character. A multiple exchange process was found to occur over Ru, Rh and Ir but, over alloys such as Pt/Pd, a stepwise process predominated.[245]

Clearly, one-atom catalyst sites are relatively structure insensitive, whereas multiatom sites will be affected by alloying, development of crystallites, and imperfections, i.e., these latter types of catalyst are structure sensitive.[243,246] Hydrogenations are generally structure insensitive, but hydrogenolyses are structure sensitive. In catalytic transfer hydrogenation where both a donor and an acceptor are involved in overall reaction, there may be a requirement for multiatom catalyst sites and the catalysts would then be structure sensitive. For this reason, it is sometimes difficult to reproduce catalytic work because, for structure-sensitive reactions, prepa-

ration of the catalyst is an important variable.

The concept of doping of catalysts can be extended to dual-catalyst systems in which either catalyst has a specific role in promoting a reaction, but neither catalyst alone can promote the reaction. The industrially important reactions of isomerization, dehydrocyclization, and hydrocracking of hydrocarbons are ones in which mixed metal/acidic oxide catalysts are used.[223,243]

For heterogeneous catalytic transfer reduction, the concepts described above can be used to provide working hypotheses of mechanisms. In an earlier review of heterogeneous catalytic transfer hydrogenation of alkenes, it was emphasized that there is a need to relate mechanisms with the ability of catalysts to form π- and σ-bonds or coordinate complexes and with the ability of the catalysts to interchange between these π- and σ-formations.[4] In discussing the hydrogenation of alkenes over palladium using a hydrogen donor, the authors of a review[4] recalled that, historically, this reaction was first regarded as the formation of a palladium hydride followed by transfer of hydride to the alkene (Scheme XXIV). Later workers preferred a mecha-

SCHEME XXIV

$$H_2D + Pd \rightarrow PdH_2 + D \xrightarrow{R_2C=CR_2} R_2CHCR_2PdH \rightarrow R_2CHCHR_2 + Pd$$

nism in which both hydrogen donor and acceptor were coadsorbed onto the palladium surface followed by direct transfer of hydrogen without formation of a hydride. However, the review authors,[4] reasoning by analogy with mechanisms for reduction of alkenes over Pd with molecular hydrogen, concluded that transfer of hydrogen as a hydride species was not unreasonable. Certainly, more recent evidence has been found for the formation of a hydride species in the decomposition of formic acid over Pd.[248] However, isotope exchange studies suggest that hydride species are not involved. H/D exchange in hydrocarbons over metals or metallic oxides proceeds via an initial dissociative step (Scheme XXV) with the alkyl radical and a hydrogen bonding to the metal (M). Subsequent recombination regen-

SCHEME XXV

$$C_nH_{2n+2} + 2M \rightleftharpoons MC_nH_{2n+1} + MH$$

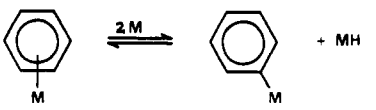
erates the alkane, C_nH_{2n+2}, and, in the presence of deuterium, this alkane will contain species, $C_nH_{2n+1}D$. Repetition of this process in a stepwise fashion incorporates more deuterium. Alternatively, the metal alkyl can lose further hydrogen atoms before recombination occurs. Then, on recombination, multiple incorporation of deuterium occurs (Scheme XXVI).[249] Examples of both of these stepwise and multiple exchange processes are well-documented. Further, intramolecular exchange of hydrogen and deuterium atoms in saturated alkanes has been observed over nickel.[300]

SCHEME XXVI

$$C_nH_{2n+2} \overset{M}{\rightleftharpoons} MC_nH_{2n+1} + MH$$
$$\overset{M}{\rightleftharpoons} M_2C_nH_{2n} + MH$$
$$\overset{M}{\rightleftharpoons} M_3C_nH_{2n-1} + MH$$

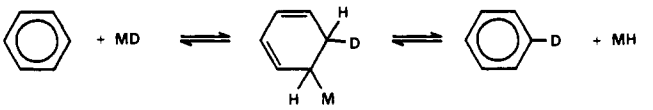
The second hydrogen is removed from a carbon atom

SCHEME XXVII



adjacent to the one from which hydrogen was first removed and gives an α,β-diadsorbed hydrocarbon species. For some cycloalkanes, a "roll-over" mechanism has been invoked to explain the unusual H/D isotope distribution observed after exchange.[250] For other cycloalkanes, particularly those with flexible rings (cyclohexanes and above), a π-allyl complex best described the isotope distribution.[251] Similarly, aromatic hydrocarbons may form π-complexes with metals (M) and these change to σ-complexes by a dissociative mechanism (Scheme XXVII).[252] However, the same effect on the isotope distribution is implied by an associative mechanism (Scheme XXVIII).[253] It is clear from these

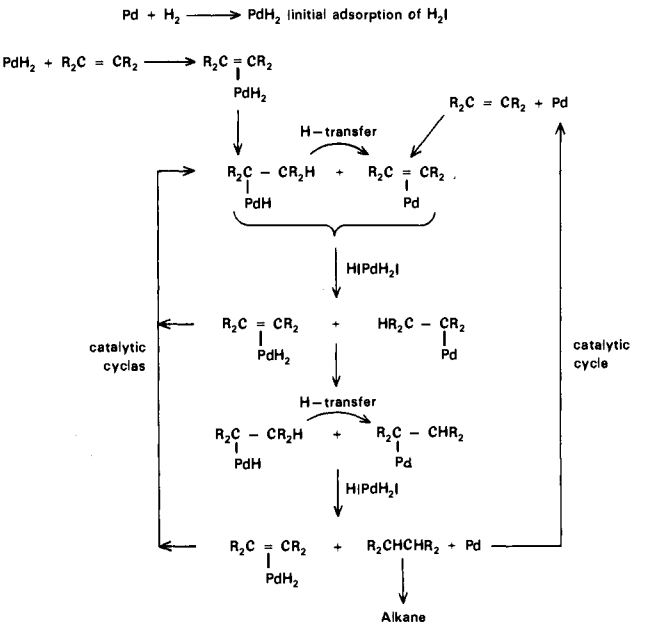
SCHEME XXVIII



exchange experiments that metal or metal oxide catalysts can bond to either saturated or unsaturated species to form π- or σ-complexes. In catalytic transfer hydrogenation, such bonding of both hydrogen donor and hydrogen acceptor simultaneously can lead to hydrogen exchange, i.e., one component (substrate) is reduced, while the other (hydrogen donor) is oxidized. A mechanism similar to the associative reaction (Scheme XXVIII) has been proposed for the hydrogenolysis of tetrazolyl ethers of phenols.[150]

A more recent development has taken the form of an attempt to unify many conflicting mechanistic and other observations on the reduction of alkenes into one

SCHEME XXIX



comprehensive hypothesis.[242] After listing many salient features of catalytic hydrogenation of alkenes over

metals, it was concluded that transfer of hydrogen between adsorbed species fitted the available facts better than transfer of hydrogen from metal to alkene. The adsorption of alkene was surmised to give an intermediate that could transfer hydrogen directly to an adjacent adsorbed species. Hydrogen is then required only to make the process continuous. Scheme XXIX indicates how such a mechanism might operate. Clearly, self-hydrogenation/dehydrogenation as in the disproportionation of cyclohexene is accommodated easily by this explanation and, interestingly, the role of palladium hydride as an intermediate is maintained. A similar mechanism may be countenanced for a hydrogen donor, H_2D, as the hydrogen source, with the first step being the production of PdH_2 (Scheme XXX). It is necessary

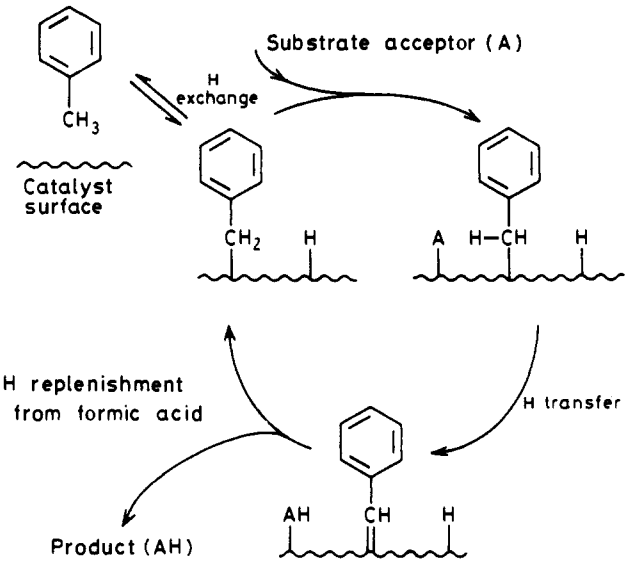
SCHEME XXX

$$H_2D + Pd \rightarrow PdH_2 + D$$

for the hydrogen acceptor to be adsorbed onto the metal, but direct transfer of hydrogen may not occur. It is a general observation of heterogeneous catalytic transfer reductions that they are not simply alternative ways of generating hydrogen which can then be used for reduction as with molecular hydrogen and a catalyst. It is not unusual to observe vigorous evolution of hydrogen gas when a hydrogen donor and a Pd catalyst are brought into contact, although no reduction of a suitable substrate occurs, whereas, the same substrate with molecular hydrogen and the same catalyst is reduced. In a similar vein, Pd catalysts are effective in transfer reductions as they are in reduction with molecular hydrogen, but many other metals that are effective with molecular hydrogen are either very weak catalysts in transfer reduction or show no catalytic properties at all. These observations suggest either that palladium is able to bond to both hydrogen donors and hydrogen acceptors and other metals are not as effective in bonding to the donors or that simultaneous bonding to both donor and acceptor is a prerequisite for reduction. With the latter alternative, direct transfer of hydrogen from donor to acceptor could occur and palladium would be seen simply as the best metal for effective bonding to and activation of both donor and acceptor. In this respect, it is pertinent that Pd(0) species often form the most active homogeneous catalysts in any comparative experiments as shown, for example, by comparison of similar Pd(0), Pt(0), and Rh(0) complexes.[247]

Very recent results of deuterium labeling experiments have shown that hydrogen can be transferred directly from a donor to an acceptor.[304] The C–O bond in 1-tetrazolyl ethers of phenols can be hydrogenolyzed in benzene/ethanol/water/formic acid with Pd as catalyst to give arenes. Most of the hydrogen appearing in the arene is derived from the formic acid. However, in toluene/ethanol/water/formic acid, most of the hydrogen appearing in the arene arises from the methyl group of the toluene and, in the absence of formic acid, toluene alone cannot effect hydrogenolysis. It appears that direct transfer of hydrogen from toluene to the 1-tetrazolyl ether occurs but formic acid is required to maintain a supply of hydrogen to the active site (Scheme XXXI). It has been noted above that hydrogenolyses tend to be structure sensitive, in keeping with the need for contiguous catalyst sites revealed by

SCHEME XXXI



these deuterium labeling experiments.

Multiple carbon bonding of small molecules (CO, C_2H_2) onto a platinum surface has been examined by single and double resonance NMR of ^{195}Pt, ^{13}C, and ^{1}H atoms.[309] For the adsorbed ethyne, it was deduced that two species were present, in keeping with earlier tentative proposals.[310] Essentially, the two adsorbates consist of ethyne (HC≡CH) bonded to Pt through both carbons and a species (C—CH_2) bonded to the metal as a resonance structure, the major canonical forms being, Pt≡CCH_2Pt, and Pt=C=CH_2. This elegant NMR work provides strong direct experimental evidence for the existence of multiply bonded carbon species on a noble-metal surface.

The above considerations lead us to suggest a mode of action for heterogeneous catalytic transfer reduction based on the mechanisms of homogeneous catalysts. The following suggestions are made with a view to stimulating new thinking in the area of heterogeneous catalytic transfer reduction, particularly in organic chemistry, rather than an attempt to create a definitive position. However, it is encouraging that most of the present knowledge of heterogeneous catalytic transfer reduction can be accommodated within the following concepts.

Palladium(0) forms tetracoordinate complexes with a variety of ligands and palladium(II) is formed readily through oxidative addition. Palladium(II) salts form dicoordinate complexes. We suppose that some surface atoms on the crystallites comprising a palladium catalyst, particularly at edge or corner sites, are sufficiently unsatisfied in a valence sense in their bonding to neighboring atoms, or become so by bond breaking to neighboring palladium atoms, that they are able to undergo oxidative addition reactions and coordinate to substrate or solvent molecules. One early step in the reductive process would be oxidative addition of a hydrogen donor (H_2D) to palladium as shown in Scheme XXXII. In many of these transfer reductions, the

SCHEME XXXII

$$H_2D + Pd \rightarrow H\text{-}Pd\text{-}DH$$

hydrogen donor is able to supply two hydrogen atoms per molecule of donor and, as illustrated in Scheme

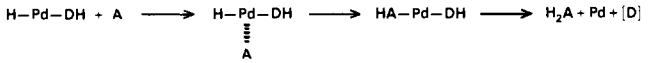
XXXII, after oxidative addition, one of these is bonded directly to palladium and the other to the remainder of the donor. An example involving phosphinic acid is given in Scheme XXXIII. The next step could entail

SCHEME XXXIII

$$H_2PO_2H + Pd \rightarrow H\text{-}Pd\text{-}PH(O_2H)$$

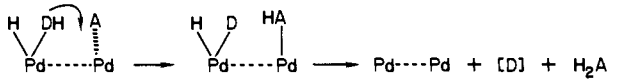
coordination of the substrate A; (hydrogen acceptor; Scheme XXXIV) followed by its insertion into the

SCHEME XXXIV



H–Pd bond. Transfer of a second hydrogen atom to HA (Scheme XXXIV) could release the product H_2A and the dehydrogenated donor (D). It is unnecessary for these oxidative additions to occur at the *same* metal atom site, as implied by the diagram shown (Scheme XXXIV). Oxidative addition of donor and acceptor may take place onto *adjacent* metal atoms (contiguous sites), followed by transfer of hydrogen and subsequent elimination of products (Scheme XXXV). In most of

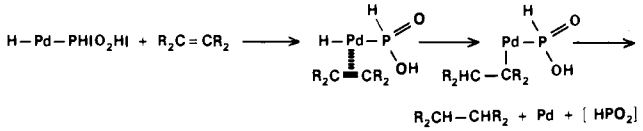
SCHEME XXXV



the later discussion of mechanism, this point will not be repeated and, for convenience, most of the schemes show single metal atom sites. However, it should be assumed that, in the absence of experimental data, contiguous sites might by involved and the mechanisms discussed would then need slight modification.

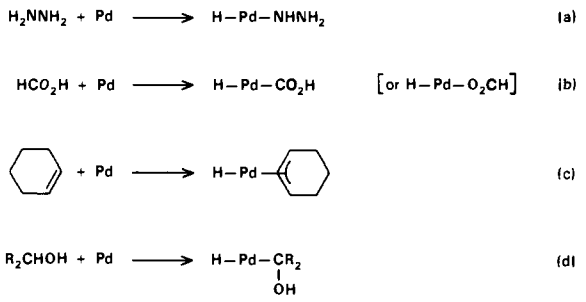
Scheme XXXIV is illustrated by the reduction of alkynes to alkenes using phosphinic acid as hydrogen donor (Scheme XXXVI); the first oxidative step is not

SCHEME XXXVI



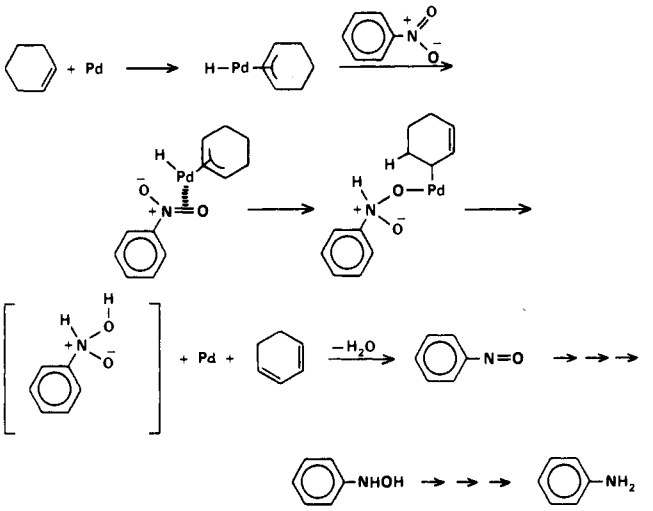
shown, but is like that of Scheme XXXIII. Reaction of the dehydrogenated donor (HPO_2) with water either before release from the Pd or immediately after gives phosphorous acid (H_3PO_3). The first oxidative addition step is illustrated further for some other typical hydrogen donors by the examples a–d of Scheme XXXVII. The first steps in the reduction of nitro-

SCHEME XXXVII



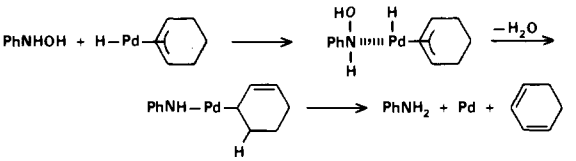
benzene with cyclohexene on the basis of this general mechanism are shown in Scheme XXXVIII. The re-

SCHEME XXXVIII



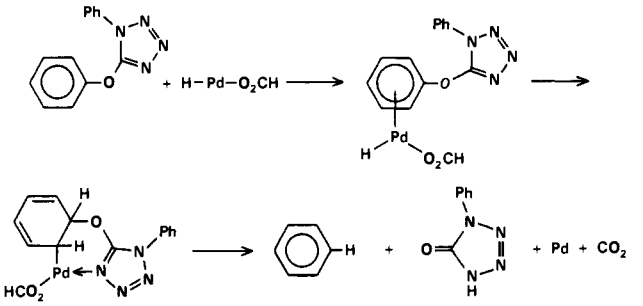
duction of nitrosobenzene to phenylhydroxylamine is presumed to follow a similar mechanism, but the reduction of the hydroxylamine to amine requires heterolytic cleavage of the N–O bond. This sort of single bond reductive cleavage requires only slight modification to the above schemes in that the substrate needs to be bonded through one of its atoms as shown in Scheme XXXIX. A special case of this mechanism has

SCHEME XXXIX



been proposed for the heterolytic cleavage of phenolic ethers to give arenes (Scheme XL).

SCHEME XL



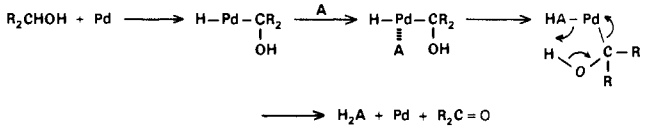
Other observations on heterogeneous catalytic systems can be accommodated by the above generalizations. For example, the disproportionation of cyclohexene is explained as is simple evolution of hydrogen, frequently observed during these reactions and illustrated in Scheme XLI for hydrazine. If this transfer of hydrogen is fast, or coordination of hydrogen acceptor is weak or binding of solvent is too strong, then no reduction will be observed. Similarly, poisoning effects on the catalyst can be ascribed to too strong a binding of foreign molecules to the Pd(0) thereby preventing initial oxidative addition of hydrogen donor.

SCHEME XLI

$$H_2NNH_2 + Pd \rightarrow H{-}Pd{-}NHNH_2 \rightarrow H_2 + Pd + [HN{=}NH]$$

It is of interest to note that, for all hydrogen donors, the addition of a second hydrogen atom to the substrate or acceptor formally proceeds through a five-membered transition state, illustrated in Scheme XLII for the transfer of hydrogen from an alcohol, R_2CHOH, to an acceptor (A). It will be recalled from earlier in this

SCHEME XLII



section that, in the catalytic reduction of an alkene with molecular hydrogen, it has been proposed that hydrogen is passed from an adjacent Pd site to the alkene and not from the palladium to which the alkene is attached.

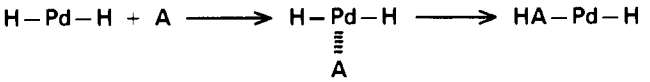
Although no formal description of this last mechanism has been presented, the above discussion can be modified slightly to include these ideas. With molec-

SCHEME XLIII

$$H_2 + Pd \rightarrow H{-}Pd{-}H$$

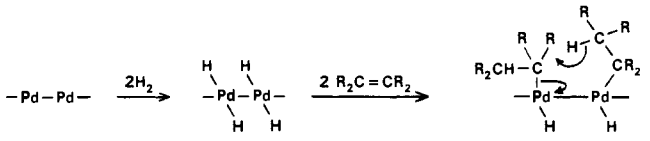
ular hydrogen, oxidative addition of H_2 gives a palladium hydride (Scheme XLIII). If an acceptor (A) binds to this species, the second insertion stage can occur (Scheme XLIV), but it is not possible to transfer a

SCHEME XLIV



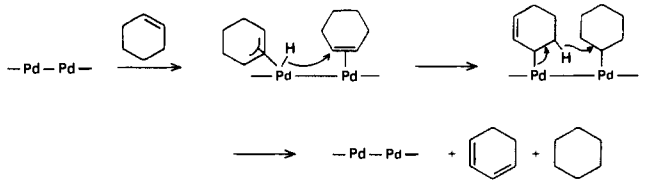
second hydrogen via a five-membered transition state even from an adjacent Pd atom. However, if a second alkene molecule binds to an adjacent palladium atom site, then hydrogen transfer can occur through a six-membered transition state (Scheme XLV). Although

SCHEME XLV



this mechanism suggests a six- rather than a five-membered transition state, the bond angles and bond lengths associated with two contiguous palladium atom sites will be quite different from those associated with a single atom site. What may be important is the absence of hydrogen transfer to the substrate at a single atom site. Similarly, the disproportionation of cyclohexene, which is believed to involve contiguous atom sites, can also be accommodated by these mechanisms (Scheme XLVI).

SCHEME XLVI



New kinetic evidence for complex formation during catalytic hydrogenolysis has appeared.[305] In the transfer hydrogenolysis of 1-tetrazolyl ethers of phenols to give arenes (Scheme XL), results of kinetic studies have shown that this palladium-catalyzed reaction has the characteristics of some enzyme-catalyzed reactions in that "burst" formation of arene is followed by a steady-state rate of formation. This form of kinetics, reminiscent of catalysis by chymotrypsin, for example,[306] implies an initial formation of a catalyst/acceptor site which breaks down to give two products, one of which (1-phenyltetrazolone) is only slowly released from the catalyst and governs the steady-state formation of arene. The initial "burst" formation of arene is due to hydrogenolysis of that portion of the acceptor ether which was initially adsorbed onto the palladium catalyst. This is the first time that direct evidence has been found for a rate-limiting catalyst/product complex in liquid phase heterogeneous catalytic transfer hydrogenolysis. Further similar experiments on other substrates would be desirable.

V. Catalytic Transfer Reduction of Specific Functional Groups

A wide range of donors and catalysts has been deployed in various combinations to carry out heterogeneous hydrogen-transfer reductions of most of the major functional groups attached to or part of both aromatic and aliphatic structures. Several important functional groups have received little study, in particular, carboxylic acids, their esters, and their amides. All of them are frequently reduced efficiently by hydride reagents, but are usually found not to be reduced under any of the conditions described in this review.

Although nitroso compounds do not appear to have been reduced specifically by heterogeneous catalytic transfer methods, their formation and subsequent reduction to amines is generally accepted as part of the reaction path for reduction of nitro compounds to amines. Additionally, formation of azoxy compounds as byproducts during reductions of nitro compounds, especially under alkaline conditions, is usually ascribed to condensation between intermediate nitroso and hydroxylamine compounds.[302]

To simplify the descriptions of, and to condense the tables, abbreviations listed in Tables VII and VIII have been used for catalysts and donors.

A. Alkenes

A tabulation of examples of catalytic hydrogen-transfer reduction of carbon-carbon double bonds in hydrocarbons, acids, ketones, aldehydes, esters, and nitriles has been published.[4] These reductions were effected with a wide range of catalysts and donors. More recent reports have extended both the range of conditions, catalysts, and donors, and the variety of alkenes which can be reduced (Table IX).

For simple alkenes, palladium on charcoal (Pd/C) appears to effect reduction using either hydrocarbon hydrogen donors, such as cyclohexene,[112a] or amines such as *N*-benzylaniline.[66] In a study of the reactions of a variety of cyclic alkenes, several hydrogen donors and various precipitated forms of palladium were shown

TABLE VII. Abbreviations for Hydrogen Donors Listed in Tables IX–XXXI

Hydrocarbons			
d-limonene	A	tetralin	E
d-phellandrene	B	vinylcyclohexene	G
cyclohexene	C	1,4-cyclohexadiene	H
(+)-1-p-menthene	D	1,3-cyclohexadiene	I
Alcohols			
propan-2-ol	J	1-butanol	M
cyclohexanol	K	benzyl alcohol	N
pentan-3-ol	L	allyl alcohol	O
Amines			
indoline	P	*N*-benzylaniline	S
piperidine	Q	hydrazine	T
tetrahydroquinoline	R		
Acids			
formic	U	phosphinic (hypophosphorous)	V
Salts			
triethylammonium formate			W
tri-*n*-butylammonium formate			X
sodium phosphinate			Y
sodium formate			Z
ammonium formate			AA
Others			
N-(1,2,5,6-tetrahydrophthaloyl)-L-leucine			BB

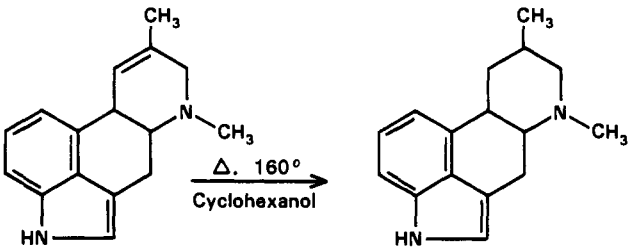
TABLE VIII. Abbreviations for Catalysts Listed in Tables IX–XXXI

palladium	
10% palladium on charcoal	a
10% palladium on charcoal/$AlCl_3$	b
20% $Pd(OH)_2$ on charcoal	c
5% palladium on charcoal	d
5% palladium on barium sulfate	e
palladium black	f
palladium on charcoal	g
10% palladium on charcoal/$FeCl_3$	h
palladium on charcoal/Fe(III) hydroxide or oxide	i
50% palladium on asbestos	j
10% palladium on charcoal/$NaBH_4$	k
1% palladium diacetate (+ 2% tri-o-tolylphosphine)	l
10% palladium on charcoal/Hg (1:0.4)	m
10% palladium on charcoal/Pb (1:0.5)	n
10% palladium on charcoal/Pb (1:1)	o
10% palladium on charcoal/Hg (1:0.3)	p
10% palladium on charcoal/Pb (1:0.7)	q
others	
5% rhodium on charcoal	r
$FeCl_3$	s
Raney nickel	t
ruthenium black	u
osmium black	v
iridium black	w
platinum black	x

to be effective.[112] Reduction of alkynes to alkenes and then alkanes has been carried out with sodium phosphinate as hydrogen donor and modified or unmodified palladium-on-carbon catalysts;[145] use of this donor for efficient reduction of double bonds has been confirmed recently.[303] Reductions with Raney nickel and propan-2-ol seem less productive.[175] Reduction of conjugated dienes with triethylammonium formate has been performed, but was slow and yielded a mixture of monoenes with 1,3-octadiene as substrate.[172] The addition of a Lewis acid, as for example $AlCl_3$, to the Pd/C catalyst promoted reductions of conjugated aromatic alkenes, such as stilbenes and tetraphenylethylene.[181] In an investigation into the efficiency of a variety of donors useful for reduction of 1-octene, $FeCl_3$ was added to Pd/C catalyst[154] and, with *d*-limonene and α-phellandrene as hydrogen donors, excellent yields were obtained for the conversion of 1-octene into *n*-octane. In contrast, limonene itself could be completely reduced using propan-2-ol as hydrogen donor and Raney nickel as catalyst, but its dehydrogenated product, *p*-cymene, was formed in significant amounts,[175] indicating a measure of disproportionation. Pinanes and *p*-cymene were formed when (±)α-pinene was reduced over 10% Pd/C/$NaBH_4$ with (+)-limonene as hydrogen donor.

Although Raney-nickel has been a useful catalyst for reduction of ketones (see Section VG), its use with alkenes was less reliable.[175] More successful uses of Raney nickel are reported for the conversions of olefinic bonds in alcohols[175] and amines.[254] For example, norborneol has been reduced in 100% yield with propan-2-ol as hydrogen donor. Stereoselective conversion of agroclavine (Scheme XLVII) to 8,9-dihydroagroclavine was

SCHEME XLVII



Agroclavine

effected in 1 h at 160 °C when cyclohexanol was used as hydrogen donor. Other clavines (Δ^6-ergolenes) listed in Table IX were reduced similarly.[254]

The desirable regioselective formation of *cis*-monoenoates from polyunsaturated acid esters such as methyl linoleate has been attempted with homogeneous catalysts.[46,106] A study involving Pd/C, Pd/black, and Raney nickel and such donors as indoline, formic acid, cyclohexene, $NaBH_4$, tetrahydroquinoline, and 2,5-dihydrofuran showed that selective reduction to monoenes could be achieved under relatively mild conditions. The ratios of the desirable *cis*-monoene to the *trans* isomer were low in all experiments. Surprisingly, the hydrogen donors, propan-2-ol, *d*-limonene and tetralin were ineffective for this reaction even at 140 °C. Highly regioselective hydrogenation of some bicyclo[2.2.1]-hepta-2,5-diene- and bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylates has been reported.[112b]

The olefinic bond in a very wide range of α,β-unsaturated carbonyl compounds has been reported to undergo heterogeneous catalytic hydrogen-transfer reduction.[4] Mostly, hydrocarbon donors and Pd/C were used and gave good yields. Further studies have added trialkylammonium formates to the list of effective hydrogen donors.[172] A variety of unsaturated ketones, aldehydes, and esters has been reduced by the triethyl and tributylammonium salts of formic acid. Crotonitrile was reduced only very slowly (see Table IX). Several alcohols have been examined as potential hydrogen donors for the reduction of unsaturated steroids,[255] but only benzyl alcohol gave acceptably selective reduction. For example, 7-methyl-6-dehydrotestosterone acetate (Scheme XLVIII) can be selectively reduced to 7-methyltestosterone in 90% yield.[186] This reduction appears to proceed through addition of hydrogen to the less hindered α-face of the steroid molecule suggesting that some control towards chiral re-

TABLE IX. Heterogeneous Hydrogen-Transfer Reductions of Olefinic Bonds

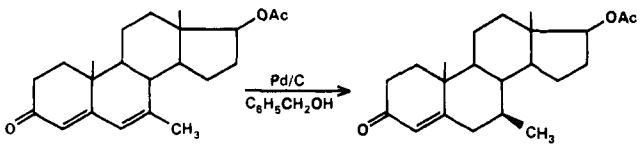
olefin	donor[a]	catalyst[a]	time (temp)[b]	product	yield[c]	ref
1-hexene	W	a	7.0	*n*-hexane	81	172
cis-4-methyl-2-pentene	J	t	0.45	2-methylpentane	50	175
				2-methyl-2-pentene	33	175
1-octene	A	h	3.0	*n*-octane	100	154
1-octene	B	h	3.0	*n*-octane	99	154
trans-4-methyl-2-pentene	B	h	0.45	2-methylpentane	38	175
				2-methyl-2-pentene	32	175
1-octene	P	d	1.0	*n*-octane	47	112
cyclohexene	P	d	1.0	cyclohexane	43	112
cyclopentene	P	d	1.0	cyclopentane	29	112
cycloheptene	P	d	1.0 (100)	cycloheptane	45	112
cycloheptene	P	d	2.0 (180)	cycloheptane	100	112
cycloheptene	Q	d	2.0 (180)	cycloheptane	100	112
cycloheptene	R	d	2.0 (180)	cycloheptane	100	112
cycloheptane	C	d	2.0 (180)	cycloheptane	84	112
cycloheptene	P	j	1.0 (120)	cycloheptane	95	112
cycloheptene	P	f	1.0 (120)	cycloheptane	87	112
cyclooctene	P	d	1.0 (90)	cyclooctane	24	112
1,3-cyclooctadiene	P	d	1.0 (90)	cyclooctane	6	112
1,3-cyclooctadiene	S	a	27.0	cyclooctene	81	66
1,5-cyclooctadiene	S	a	4.0	cyclooctene	89	66
1,5-cyclooctadiene	P	d	1.0 (90)	cyclooctane (cyclooctene)	9 (37)	112
				1,3-cyclooctadiene	5	112
1,3-cyclohexadiene	W	a	21.0	cyclohexene (cyclohexane)	72 (8)	172
1,3-octadiene	W	a	3.0	1-octene (2-octene)	28 (51)	172
trans,trans,trans-1,5,9-cyclododecatriene	S	a	47.0	*cis*-(or *trans*-)cyclododecene	28/45	66
α-methylstyrene	P	a	1.0 (90)	cumene	97	112
trans-stilbene	J	c	4.0	1,2-diphenylethane	40	175
trans-stilbene	C	b	46	1,2-diphenylethane	96	181
tetraphenylethylene	C	b	46.0	tetraphenylethane	93	181
1-phenylcyclohexene	C	b	46.0	phenylcyclohexane	86	181
1-phenyl-3,4-dihydronaphthalene	C	b	46.0	1-phenyltetralin	77	181
methyl linoleate	C	d	3 (140)	methyl stearate (monoene)	48 (40)	106
methyl linoleate	P	d	3 (140)	methyl stearate (monoene)	7 (83)	47
methyl linoleate	C	d	3 (140)	methyl stearate (monoene)	0 (40)	47
methyl linoleate	C	d	3 (140)	methyl stearate (monoene)	6 (79)	47
methyl linoleate	C	d	3 (140)	pinanes and *p*-cymene	1 (73)	47
(±)-α-pinene	A	k	0.5	1-*p*-menthene (1-*p*-cymene)	50 (20)	175
limonene	J	t	2	*p*-menthane	4	175
norborneol	J	t	4	norbornanol	100	175
α-terpineol	J	t	6	*cis,trans*-8-hydroxy-*p*-menthane	90	175
elymoclavine	J + L	t	3.0 (100)	8,9-dihydroelymoclavine	90	254
agroclavine	K	t	1.0 (160)	8,9-dihydroagroclavine	95	254
1-methylelymoclavine	K	t	1.0 (160)	1-methyl-8,9-dihydroelymoclavine	91	254
1-methylagroclavine	L	t	1.0 (160)	1-methyl-8,9-dihydroagroclavine	89	254
citral	W	a	44	citronellal	91	172
crotonaldehyde	W	a	8	butanal	81	172
mesityl oxide	W	a	3	4-methyl-2-pentanone	84	172
3-methyl-2-cyclopentenone	W	a	2.5	3-methylcyclopentanone	87	172
2-cyclopentenone	X	a	1.3	cyclopentanone	83	172
benzalacetone	X	a	2.5	4-phenyl-2-butanone	86	172
β-ionone	X	a	20	4-(1,3,3-trimethylcyclohex-1-enyl)butan-2-one	69	172
methyl crotonate	W	a	3.3	methyl butanoate	83	172
methyl cinnamate	W	a	20	methyl dihydrocinnamate	86	172
methyl fumarate	W	a	2.3	diethyl succinate	81	172
dimethyl (*E,E*)-2,5-dimethyl-2,4-hexadienedioate	W	a	2	dimethyl (*E*)-2,5-dimethyl-2-hexenedioate	96	172
methyl sorbate	W	a	2	methyl 2-hexenoate	65	172
methyl sorbate	X	a	2	methyl 2-hexeneoate	62	172
methyl sorbate	X	1	2	methyl 2-hexenoate	38	172
crotononitrile	W	a	48	*n*-butanonitrile	60	172
cis-2-phenyl-3-*p*-tolylpropenoic acid	A	a	0.1 (195)	methyl 2-phenyl-3-*p*-tolylpropanoate	84	154
α-acetamidocinnamic acid	D	a	51 (115)	*N*-acetylphenylalanine	31	154
methyl *cis*-2-phenyl-3-*p*-tolylpropenoate	B	a	4.0	methyl 2-phenyl-3-*p*-tolylpropanoate	100	154
7-methyl-6-dehydrotestosterone acetate	N	a	3.0 (80)	7β-methyltestosterone acetate	90	166
17β-hydroxy-5α-androst-1-en-3-one	N	a	3	17β-hydroxy-5α-androstan-3-one	100	255
17β-hydroxy-5α-androst-1-en-3-one	K		3	17β-hydroxy-5α-androstan-3-one	5	255
17β-hydroxy-5α-androst-1-en-3-one	L	a	3	17β-hydroxy-5α-androstan-3-one	5	255
17β-hydroxy-5α-androst-1-en-3-one	M	a	3	17β-hydroxy-5α-androstan-3-one		255
17β-hydroxy-5α-androst-1-en-3-one	O	a	3	no reduction		270
17β-hydroxy-4-androsten-3-one	N	a	3	17β-hydroxy-5α-androstan-3-one	5	255
				17β-hydroxy-5β-androstan-3-one	20	255
17α-pregn-5-en-20-yne-3β,17-diol	N	a	3	17α-pregn-5-ene-3β,17-diol	100	255
3β-hydroxy-5,16-pregnadien-20-one	N	a	3	3β-hydroxypregn-5-en-20-one	100	255
3β-hydroxy-16-methyl-5,16-pregnadien-20-one	N	a	3	no reduction		255

TABLE IX (Continued)

olefin	donor[a]	catalyst[a]	time (temp)[b]	product	yield[c]	ref
17β-hydroxy-1,4-androstadiene-3-one	N	a	3	17β-hydroxy-5α-androstan-3-one	5	255
				17β-hydroxy-5β-androstan-3-one	25	
				17β-hydroxy-4-androsten-3-one	72	
17β-hydroxy-4,6-androstadiene-3-one	N	a	3	17β-hydroxy-5α-androstan-3-one	3	255
				17β-hydroxy-5β-androstan-3-one	15	
				17β-hydroxy-4-androstene-3-one	82	

[a] For key to letters, see Tables VII and VIII. [b] Time in hours followed by temperature (°C) in parentheses. [c] Percentage yield of product followed by percentage of side-products in parentheses.

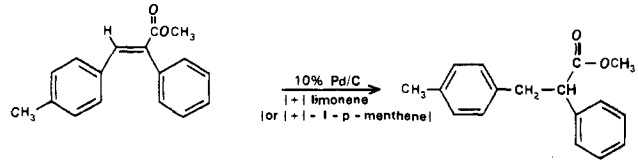
SCHEME XLVIII



ductions using hydrogen transfer is possible.

Evidence for asymmetric induction has been sought in order to support[154] the idea that catalytic transfer reduction is not simply a catalytic hydrogenation using an alternative hydrogen source. Reduction of the stilbene in Scheme XLIX gave only a racemic ester,

SCHEME XLIX



although in good yield. A similar attempt to reduce α-acetamidocinnamic acid produced only racemic *N*-acetylphenylalanine. Evidence that optically active donors such as (+)-limonene disproportionate rapidly in the presence of Pd/C was obtained. A more stable chiral transfer agent, 1,2,5,6-tetrahydrophthalic anhydride, failed to give chiral reduction of methyl 2-phenyl-3-*p*-tolylpropenoate (Scheme XLIX). As these transfer reductions may result from successive oxidative additions of hydrogen donor and acceptor to a catalyst atom site followed by cis elimination of product, lack of chirality in the product might reflect only the secondary importance of chirality in such a mechanism, i.e., the overall chirality of the donor/acceptor/catalyst transition state may be very slight. Further attempts to investigate the possibility of forming chiral products are worth encouraging, although it might be more useful to use a chiral heterogeneous catalyst surface rather than a chiral hydrogen donor.

B. Alkynes

Alkynes are frequently used as intermediates in organic synthesis. Hydrogenation with molecular hydrogen and specially modified palladium catalysts[256] affords excellent yields of *cis*-alkenes, while dissolving metal reductions can be used to obtain[5,256] *trans*-alkenes. The requirement for special catalysts results from observations showing that reduction of alkenes to alkanes is much easier than the first stage reduction of alkyne to alkene. Consequently, in contrast to the large body of work reported for reduction of alkenes to alkanes by catalytic transfer hydrogenation, until recently little real use has been made of this method for conversion of alkynes into alkenes. The efficiency of heterogeneous hydrogen-transfer reduction to alkynes has been demonstrated (Table X). When Pd/C was used as a catalyst, complete conversion of 1,2-diphenylethyne into 1,2-diphenylethene was observed when sodium phosphinate was the hydrogen donor.[145] This result is in keeping with the previously reported reductions of stilbenes under a variety of transfer conditions.[4] In a study into the utility of *N*-benzylaniline as a hydrogen donor, 1,2-diphenylethane was also obtained from 1,2-diphenylethyne when the donor/substrate ratio was high.[66] Useful reductions of disubstituted alkynes to *cis*-alkenes have resulted from a more detailed study of the reaction conditions. *cis*-Stilbene could be obtained from 1,2-diphenylethyne by careful temperature control when using Pd/C and a slight excess of triethylammonium formate as hydrogen donor.[172] Similar conditions did not work so well with 3-hexyne and 1-hexyne and very poor results were achieved with 1-octyn-3-ol. When the donor/substrate ratio was controlled, mixtures of *cis*/*trans*-stilbenes could be obtained from 1,2-diphenylalkynes,[66] but the isomer ratios were not predictable because interconversion of the isomers was occurring during reaction. In another study, the reduction of ethynes of more diverse structure was undertaken. Although conversion of the conjugated alkyne to the (*E*,*Z*)-dialkene for example (Scheme L) occurred in an acceptable yield, many other conjugated ethynes (see Table X) afforded mixed products, with both isomerization of the alkene and saturation of the alkene to alkane occurring.[129] Most of these reductions involved lengthy reaction times. Greater control over stereo- and regioselectivity has been sought by modification of palladium catalysts.[145] Metals such as lead and mercury, which exhibit high electrolytic overvoltages for production of hydrogen during electrolysis, when used in conjunction with palladium, were found to decrease the rate of formation of 1,2-diphenylethane and to give efficient reduction of 1,2-diphenylethyne to *cis*-1,2-diphenylethene. Commercially available "Lindlar" catalyst also gave stilbenes. Optimum reduction to 1,2-diphenylethene occurred with Pd/Hg ratios of 1/0.7. Using the Pd/Hg catalyst or a similar Pd/Pb catalyst, other alkynes were reduced stereo- and regioselectively to the corresponding alkenes.[145]

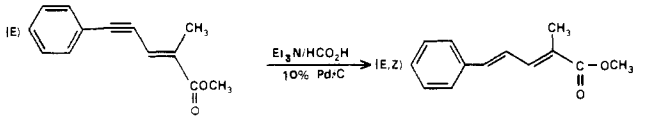
Cis/trans-interconversion observed in such hydrogen-transfer reductions after initial formation of the cis isomer was shown to be mediated by the catalyst metal.[145] Although a complex propyne (Scheme LI) was reduced to the corresponding aminoalkene, no cleavage of the normally labile C–O bond was observed when using a Pd/Pb (1/1) catalyst. Investigation of the efficiency of such modified catalysts and those modified

TABLE X. Heterogeneous Hydrogen Transfer Reduction of Alkynes

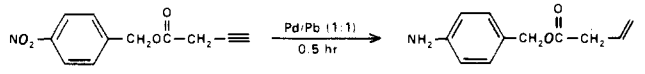
acceptor	donor	catalyst	reactn time, h	product	yield,[a] %	ref
diphenylethyne	J	t	4.0	1,2-diphenylethane (traces of *trans*-stilbene)	26	175
diphenylethyne	W	a	2.0	*cis*-stilbene (2% dibenzyl)	93	172
diphenylethyne	S	a	5.0	*cis*- and *trans*-stilbene (dibenzyl)	17/65 (5)	66
diphenylethyne	S	a	11	dibenzyl	81	66
diphenylethyne	Y	a	0.25	1,2-diphenylethane	100	145
diphenylethyne	Y	q	120	*cis*-stilbene	83	145
diphenylethyne	Y	n	2.6	*cis*-stilbene	85	145
3-hexyne	W	a	1.3	*cis*-3-hexene (hexane)	70 (18)	172
3-hexyne	U	i	30	*cis*-3-hexene (hexane)	85 (6)	172
1-hexyne	W	a	3	1-hexene	49	172
1-octyn-3-ol	W	a	4	3-octanol	56	172
$C_6H_5C{\equiv}C(CH_2)_3CH_3$	W	a	24	(*Z*)-$C_6H_5CH{=}CH(CH_2)_3CH_3$ ($C_6H_5(CH_2)_5CH_3$)	48 (12)	129
4-$OCHC_6H_4C{\equiv}CC_6H_5$	W	a	24	(*Z*)-$OCHC_6H_4CH{=}CHC_6H_5$	58	129
4-$NO_2C_6H_4C{\equiv}CC_6H_5$	W	a	18	4-$NH_2C_6H_4(CH_2)_2C_6H_5$	71	129
(*E*)-$C_6H_5C{\equiv}CCH{=}C(CH_3)CO_2CH_3$	W	a	10	(*E,Z*)-$C_6H_5CH{=}CHCH{=}C(CH_3)CO_2CH_3$	84	129
(*E*)-*n*-$C_6H_{11}C{\equiv}CCH{=}C(CH_3)CO_2CH_3$	W	a	10	*n*-$C_6H_{17}CO_2CH_3$ ((*E*)-$C_6H_{13}CH{=}CHCO_2CH_3$)	23 (14)	129
(*E*)-*n*-$C_4H_9C{\equiv}CCH{=}CHCO_2CH_3$	W	a	48	(*E,Z*)-*n*-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$	(63)	129
(*E*)-*n*-$C_4H_9C{\equiv}CCH{=}CHCO_2CH_3$	W	a	72	*n*-$C_6H_{17}CO_2CH_3$ ((*E*)-*n*-$C_6H_{13}CH{=}CHCO_2CH_3$)	24 (20)	
				(*E,Z*)-*n*-$C_4H_9{=}CHCH{=}CHCO_2CH_3$	(59)	129
(*Z*)-*n*-$C_4H_9C{\equiv}CCH{=}CHCO_2CH_3$	W	a	48	*n*-$C_6H_{17}CO_2CH_3$((*Z,Z*)-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$)	41 (5)	
				(*Z,E*)-$C_4H_9CH{=}CHCH{=}CHCHCO_2CH_3$	(54)	129
(*Z*)-*n*-$C_4H_9C{\equiv}CCH{=}CHCO_2CH_3$	W	a	72	*n*-$C_6H_{17}CO_2CH_3$((*Z*)-*n*-$C_6H_{13}CH{=}CHCO_2CH_3$)	24 (12)	129
				(*Z,E*)-*n*-$C_4H_9CH{=}CHCH{=}CHCO_2CH_3$	(30)	
(*E*)-*n*-$C_4H_9C{\equiv}CCH{=}C(CH_3)CO_2CH_3$	W	a	48	(*E,Z*)-*n*-$C_4H_9CH{=}CHCH{=}C(CH_3)CO_2CH_3$	70	129
p-$CH_3C_6H_4C{\equiv}CC_6H_5$	S	a	10	*cis*- and *trans*-*p*-$CH_3C_6H_4CH{=}CHC_6H_5$	28/72	66
p-$CH_3OC_6H_4C{\equiv}CC_6H_5$	S	a	5	*p*-$CH_3OC_6H_4CH{=}CHC_6H_5$(*cis/trans*)	10/62	66
p-$ClC_6H_4C{\equiv}CC_6H_5$	S	a	5	*p*-$ClC_6H_4CH{=}CHC_6H_6$(*cis/trans*)	79/13	66
$CH_3C{\equiv}CC_6H_5$	S	a	30	$CH_3CH{=}CHC_6H_5$(*cis/trans*)	39/13	66
$C_6H_5C{\equiv}CH$	Y	m	2.5	styrene	97	145
methyl stearolate	Y	n	20	methyl oleate	97	145
1-ethynyl-1-cyclohexene	Y	m	1.5	1-ethenyl-1-cyclohexene	81	145
1-ethynyl-cyclohexanol	Y	o	4.5	1-ethenylcyclohexanol	97	145
1-phenylpropyne	Y	p	1.75	1-phenylpropene	76	145
1-phenylpropyne	Y	q	3.6	1-phenylpropene	76	145
3-[(*p*-nitrobenzoyl)oxy]propyne	Y	o	0.5	3-[(*p*-aminobenzyl)oxy]propene	70	145

[a] The numbers in parentheses refer to the percentage yield of secondary product, also shown in parentheses in the product column.

SCHEME L



SCHEME LI



with other metals[256] such as Mn^{2+} for selective reductions of other functional groups could well be rewarding.

C. Arenes

A wide range of conditions for carrying out heterogeneous hydrogen-transfer reductions of arenes has been described in both this review and others.[4] Most of the substrates which have been reduced have substituents in aromatic structures, the aromatic rings themselves being found to be inert towards most of the hydrogen-transfer conditions described. Reductions of aromatic ring systems are frequently undertaken in organic synthesis and can often be effected by catalytic hydrogenation[257] or by dissolving metal reductions as in the Birch reduction (sodium in liquid NH_3, lithium in amines, or sodium amalgam in aqueous base).[21] Regioselective partial reductions are difficult to achieve by these methods. Unexpected selectivity was observed in the hydrogen-transfer reduction of 1,3-diphenylpropane with Raney nickel and propan-2-ol to give (3-phenylpropyl)cyclohexane.[175] Other two-ring aromatic hydrocarbons were also shown to be reduced only partially (Table XI). Selective hydrogenation of one of the rings of benzalacetophenone proceeded after initial reduction of the α,β-unsaturated ketone to 1,3-

TABLE XI. Heterogeneous Transfer Hydrogenation of Arenes with Propan-2-ol as Hydrogen Donor and Raney Nickel Catalyst[175]

substrate phenols	product(s)[b]	yield[a]
phenol	cyclohexanol	76
o-cresol	2-methylcyclohexanol	55 (43/57)
m-cresol	3-methylcyclohexanol	49 (67/33)
p-cresol	4-methylcyclohexanol	44 (41/59)
p-*tert*-butylphenol	4-*tert*-butylcyclohexanol	
thymol	menthol (48)	15
	neomenthol (42)	
	menthone (10)	
1-naphthol	2-tetralone (1)	100
	2-tetralol (1)	
	tetralin (39)	
	5,6,7,8-tetrahydro-1-naphthol (49)	
	1-decalol (11)	

polycyclic aromatic hydrocarbons	product	yield
biphenyl	phenylcyclohexane	100
diphenylmethane	phenylcyclohexylmethane	90
1,2-diphenylethane	1-phenyl-2-cyclohexylethane	100
naphthalene	tetralin	100
1,3-diphenylpropane	1-phenyl-3-cyclohexylpropane	100
benzalacetophenone	1-(3-phenylpropyl)cyclohexane	100

[a] Percentage yield after 24-h refluxing with slow distillation. Cis/trans ratio in parentheses. [b] Proportions of products shown in parentheses.

TABLE XII. Heterogeneous Transfer Reduction of Aromatic Dinitro Compounds with Pd/C Catalyst and Cyclohexene as Hydrogen Donor[2]

nitro compd	reactn time, min	product	yield, %
4-methoxy-2,3-dinitroanisole	10	3,6-dimethoxy-2-nitroaniline	85
4-methoxy-2,5-dinitroanisole	10	3,6-dimethoxy-4-nitroaniline	85
4-methoxy-2,6-dinitroanisole	15	2,5-dimethoxy-3-nitroaniline	70
2,6-dinitroaniline	30	2-amino-6-nitroaniline	95
4-chloro-*N*-methyl-2,6-dinitroaniline	30	2-amino-*N*-methyl-6-nitroaniline	85
3,6-dimethoxy-2-nitroaniline	120	2,3-diamino-4-methoxyanisole	70
3,6-dimethoxy-*N*-methyl-2-nitroaniline	120	2-amino-4-methoxy-3-(methylamino)anisole	80
6-nitroindazole	60	6-aminoindazole	90
2-(2,6-dinitroanilino)-*N*-methylpropionamide	60	3,4-dihydro-3-methyl-5-nitroquinoxalin-2(1*H*)-one	60
		2-(2-amino-6-nitroanilino)-*N*-methylpropionamide	30
1,2-dinitrobenzene	10	1,2-nitroaniline	>90[a]
1,3-dinitrobenzene	20	1,3-nitroaniline	>90[a]
1,4-dinitrobenzene	10	1,4-nitroaniline	>90[a]

[a] Personal communication (I. D. Entwistle).

diphenylpropane. Some indoles, particularly tryptophan derivatives, have been reduced to indolines with formic acid as donor.[299]

A practical procedure for obtaining cyclohexanones utilizes the transfer reduction of phenols to give the precursor cyclohexanols (Table XI).[175] Although benzene is not reduced on refluxing it with propan-2-ol over Raney nickel, phenols are. By keeping the hydrogen donor to phenol ratio low it was shown that cyclohexanone was an intermediate in the reduction to cyclohexanol. Where geometrically isomeric cyclohexanols were formed, the cis isomer was preferentially formed initially, but equilibrated with the trans isomer as the reaction progressed. The mixture of products obtained from α-naphthol resulted mainly from reduction of the nonphenolic ring and reduction of the intermediate tetralone.

D. Nitroalkenes

Reduction of β-nitrostyrene with formic acid and palladium gave the oxime of phenylacetaldehyde, presumably following rearrangement of an intermediate (β-nitrosoethyl)benzene.[128] This isolated observation was confirmed and extended by the reduction of a variety of nitroalkenes to give ketones or aldehydes when using Raney nickel catalyst and sodium phosphinate as donor.[301] Presumably, under the reaction conditions, intermediate hydroxylamines were hydrolyzed to the corresponding free carbonyl compounds.

E. Nitroarenes

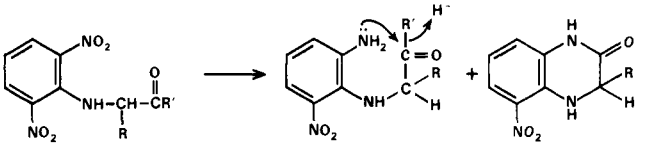
The effectiveness of catalytic transfer hydrogenation of aromatic nitro compounds to the corresponding amino compounds, utilizing unsaturated hydrocarbons as hydrogen donors, was demonstrated 30 years ago.[146] Subsequent general application of this mild, convenient technique in synthesis was slow to follow.[4] The earlier reported much wider use of hydrazine as hydrogen donor for reduction of nitro groups with a variety of metal catalysts has been reviewed[216] and, during the last decade, both types of donor have been utilized. More recent work is covered in Tables XII–XVII.

The use of cyclohexene as hydrogen donor with catalyst-to-substrate ratios of 1:100 in earlier work[146] resulted in inordinately long reaction times and many nonspecific reductions were recorded. In a work designed to take advantage of one of the little studied aspects of this last work, namely the monoreduction of polynitrobenzenes, it was reported[2] that use of much greater proportions of catalyst to substrate afforded rapid reduction of nitroarenes to aminonitroarenes.[2]

Typically, a dinitroarene was refluxed in ethanol with a large excess of cyclohexene in the presence of Pd/C catalyst with a catalyst/substrate ratio of 1/2. Formation of the half-reduced product, an aminonitroarene, was rapid and, in many cases, complete in 10–15 min. Because reduction of the aminonitroarenes was considerably slower than their rate of formation, selective reaction to a half-reduced stage could be achieved readily. For the examples reported[2] (Table XII), transfer hydrogenation to the half-reduced state could be the method of choice, since high yields are obtained easily and quickly; catalytic molecular hydrogenation of 4-methoxy-2,3-dinitroanisole gives the difficulty isolable 4-methoxy-2,3-diaminoanisole in low yield,[258] but catalytic transfer hydrogenation gives a high yield of 3,6-dimethoxy-2-nitroaniline (Table XII).

During reduction of *N*-methyl-4-chloro-2,6-dinitroaniline, concomitant removal of halogen from the aromatic ring was observed with this method, but the internuclear coupling reactions found when using hydrazine as hydrogen donor for removal of halogen[216] were not observed. The reaction shown (Scheme LII)

SCHEME LII

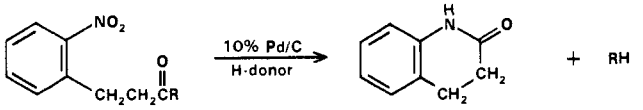


was observed on reduction of 2-(2,6-dinitroanilino)-3-methylacetamide (R = R′ = CH_3) to give the 3,4-dihydro-4-methyl-5-nitroquinoxalin-2(1*H*)-one. For compounds undergoing reaction (Scheme LII), and containing common amino acid residues with side chains (R), difficulty in effecting formation of quinoxalinones was experienced only in the case of cysteine (R = CH_2SH), when the side chain was reduced to methyl. The reaction sequence (Scheme LII) has been examined as a means of sequencing amino acid residues in peptides.[186] Transfer reduction of an N-terminal 2-(3-nitro)pyridyl derivative of an octapeptide gave a tetrahydropyridopyrazine containing the N-terminal amino acid residue and left a residual heptapeptide.

Repetition of the reduction successively removed the first five amino acid residues and allowed their identification by mass spectrometry of the corresponding tetrahydropyridopyrazines. On the small scale used, after removal of the fifth residue, further residues could not be identified because of the buildup of impurities carried through at each reduction/cyclization step. Although this routine was not as satisfactory on a small scale as the standard Edman technique[259] removal of protecting groups in peptides by catalytic transfer reduction has become of great interest (see section VIB).

In a further study, it was shown that the 2-nitrodihydrocinnamoyl group could be used to protect alcohols and amines and the latter could be recovered by hydrogen-transfer reduction of the esters (Scheme LIII,

SCHEME LIII



R = OAlk or OAr) or amides (Scheme LIII, R = NHAlk or NHAr). The use of sodium phosphinate as a donor was compared with that of cyclohexene;[170] the advantages of being able to remove an amide protecting group at room temperature were demonstrated; Table XIII lists examples of some of the 2-nitrocinnamoyl derivatives which were reduced to recover the starting alcohol or amine.

In a search for more active hydrogen donors for transfer hydrogenation, it was found that formic, phosphinic (hypophosphorous), and phosphorous acids or their salts in the presence of a catalyst would reduce nitro compounds to amines in high yield.[128] As alternative donors to cyclohexene and hydrazine, these acids and their salts have several advantages, not the least of which is their lower cost.

In typical reductions with phosphinic acid or phosphinates, a methanolic, ethanolic, or tetrahydrofuran solution of the nitroarenes was stirred with phosphinic acid and 10% Pd/C catalyst. After an initial release of some free hydrogen gas, the mixture was warmed to about 60–80 °C for some 20 min and filtered. For reductions with aqueous sodium phosphinate, which is slightly alkaline, neutralization of the mixture before extraction of the aniline is avoided. A definite advantage of this method is that, unlike reductions employing cyclohexene as donor, loss of aromatic halogen groups is avoided. For example, with sodium phosphinate, 2,6-dinitrochlorobenzene was reduced to 2,6-diaminochlorobenzene in 75% yield; in contrast, reduction with sodium formate or formic acid dechlorinated the arene and gave only 1,3-diaminobenzene.

Reductions of the following nitroarenes[128] in 75–90% yields were effected using Pd/C catalyst and one of phosphinic acid, sodium phosphinate, phosphorous acid, or sodium phosphite: 1-chloro-4-nitrobenzene, 1-iodo-4-nitrobenzene, 1-chloro-2,6-dinitrobenzene, 2-chloro-1-fluoro-4-nitrobenzene, 4-chloro-3-nitrobenzylidyne fluoride, 1,3,5-trichloro-2-nitrobenzene. Selective monoreduction of dinitroarenes could not be achieved with donors other than cyclohexene because, with them, the rate of reduction of a nitroaniline is greater than its rate of formation from a dinitroarene.

Reductions with formic acid were equally facile, and

TABLE XIII. Heterogeneous Transfer Hydrogenolysis (Deprotection) of the (2-Nitrophenyl)propionyl Protecting Group (R)[a] from Amines and Hydroxy Compounds[170]

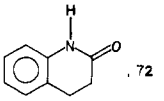
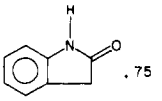
amide or ester	donor	reactn time, min	% deprotection
3-RNH-quinoline	C	30	90
	Y	15	95
3,4-$Cl_2C_6H_3NHR$	C	60	90
	Y	60	80 (90)
4-$RNHC_6H_4CH(COOC_2H_5)_2$	C	60	85
	Y	30	90
$RNHCH(CH_3)CONHCH_3$(DL)	C	20	85
	Y	30	75
2-R-naphthalene	Y	30	90
$RN(CH_3)C_6H_5$	Y	35	85
2-RNH-3-C_6H_{17}NH-1,4-naphthoquinone	Y	30	90

[a] R = 3-(2-nitrophenyl)propionyl.

were complete usually within 15 min. However, for this hydrogen donor, reduction was terminated rapidly by the presence of the anion of a strong acid, such as Cl^-. The effect of such catalyst poisoning prevented hydrogen transfer from formic acid to nitroarenes containing a halogen substituent other than fluorine because of initial formation of some hydrogen halide acid. Yields of aniline up to 95% were obtained for reductions of 4-nitrobenzyl alcohol, 3-nitroaniline, 2-nitroanisole, 1-nitronaphthalene, 4-fluoronitrobenzene, 2,6-dinitroaniline, 2-nitrobenzoic acid, 2- and 4-nitrobenzonitrile, 4-fluoro-3-nitrobenzylidyne fluoride, 1-fluoro-2-nitro-4-(methylsulfonyl)benzene, 2-methyl-4-nitroimidazole, and 5-nitro-2-(trifluoromethyl)benzimidazole. A number of arenes containing heterocyclic sulfur atoms were not reduced in formic acid, even at 100 °C after 1 h as in the cases of 2-nitrothiophene, 5-nitrobenzisothiazole, 5-nitro-2,1,3-benzothiadiazole, 4-chloro-7-nitrobenzisothiazole, and 5-nitro-1,2,3-benzothiadiazole. In contrast, 3-methyl-5-nitrobenzo[*b*]thiophene was reduced to the corresponding amine.

Although a weight ratio of nitro compound to catalyst metal as high as 5:1 in many of the reported reductions may appear to be disadvantageous, filtration of the catalyst from the reaction mixture followed by washing with hot ethanol gave back the catalyst without significant loss of its activity. Apart from halogen substituents other groups such as NR_2, CF_3, SO_2CH_3, CH_2OH, OH, CO_2H, and OCH_3 did not interfere with reduction.[128] Reduction of nitroarenes containing benzyl-protected phenolic groups without concomitant hydrogenolysis of the benzyl–O bond has been reported.[260] In a subsequent report,[261] the difficulty experienced with termination of reductions by halogen when using formic acid as a hydrogen donor was overcome by a formate salt. Triethylammonium formate at 80–100 °C reduced the nitroarenes shown in Table XIV. Similar work with a $Pd/AlPO_4/SiO_2$ catalyst has been reported.[262] The lengthy reduction time for 2-nitrocinnamate is comparable to that observed in its reduction with cyclohexene as hydrogen donor.[170] The concomitant reduction of the side-chain olefinic bond appears to be favored by either lactam formation, which is not possible in the 3-nitrocinnamate case, or by an electronic effect of NO_2 or NH_2 in the ortho position. A number of reductive eliminations of halogen[261] without reduction of nitroarene have been carried out by using less vigorous conditions with triethylammonium formate (see section VID). Reaction times

TABLE XIV. Heterogeneous Transfer Reduction of Aromatic Nitro Compounds with Triethylammonium Formate as Hydrogen Donor[261]

substituted benzene	catalyst	Et_3N, mol	HCO_2H, mol	time, h	product,[a] % yield
NO_2	d	0.214	0.165	2.3	NH_2, 100
1-CO_2CH_3-4-NO_2	d	0.214	0.165	2	1-CO_2CH_3-4-NH_2, 97
1-OCH_3-2-NO_2	d	0.214	0.165	4	1-OCH_3-2-NH_2, 94
1-OCH_3-4-NO_2	d	0.214	0.165	4	1-OCH_3-4-NH_2, 89
1-$NHCOCH_3$-4-NO_2	d	0.214	0.165	4.5	1-$NHCOCH_3$-4-NH_2, 85
1-NO_2-2-Br	d	0.039	0.033	1.3	1-NH_2-2-Br, 94
1-CH=$CHCO_2H$-2-NO_2	d	0.285	0.220	5.3	 .72
1-CH=$CHCO_2CH_3$-3-NO_2	d	0.194	0.150	3.5	1-CH=$CHCO_2CH_3$-3-NH_2 } 75 1-$(CH_2)_2CO_2CH_3$-3-NH_2 }
1-CO_2H-2-NO_2	d	0.214	0.165	23	 .75
1-$COCH_3$-2-NO_2	d	0.357	0.275	25	1-CH_2CH_3-2-NH_2, 50

[a] Substituted benzene.

experienced by using formate salts as donor are greater than those reported for similar nonhalogenated nitroarene reductions using formic acid as hydrogen donor.

Reductions of nitroarenes to aminoarenes with hydrazine as hydrogen donor have been reported for a wide range of catalysts[216] such as Pd/C, Cu, Fe, Ni, Rh/C, and Ru/Ca. As a general method, the technique has been limited by side reactions and the need to use a large excess of hydrazine. Control of reduction rates with the more active catalysts such as Pd/C is difficult.

Dehalogenations are common during catalytic transfer reduction and substitution reactions may be observed also. More recently, successful attempts to gain greater control of these reductions by using less active catalysts and variation of the solvent have been reported.[263] In the presence of a 50% excess of hydrazine hydrate, a number of nitrobenzenes were reduced with Fe(III) chloride on active carbon. An indication of how much less active Fe(III) is as a catalyst than Pd is found in the lengthy reduction times (Table XV). However, high yields of amines were obtained and reduction of 5-chloro-2,4-dimethoxynitrobenzene to the corresponding aniline was effected without loss of the chloro group.

In a later report, an examination of the effects of various forms of Fe(III) oxides and hydroxides on this reduction were examined, because it had been surmised that Fe(III) was present on the active carbon support as the oxide or hydroxide. Two oxides, β-FeO(OH) and β-Fe_2O_3·H_2O, were found to be the most effective. Yields and reaction times were similar to those obtained by the direct use of $FeCl_3$·$6H_2O$ on the active carbon. A more extended study of solvent requirements for reduction of nitroarenes with a variety of catalysts such as $FeCl_3$ and Raney nickel with hydrazine has been carried out.[152]

Investigation of individual steps in the reaction Scheme LIV (R = Ph) has shown[264] ease of reduction to decrease in the order nitrobenzene > *N*-phenylhydroxylamine > nitrosobenzene, so it is easy to understand the reason for the difficulty usually experienced in stopping reduction at either the nitroso or hydroxylamine stage. During the course of studies on

TABLE XV. Heterogeneous Transfer Reduction of Nitroarenes with Fe(III) Catalysts and Hydrazine as Hydrogen Donor[263]

nitroarene	reactn cond[a]	temp, °C	time, h	yield,[b] %
3-nitrotoluene	20.6/2	reflux	5	99
4-nitroanisole	18.5/2	reflux	5	96
4-nitroanisole	20.1/1	reflux	5	98
2-nitroanisole	21.3/1	reflux	5	98
3,4-dimethylnitrobenzene	52.1/1.1	reflux	8	99
4-nitroacetanilide	136.7/2	reflux	8	92
4-nitrodiphenyl ether	28.4/1	reflux	5	98
4,4′-dinitrodiphenyl ether	375.2/5	reflux	5	98
2,5-diethoxy-4-nitrobenzanilide	195.0/4	58–60	13	98
5-chloro-2,4-dimethoxynitrobenzene	47.0/1.4	50–55	26	97
4-methoxy-3-nitroacetanilide	205.0/2.2	reflux	28	94
4-methoxy-4′-nitrodiphenylamine	100.0/5	reflux	14	91
Partial Reduction				
1,3-dinitrobenzene	102.8/2.4	45–48	6	97
2,4-dinitroanisole	106.4/2.4	25–30	8	66
2,4-dinitrophenol	800.0/4.2	55–58	9	89

[a] Fe(mg)/C(g) per 0.1 mol RNO_2. [b] Yield of amino compound.

SCHEME LIV

$$RNO_2 \rightarrow RNO \rightarrow RNHOH \rightarrow RNH_2$$

transfer hydrogenation of nitroarenes,[2] it was observed that *N*-(3-nitrophenyl)hydroxylamine was formed as an intermediate during reductions of 1,3-dinitrobenzene when using both cyclohexene and formic acid as hydrogen donors. Further rapid reduction to 3-nitroaniline prevented isolation of the hydroxylamine in high yield. By use of hydrazine as hydrogen donor and rhodium on charcoal as a milder catalyst, *N*-3-(nitrophenyl)hydroxylamine was further reduced only slowly to 3-nitroaniline and 1,3-diaminobenzene, and could be isolated easily. Preparation of this hydroxylamine and others shown in Table XVI in fair to excellent yields was readily achieved.[179]

Significantly higher yields of hydroxylamines from some nitroarenes were obtained subsequently[265] by carrying out the reactions below 10 °C.

TABLE XVI. Formation of *N*-Phenylhydroxylamines by Catalytic Hydrogen Transfer Reduction[179]

substituent[a]	yield, %[b]	catalyst	donor
3-NO_2	55	r	T
	84	d	Y
3-CH_3	77	r	T
4-CH_3	24	r	T
4-Cl	72	r	T
4-Cl	75	d	Y
(*E*)-4-CH=$CHCO_2CH_3$	52	r	T
(*E*)-4-CH=$CHCO_2CH_3$	64	d	Y
2-Cl-5-CF_3	45	r	T
2-Cl-5-CF_3	90	d	Y
2,5-$(OMe)_2$	33	r	T
3-Cl-4-CH_3	77	r	T
2-$CO_2C_2H_5$	30	d	Y
3-OH	70	d	Y
3-Br	50	d	Y
(*E*)-3-CH=CHC_6H_5	52	d	Y
3-$OCONHC_6H_5$	85	d	Y
3-$OCONHC_6H_4CH_3$-*m*	74	d	Y
3-$OCONHC_6H_{11}$-c	93	d	Y
3-$NHCOCH_2Cl$	75	d	Y
4-NO_2	78	d	Y
2-CN-3-Cl	90	d	Y
2-Cl-5-$NHCON(CH_3)_2$	74	d	Y
4-nitropyridine N-oxide	70	d	Y
2-chloro-3-nitropyridine	66	d	Y
5-nitro-2,1,3-benzothiadiazole	44	d	Y

[a] Refers to positions and types of substituent(s) in phenyl ring of nitrobenzene, except for the last three entries where full names are given. [b] Isolated yield of substituted *N*-phenylhydroxylamine.

The dissolving metal process most widely used to obtain *N*-phenylhydroxylamines from nitroarenes, i.e., zinc and aqueous ammonium chloride, is frequently carried out in a two-phase system by addition of an organic solvent to assist removal of the product from the metal surface. In the presence of an inorganic hydrogen donor such as phosphinic acid or sodium phosphinate, aqueous tetrahydrofuran becomes a two-phase solvent system.

In this two-phase system with Pd/C catalyst and a phosphinate as hydrogen donor, nitroarenes were reduced readily to *N*-phenylhydroxylamines. Although yields were comparable[179] to those obtainable with the Rh/hydrazine reductions described above, overreduction to anilines occurred if careful control of reagent concentration was not maintained. Many of the *N*-phenylhydroxylamines listed in Table XVI could not be prepared by other conventional methods and the hydrogen-transfer method appears now to be the method of choice for reduction of nitroarenes to the corresponding *N*-arylhydroxylamines.

A direct comparison of the hydrogen-transfer reduction of aliphatic and aromatic nitro compounds has not been made. However, phenylacetaldehyde oxime was obtained from the Pd-C catalyzed reduction of β-nitrostyrene using sodium phosphinate as hydrogen donor. 2-Nitropropane has been reduced to the hydroxylamine.[128]

Generally, transfer reduction of nitroarenes to *N*-arylhydroxylamines by use of Pd/C and hydrazine has not proved effective because of further rapid reduction of the hydroxylamines to anilines. Interestingly, specific reductions of 2- and 4-chloronitroarenes to the corresponding (chloroaryl)hydroxylamines has been reported,[266] (see Table XVII); at least one such reaction went explosively.[267]

TABLE XVII. Chloroarylhydroxylamines Obtained by Heterogeneous Transfer Reduction of Nitroarenes[266]

$O_2NC_6H_3XY$				
X	Y	temp, °C	time, h	yield, %
2-Cl	H	45	2.0	77
4-Cl	H	40	1.0	58
2-Cl	3-Cl	45	1.0	74
3-Cl	4-Cl	45	0.5	87
3-Cl	4-CH_3	55	3.0	58
2-Cl	5-CH_3	55	2.5	100

TABLE XVIII. Heterogeneous Transfer Hydrogenolysis of N–N Bonds in Azobenzenes[167]

substrate	product	yield, %
azobenzene	aniline	90
hydrazobenzene	aniline	95
2,2′-dimethylazobenzene	2-methylaniline	83
3,3′-dimethylazobenzene	3-methylaniline	85
2,2′-dibromoazobenzene	2-bromoaniline	81
3,3′-diacetylazobenzene	3-acetylaniline	86

F. Azo Compounds

The N=N double bond in azo compounds can be reduced readily to give hydrazo compounds, but the latter are readily hydrogenolyzed. Catalytic hydrogen-transfer reduction of azobenzene was reported earlier to give aniline in 97% yield.[1] More recently, as an alternative to 10% Pd/C, 5% Pd-on-asbestos has been used as the catalyst. Slow (48 h), but high yielding, reductive cleavage of N=N bonds was observed with cyclohexene as hydrogen donor. More rapid (16 h), but lower yielding reactions, were noted when the higher temperature of the refluxing hydrogen donor, tetralin, was used, (Table XVIII).[187] Co-ordination of the hydrogen donor and substrate to the same Pd atom, followed by H transfer from the allylic position has been proposed for the mechanism of the first stage of this reaction.

G. Ketones and Aldehydes

Studies of hydrogen-transfer reduction of ketones, in which primary and secondary alcohols were used as donors with a variety of heterogeneous catalysts, have been reported over several decades. Widespread acceptance of such transfer methods as useful options compared with catalytic hydrogenation, dissolving metal reductions, hydride reductions, or Meerwein–Pondorff–Verley reductions, has not occurred. Although a wide range of catalysts has been found to cause cross-oxidation/reduction between alcohols and carbonyl compounds, the high temperatures and often specific catalyst requirements have not made the method attractive in synthesis.[114,157] Earlier work has been reviewed.[268]

More recently, several practical applications have been reported. With transition-metal catalysts, such as ruthenium, osmium, and iridium blacks, cyclohexanones were reduced readily to cyclohexanols using propan-2-ol as hydrogen donor.[137] These catalysts proved to be superior to Raney nickel[269] or old, non-pyrophoric nickel, the use of which was reported earlier for reduction of ketones by hydrogen transfer.[270]

Although lengthy reaction times were recorded (up to 24 h for complete reduction), stereoselectivity has been observed in the reduction of 2-methylcyclohexanone (Table XIX).[137]

TABLE XIX. Hydrogen-Transfer Reduction of Ketones to Alcohols Using Propan-2-ol as Hydrogen Donor[137]

ketone	catalyst	reactn time, h	yield alc, %
4-*tert*-butylcyclohexanone	U	81	100
	V	22	100
	W	90	90
3-*tert*-butylcyclohexanone	X	44	75
	U	57	100
	V	92	95
	W	118	83
2-methylcyclohexanone	U	5.5	99
	V	72	100
	W	24	67
cholestan-3-one	U	24	58
	V	70	30
	W	70	28

TABLE XX. Hydrogen-Transfer Reduction of Ketones Using Propan-2-ol as Hydrogen Donor over Raney Nickel Catalyst[175]

ketone	reactn time, min	yield alc, %
cyclohexanone	70	96
4-methylcyclohexanone	90	79
menthone	120	76[a]
2-pentanone	180	32
3-pentanone	210	32
4-methylpentanone	240	31
2-octanone	240	25
benzophenone	60	80[b]

[a] Neomenthol was also formed. [b] Diphenylmethane (20%) was also formed.

The use of metal borides of Fe, Ru, Os, Co, Ir, Ni, Pd, and Pt, which act as catalysts for reductions with molecular hydrogen,[271] was studied in attempts to obtain greater selectivity.[137] These borides were effective catalysts for the reduction of 4-*tert*-butylcyclohexanone by propan-2-ol but did not improve the stereoselectivity of the reduction. At very much higher temperatures, e.g., 200 °C, copper(II) oxide and copper chromite effected hydrogen transfer.[137]

Wider application of propan-2-ol as a donor for hydrogen-transfer reduction was later reported[175] and reductions of ketones were achieved by using Raney nickel as catalyst (Table XX). Refluxing a 10% solution of a ketone in propan-2-ol with a one-tenth molar ratio of Raney-nickel catalyst gave varied yields of the corresponding alcohols over much shorter reaction times than those required for Ru, Os, or Ir.[137] A slight variation in the ratio of *cis*- to *trans*-2-methylcyclohexanol was found to be related to the reaction time. Acyclic ketones gave notably low yields.

Reduction of ketones and aldehydes in the presence of cyclohexene as hydrogen donor has not been reported to any extent probably because of the very long reaction times required, and possibly because of reported observations of catalyst poisoning by aldehydes.[1] Several instances have been reported where complete or partial reduction of ketone to the corresponding hydrocarbon has been observed to occur as an overreduction during attempts to produce an hydroxyl group. Notably, diphenylmethane is formed from benzophenone by using propan-2-ol as donor[175] and 1-phenylethanol is produced from the 1-phenyltetrazolyl ether of 4-acetylphenol with formic acid.[150]

Successful reduction of quinones with a range of hydrogen donors has been reported.[184] The high oxidizing

TABLE XXI. Hydrogen-Transfer Reduction of Quinones Using Pd/C as Catalyst[184]

quinone	H donor	yield,[a] %	
1,4-benzoquinone	V	70–80	H
1,4-naphthoquinone	V	62	HD
2-methyl-1,4-naphthoquinone	C	80	HD
2,8-dimethyl-1,4-naphthoquinone	V	83	HD
2,3-dichloro-1,4-naphthoquinone	V	73	HD
3-chloro-2-(phenylamino)-1,4-naphthoquinone	V	52	HD
2-acetamido-3-(isopropylamino)-1,4-naphthoquinone	C	85	HD
2-hydroxy-1,4-naphthoquinone	V	60	HT
2-(argentiooxy)-1,4-naphthoquinone	V	51	HT
2-amino-3-chloro-1,4-naphthoquinone	C	70	NH
1,2-naphthoquinone	C	70	HD
1-acetamido-2-chloro-9,10-anthraquinone	V	30–35	HX
9,10-anthraquinone	V	50	HI
9,10-phenanthraquinone	V	54	
1,2-phenanthraquinone	C	95	
menaquinone	V		
plastoquinone	V		

[a] Percentage yields are reported for hydroquinones (H), hydroquinone diacetate (HD), hydroquinone triacetate (HT), 1-acetamido-*x*-acetoxy-2-chloroanthracene (HX), 9-acetoxy-10-hydroxyphenanthrene (HI), and N-acetamidohydroquinone (NH).

potentials of quinones means that many reducing agents can effect their conversion to hydroquinones. An earlier observation that benzoquinone could be reduced by hydrogen transfer was confirmed. However, more useful reductions occur in the presence of catalysts and reducing agents, which are also hydrogen donors. Treatment of quinones with Pd/C and one of the hydrogen donors, cyclohexene, phosphinic acid, or sodium phosphinate in benzene, ethanol, or tetrahydrofuran rapidly (5–60 min), yielded the corresponding hydroquinones. Unlike in the reduction of nitroarenes,[128] formic acid and formates were ineffective hydrogen donors for quinones.

Yields reported in Table XXI[184] were either for isolated pure hydroquinone or for the diacetate derivative. In all examples, complete conversion of the quinone was observed, except for 1-acetamido-2-chloro-9,10-anthraquinone.

Several methods for catalytic transfer hydrogenation have been described for the cleavage of C–O bonds in alcohols[181] and phenols[150] as discussed in section VI on hydrogenolysis. Such methods have been derived from the observation that reduction of aromatic aldehydes and ketones[188] to hydrocarbons could be effected by using the cyclohexene/Pd/C(donor/catalyst) system previously employed for other reductions,[2] but with the addition of a Lewis acid promotor such as ferric chloride. Good yields of hydrocarbon were obtained from benzaldehydes and acetophenones using 40% by weight of catalyst to acceptor, together with 4% of the promotor Lewis acid. The greater yields observed for ketones than for aldehydes appear to result from losses through competing decarbonylation of aldehydes, a reaction well known in homogeneous catalysis.[272] These Lewis acid assisted reductions were generally complete in 3–5 h; formation of lactones provides evidence for the intermediacy of alcohols. Trapping of the intermediate alcohols was later achieved by partial reduction of aromatic aldehydes in the presence of acetic anhydride (see Table XXII).[154] The reduction of 4-chloroacetophenone to ethylbenzene indicated that reductive

TABLE XXII. Hydrogen-Transfer Reductions of Aldehydes and Ketones Using $FeCl_3$-Promoted Pd/C Catalysis[154,188]

aldehyde or ketone	donor	reactn time, h	product[a]	yield, %
benzaldehyde	A	3	H	80
benzaldehyde	B	3	H	59
benzaldehyde	E	3	H	55
benzaldehyde	F	3	H	94
benzaldehyde	G	3	H	80
benzaldehyde	C	3	H	80
benzaldehyde	C[h]	12	H	72
p-methoxybenzaldehyde	C	12	H	80
p-(dimethylamino)benzaldehyde	C	12	H	75
o-carboxybenzaldehyde	C	12	H	35 (45)[b]
m-methoxy-*p*-hydroxybenzaldehyde	C	12	H	70
acetophenone	A	12	H	100
p-hydroxyacetophenone	A	12	H	90
p-methoxyacetophenone	A	12	H	90
o-carboxyacetophenone	A	12	H	0 (80)[b]
benzophenone	A	12	H	100
p-anisaldehyde	C[h]	12	E	83
2,6-dimethylbenzaldehyde	C[h]	12	E	77
p-isopropylbenzaldehyde	C[h]	12	E	81
α-naphthaldehyde	C[h]	12	E	68
cyclopropyl phenyl ketone	A	4	H	100[c]
4-benzoylbutyric acid	A	4	H	60[d]
(*E*)-1,2-dibenzoylethene	A	4	H	68[e]
6-methoxytetralone	A	4	H	33,[f] 20[g]
4-chloroacetophenone	A	4	H	100

[a] H = complete reduction of C=O to CH_2 (hydrocarbon); E = ester of intermediate alcohol. [b] Yield of lactone. [c] n-Butylbenzene. [d] 5-Phenylpentanoic acid. [e] 1,4-Diphenylbutane. [f] 6-Methoxytetralin. [g] 2-Methoxynaphthalene. [h] Cyclohexene with added acetic anhydride.

elimination of halogen occurred readily. Dehydrogenation of 6-methoxytetralin, the reduction product of 6-methoxytetralone occurred. A study of suitable donors (Table XIII) showed that other unsaturated hydrocarbons could effect reduction of benzaldehydes and acetophenone to the corresponding hydrocarbons.[154] Useful hydrogen donors were found to be *d*-limonene, α-phellandrene, bicyclo[4.3.0]nona-3,7-diene, and to a lesser extent, 4-vinylcyclohexene. In suitable cases, catalytic transfer reduction of aromatic aldehydes and ketones can be an alternative to hydride, Clemmensen, or Wolf–Kishner reduction.

H. Nitriles

A previous review on catalytic transfer reduction[4] referred to be complete reduction of some α,β-unsaturated nitriles to give methyl groups (C≡N → CH_3). It was also pointed out that aliphatic nitriles appeared to be more resistant to transfer reduction. This earlier work utilized Pd/C as catalyst and a relatively high temperature with hydroaromatic hydrogen donors (refluxing *p*-menthene and tetralin). In fact, work reported on nitriles seemed to be very variable. Thus, the aliphatic nitrile, 1-cyano-4-oxopentane, has been shown to be reduced to 1-amino-5-oxohexane which, in turn, cyclizes to give 2-methyl-3,4,5,6-tetrahydropyridine.[273] The newly formed C=N bond remained unreduced, and the method has been proposed as a simple route to these tetrahydropyridines. However, in a more complex molecular series, a similar oxo nitrile system, under identical conditions, was reduced, cyclized and the C=N bond also reduced to yield piperidines rather than tetrahydropyridines. Indoles have been reduced to indolines[299] although, not infrequently, indolines themselves have been used as hydrogen donors (Table IV). For the above reductions, a Pd/C catalyst was used with formic acid as the hydrogen donor. Under very similar conditions, the 1-phenyltetrazolyl ether of 4-cyanophenol was hydrogenolyzed in high yield to give 4-cyanobenzene; no reduction of the cyano group was observed.[150] In another series of experiments, using the same catalyst and hydrogen donor, 3- and 4-nitrocyanobenzene were reduced to the corresponding 3- and 4-amino compounds, without concomitant reduction of the cyano group.[128] In contrast to these results, the cyano group in the 6-cyano-3-pyridazyl ether of phenol was rapidly reduced to aminomethyl group.[150] Clearly, further investigation of the reactivity of cyano groups to catalytic transfer reduction is desirable.

I. Azides

Several azides have been reduced to the corresponding primary amines through catalytic transfer reduction with palladium and ammonium formate.[298]

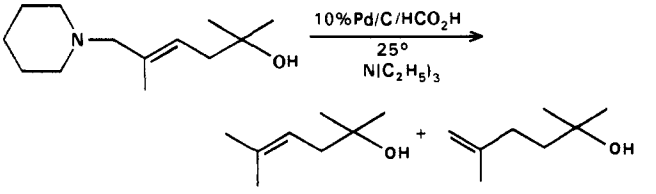
VI. Hydrogenolyses

A. C–N Bonds

Cleavage of the C–N bond in amides is exemplified by a procedure for sequencing the amino acid residues in peptides;[2] initial rapid hydrogen-transfer reduction of a nitro group to amino in a suitable N-terminal arene derivative of a peptide provides anchimeric assistance for amide bond cleavage (see section on reduction of nitro groups, Schemes LII and LIII).

Significant use has been made of the hydrogenolytic cleavage of C–N bonds in deprotonation of peptides. Most of these deprotonations have involved reduction of the *N*-(benzyloxycarbonyl) group (discussed in section VIB), rather than the more common catalytic debenzylation of a benzylamine.[193] The efficacy of heterogeneous catalytic hydrogen-transfer reduction for cleavage of some C–N bonds has been demonstrated by the hydrogenolysis of tertiary allylic amines (Scheme LV) using trimethylammonium formate as donor, Table

SCHEME LV



XXIII.[129] Lack of regiospecificity in the reaction could possibly be overcome by a different choice of catalyst. For example, use of Pd/Hg or Pd/Pb catalysts did not cause double bond migration in alkenes.[145]

B. C–O Bonds

1. Aliphatic

Catalytic hydrogenation has been used in several procedures designed to remove peptide protecting

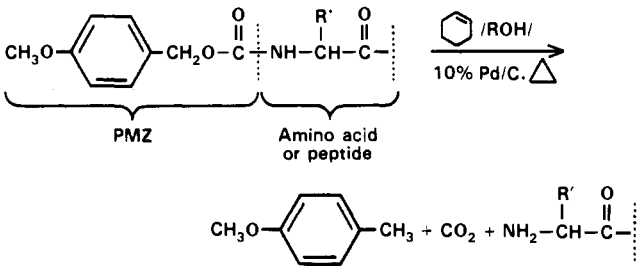
TABLE XXIII. Heterogeneous Transfer Hydrogenolysis of C–N Bonds Using Trimethylammonium Formate[129]

compd[a]	catalyst	reactn time, h	temp, °C	products (% yield)
(*E*)-MCH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	A	18	100	(*Z*)-3- and 4-hexenal dimethyl acetal (61), hexanal dimethyl acetal (11)
(*E*)-P*CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	A	18	100	(*Z*)-3- and 4-hexenal dimethyl acetal (67), hexanal dimethyl acetal (19)
(*E*)-P*CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$	A	18	100	(*Z*)-3- and 4-hexenal dimethyl acetal (93), hexanal dimethyl acetal (7)
(*E*)-(CH$_3$P*)$^+$CH(CH$_3$)CH=CHCH$_2$CH(OCH$_3$)$_2$I$^-$	A	13	100	(*Z*)-3- and 4-hexenal dimethyl acetal (63), hexanal dimethyl acetal (5)
(*E*)-P*CH$_2$C(CH$_3$)=CHCH$_2$C(CH$_3$)$_2$OH	A	18	100	(CH$_3$)$_2$C=CHCH$_2$C(CH$_3$)$_2$OH (59), CH$_2$=C(CH$_3$)CH$_2$CH$_2$C(CH$_3$)$_2$OH (3)
(*E*)-P*CH$_2$C(CH$_3$)=CHCH$_2$C$_6$H$_5$	A	72	25	(CH$_3$)$_2$C=CHCH$_2$C$_6$H$_5$ (60), CH$_2$=C(CH$_3$)(CH$_2$)$_2$C$_6$H$_5$ (8), (CH$_3$)$_2$CH(CH$_2$)$_2$C$_6$H$_5$ (22)
(*E*)-P*C(CH$_3$)$_2$CH=CHCH$_2$CH(OCH$_3$)$_2$	A	48	100	(CH$_3$)$_2$C=CH(CH$_2$)$_2$CH(OCH$_3$)$_2$ (31), (CH$_3$)$_2$CHCH=CHCH$_2$CH(OCH$_3$)$_2$ (31)

[a] MH = morpholine, P*H = piperidine.

groups by C–O bond cleavage. Removal of the benzyloxycarbonyl (Z) protecting group can be effected by acid hydrolysis or, more safely achieved, by a catalytic hydrogenation requiring several hours. More recently, rapid selective removal of benzyloxycarbonyl groups has been reported.[185] Using catalyst/substrate ratios of 1/1 by weight, complete deprotection could be achieved in up to 15 min at 65 °C, only slightly longer reaction times being needed at ratios of 1/5. Peptides protected with 4-methoxybenzyloxycarbonyl (PMZ) groups were deprotected even more rapidly (Scheme LVI). Examples are listed in Table XXIV. Hydrogenolysis of Z-Leu-Ala-OBz removed both the *N*-benzyloxycarbonyl and the C-terminal benzyl group in 4 min. No evidence of racemization was observed.[185] The presence of sulfur atoms slowed the deprotonation.

SCHEME LVI

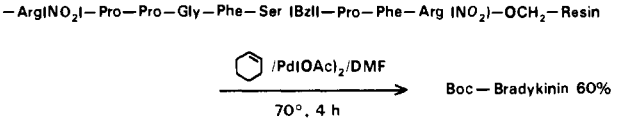


In a later study, the effectiveness of catalytic transfer hydrogenation using Pd/C with cyclohexene for removal of Z-protecting groups from peptides was confirmed.[274] The use of freshly prepared palladium black facilitated the removal of the benzyl group from protected histidyl compounds and of a nitro group from arginyl residues. Dissolution difficulties were partially overcome by using acetic acid as the solvent. High catalyst/substrate ratios, similar to those used for reduction of nitroarenes,[2] were found acceptable for peptide cleavage as several hydrogenations could be effected with recovered catalyst before its efficacy diminished.[274]

Removal of a peptide bound through a benzylic ester link to a cross-linked polystyrene resin has been effected by catalytic hydrogenation.[275,276] A synthetic application of the method utilizing cyclohexene as a hydrogen donor over Pd(OAc)$_2$ has been made for the synthesis of bradykinin (Scheme LVII).[167,173]

Good yields of homogeneous and nonracemized products are readily obtained when cyclohexene is used as hydrogen donor at temperatures greater than 65 °C (refluxing methanol or ethanol). In certain cases, especially when *tert*-butyl derived protecting groups are also present, the danger of thermal decomposition at more elevated temperatures might discourage the use of transfer hydrogenolysis. Several other donors have been investigated.

SCHEME LVII



1,3- and 1,4-cyclohexadienes are more easily dehydrogenated than is cyclohexene, and can effect deprotection of *N*-(benzyloxycarbonyl)-L-alanine in ethanol at 25 °C.[126] Under similar conditions cyclohexene does not transfer hydrogen. Although most of the solvents commonly used for catalytic hydrogenolysis of peptides with molecular hydrogen were found to be useful, glacial acetic acid was the most effective solvent for transfer hydrogenation with cyclohexadienes. Removal of an *N*-(benzyloxycarbonyl) group from methionine, but not from *S*-(benzyloxy)cysteine, was achieved in several solvents, including liquid ammonia. Ammonia also supports catalytic hydrogenolysis of protecting groups from *S*-benzylcysteine and methionine-containing peptides.[277] Although 1,4-cyclohexadiene is a very effective hydrogen donor for removal of *N*-(benzyloxycarbonyl), benzyl ether, and benzyl ester protecting groups, the present high cost of this donor may restrict its general use.

Acceptance of the advantages of heterogeneous catalytic hydrogen-transfer procedures for hydrogenolysis of protected peptides was increased with the observation that deprotection can be achieved more inexpensively and with shorter reaction times at 25 °C by using formic acid or formate salts as the donor.[168,169] In a typical procedure,[168] a 1:1 mixture of catalyst (10% Pd/C) and the protected peptide are stirred in 44% formic acid in methanol under nitrogen. For simple protected amino acids[169] (Table XXIV), reaction times as short as 10 min are recorded, but several hours in 88% formic acid were required for a larger polypeptide. Commonly, formic acid is used to remove *tert*-butoxycarbonyl groups from suitably protected peptides and therefore, when formic acid is used as a hydrogen donor for removal of benzyloxycarbonyl groups, simultaneous removal of the *tert*-butoxycarbonyl group can be ex-

TABLE XXIV. Heterogeneous Transfer Hydrogenolysis of Protected Amino Acids and Peptides

protected amino acid or peptide	catalyst	donor	reactn time, h	temp, °C	product	yield, %	ref
Z-Ser(OBu^t)-OMe	a	C	0.25	65	Ser-(OBu^t)-OMe	90	185
Z-Phe-OH	a	C	0.25	65	Ser-Phe-OH	90	185
Z-PheNH$_2$	a	C	0.25	65	Phe-NH$_2$	90	185
Z-Pro-OH	a	C	0.25	65	Pro-OH	90	185
Z-Tyr-OMe	a	C	0.25	65	Tyr-OMe	90	185
Z-Val-OMe	a	C	0.25	65	Val-OMe	90	185
PMZ-Val-OMe	a	C	0.08	65	Val-OMe	100	185
Z-Leu-OMe	a	C	0.25	65	Leu-OMe	100	185
PMZ-Leu-OMe	a	C	0.03	65	Leu-OMe	>90	185
Z-Leu-Ala-OBz	a	C	0.07	65	Leu-Ala	100	185
Z-Val-Phe-OMe	a	C	0.25	65	Val-Phe-OMe	100	185
Z-Phe-Leu-Gly-OMe	a	C	0.25	65	Phe-Leu-Gly-OCH$_3$	100	185
Z-Pro-Phe-Leu-Gly-OMe	a[b]	C	0.25	65	Pro-Phe-Leu-Gly-OMe	100	185
Z-Gly-Leu$_2$-Gly$_2$-OEt	a[c]	C	0.25	65	starting material	0	185
Z-Met-OMe	a	C	0.25	65	starting material	0	185
Z-Ala-Met-OMe	a	C	2.5	65	toluene in small quantity	0	185
Z-Gly-Gly	a	C	2.0	75	Gly-Gly	80	274
Z-Ser-Gly-OBzl	a	C	1.5		Ser-Gly	90	274
Z-Pro-Val-Gly-OEt	a	C	1.5		Pro-Val-Gly-OEt	84	274
Z-Ala-Asp(OBzl)-Ser-Gly	a	C	2.0		Ala-Asp-Ser-Gly	93	274
Boc-Lys(Z)	f	C	9.75		Boc-Lys		274
	a	C	1.5				
Boc-Phe-Arg(NO$_2$)-Trp-Gly	f	C	6.0		Boc-Phe-Arg-Trp-Gly	77/88	274
	a	C	7.0			91.5	274
Boc-His(N^τ-Bzl)	f	C	3.0		Boc-His	97	274
Boc-Tyr(Bzl)	f	C	3.0		Boc-Tyr	93	274
Z-β-Ala-Tyr-Ser-Met-OMe	f	C	1.0		β-Ala-Tyr-Ser-Met	90	274
Asn-Glu(OBzl)-Glu(OBzl)-Gly-Leu-Phe-Glu$_2$-Arg(NO$_2$)-OBzl	f	C	6.0		Asn-Glu-Glu-Gly-Leu-Phe-Gly-Gly-Arg	83	274
Z-Leu-OC$_4$H$_9$-t	f	T	1.5	50	Leu-OBu^t	90	174
Boc-Tyr(Bzl)	f	T	1.0	50	Boc-Tyr	96	174
Boc-Ser(Bzl)	f	T	8.0	50	Boc-Ser	60	174
Boc-Arg(NO$_2$)-Leu-OBu^t	f	T	1.0	50	Arg-Leu	90	174
Z-Arg(NO$_2$)-Gly-NH$_2$	f	T	0.5	50	Arg-Gly-NH$_2$	95	174
Z-Phe-Leu-OBu^t	f	T	0.5	50	Phe-Leu-OBu^t	95	174
Z-Ser-Phe-Leu-OBu^t	f	T	0.5	50	Ser-Phe-Leu-OBu^t	95	174
Z-Trp-Leu-OBu^t	f	T	0.5	50	Trp-Leu-OBu^t	95	174
Z-Glu-Trp-Leu-OBu^t	f	T	4.0	50	Glu-Trp-Leu-OBu^t	90	174
Z-Val-Gln-Trp-Leu-OBu^t	f	T	1.5	50	Val-Glu-Trp-Leu-OBu^t	95	174
Z-Ala-OH	a	H	0.75	25	Ala	95	126
Boc-Lys(Z)-OH	a	H	0.75	25	Boc-Lys	88	126
Z-Ser-OBzl	a	H	0.75	25	Ser	99	126
Boc-Tyr(Bzl)-OH	a	H	0.75	25	Boc-Tyr	100	126
Z-Phe-OH	a	H	0.75	25	Phe	99	126
Z-Met-OH	f	H	0.75	25	Met	83	126
Boc-Hist(N-Bzl)-OH	f	H	0.75	25	His	100	126
Z-Gly-Pro-OH	a	H	0.75	25	H-Gly-Pr-OH	99	126
Boc-Phe-Gln-OBzl	a	H	0.75	25	Boc-Phe-Gln-OH	84	126
Z-Lys(Boc)-Thr(Bu^t)-OMe	a	H	0.75	25	H-Lys(OBu^t)-Thr(OBu^t)-OMe	99	126
Z-Arg(NO$_2$)-Pro-Pro-OBu^t	f	H	0.75	25	H-Arg-Pro-Pro-OBu^t	99	126
Z-Lys(Bu^{t}O)-Asn-Phe-Phe-OMe	a	H	0.75	25	H-Lys(Boc)-Asn-Phe-Phe-OMe	85	126
Boc-Ile-Ile-Lys(Z)-Asn-Ala-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl	f	H	20	25	Boc-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu	79	126
Boc-Tyr(Bzl)-Lys(Z)-Lys(Z)-Glu-Glu(OBzl)-OBzl	f	H			Boc-Tyr-Lys-Lys-Gly-Glu	95	126
Boc-Ala	a	I	8	25	Ala	100	126
Z-Phe-Met-NH$_2$	f	U	1	RT[a]	Phe-Met-NH$_2$	87.5	169
Boc-Trp-Ser(Bzl)-Tyr-OMe	f	U	3	RT	Trp-Ser-Tyr-OMe	81	169
Boc-Ala-Tyr(Bzl)-Gly-Leu-OEt	f	U	3	RT	Ala-Tyr-Gly-Leu-OEt	80	169
Boc-Leu-Phe-Gly$_2$-Arg(NO$_2$)-OBzl	f	U	10	RT	Leu-Phe-Gly-Gly-Arg	76	169
Z-Lys	f	U	0.16	RT	Lys	100	168
Z-Gly-Gly	f	U	0.16	RT	Gly-Gly	90	168
Z-Phe-Phe-OEt	f	U	0.16	RT	Phe-Phe-OEt	97	168
Z-Gly-Arg(NO$_2$)	f	U	5	RT	Gly-Arg	86	168
Z-Lys(N^ϵ-Bzl)	f	U	10	RT	Lys	81	168
Boc-Asp(OBzl)	f	U	0.16	RT	Boc-Asp	98	168
Z-Met-Gly-OEt	f	U	0.16	RT	Met-Gly-OEt	92	168
Z-Cys(S-Bzl)-Phe-OEt	f	U	*d*				168
Boc-Asp(β-OBzl)	a	AA	0.05	RT	Boc-Asp	98	225
Boc-Glu(γ-OBzl)	a	AA	0.05	RT	Boc-Glu	81	225
Boc-Tyr(Bzl)	a	AA	0.16	RT	Boc-Tyr	85	225
Boc-Ser(Bzl)	a	AA	0.5	RT	Boc-Ser	70	225
Boc-Thr(Bzl)	a	AA	1.5	RT	Boc-Thr	90	225
N^α-Boc-Lys(ϵ-Z)	a	AA	0.08	RT	Boc-Lys	95	225
Z-Phe	a	AA	0.08	RT	Phe	95	225
Z-Trp	a	AA	0.08	RT	Trp	95	225

TABLE XXIV (Continued)

protected amino acid or peptide	catalyst	donor	reactn time, h	temp, °C	product	yield, %	ref
Z-Phenylalaninol (*N*-Z-2-amino-3-phenyl-1-propanol)	a	AA	0.08	RT	L-phenylalaninol (2-amino-3-phenyl-1-propanol)	98	225
Boc-Arg(N^5-NO_2)-Leu-OBu^t	a	AA	0.08	RT	Arg-Leu	89	225
Z-Trp-Leu-OBu^t	a	AA	0.08	RT	Trp-Leu-OBu^t	98	225
Z-Phe-OBu^t	a	AA	0.08	RT	Leu-OBu^t	98	225
Z-Phe-Leu-OBu^t	a	AA	0.08	RT	Phe-Leu-OBu^t	98	225
Z-Gly-Gly-Phe-Leu-OBu^t	a	AA	0.08	RT	Gly-Gly-Phe-Leu-OBu^t	92	225

[a] Room temperature. [b] a plus dry HCl. [c] a in 10% AcOH. [d] Incomplete reaction.

pected. The use of formic acid[169] or its methanolic solutions[168] appears to have advantages over cyclohexene,[185] cyclohexadienes,[126] and hydrazine but removal of *N*-(benzyloxycarbonyl) from *N*-(benzyloxycarbonyl)-*S*-benzylcysteinylphenylalanine[261] was not successful. A further elaboration in the use of formate anion as a donor has been reported for the deprotection steps in the synthesis of the biologically active peptide, leucine–enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH).[225] Removal of a Z-protecting group at various stages in the synthesis was effected by 10% Pd/C, (one-tenth to one-half by weight of the peptide) and ammonium formate (2–4 equiv) in methanol or dimethylformamide or a mixture of methanol and acetic acid. Other hydrogenolyses involving short reaction times for a variety of deprotections include those of benzyl ethers, nitro compounds, and benzyl esters.[225] These results confirmed the accelerative effect of sodium and ammonium formate in transfer reductions.[261]

Similar cleavages can be effected with palladium-impregnated polymer[278a,b] which is claimed to have advantages in column reactors.

As a method of choice for reduction of some functional groups and deprotection of protected peptides, heterogeneous catalytic hydrogen transfer owes much to the observation that high catalyst to substrate ratios greatly accelerate the reduction process.[2] The choice of donor for either hydrogenolysis of protected peptides or reduction of functional groups is similar. It is, therefore, to be expected that additional donors could be used for deprotection of peptides. This supposition is supported by the observation that simple amines and alcohols protected by benzyloxycarbonyl groups can be recovered easily at room temperature by transfer reductions over Pd/C using phosphinic acid or sodium phosphinate (Table XXV).[170] The need for water with these inorganic donors will make recovery of deprotected peptides more difficult.

Wide use of *O*-benzyl protection is made in synthetic organic chemistry,[279] and, in particular, in carbohydrate chemistry.[280] Catalytic or chemical hydrogenolysis is frequently required for debenzylation under mild conditions. In a brief study of the effect of catalytic hydrogen-transfer cleavage of O-benzylated carbohydrates, successful deprotection has been observed[281a] by using Pd/C and a 10% solution of formic acid in methanol or 2-propanol.[281b] Additional deprotections of carbohydrates were also noted; reaction conditions appear not to have been optimized (Table XXVI). It was observed that *O*-benzylidene, *tert*-butyldimethylsilyl, and *O*-trityl groups (see examples in Table XXVI) could be removed also, but *O*-mesyl and *O*-acyl groups were unaffected. Cyclohexadiene was not found to be a better hydrogen donor. Cleavage of benzyl ethers with cyclohexene as

TABLE XXV Hydrogenolysis of Z-Protected Compounds Using Sodium Phosphinate as Donor with Pd/C as Catalyst[170]

Z-protected compound	reactn time, min	product	yield, %
2-(Z-oxy)naphthalene	45	2-naphthol	81
3,4-$Cl_2C_6H_3NH$-Z	60	3,4-dichloroaniline	75
5-(Z-amino)quinoline	15	5-aminoquinoline	80

donor and Pearlman's catalyst (20% $Pd(OH)_2$ on C) in refluxing ethanol, has been reported.[226] The highly selective cleavage of *O*-benzyl ethers reported in this work should have wide synthetic utility. It is not clear whether selectivity is achieved by using cyclohexene as donor, or by using $Pd(OH)_2$ as catalyst. The effectiveness of phosphinate as donor for this type of C–O cleavage has been reported.[303]

An alternative approach to reductive cleavage of ethers, based on conditions reported earlier for reduction of carbonyl groups, was employed for structurally simpler benzylic and benzhydrolic ethers and acetals.[176] A mixture of ether or acetal together with 10% Pd/C (20% of substrate weight) and a Lewis acid such as $AlCl_3$ (20 mg per 10 mmol substrate) was refluxed with cyclohexene for 24 h. In all cases (Table XXVII), high yields of the alcohols were obtained (Schemes LVIII and LIX). The role of $AlCl_3$ in this cleavage appears

SCHEME LVIII

$$ArCR'R''OR''' \xrightarrow{Pd/C/AlCl_3} ArCHR'R'' + R'''OH$$

SCHEME LIX

$$ArCR'(OR'')OR''' \xrightarrow{Pd/C/AlCl_3} ArCH_2R' + 2R''OH$$

SCHEME LX

$$ArCR'R''OH \xrightarrow[Pd/C/AlCl_3]{cyclohexene} ArCHR'R''$$

to be related to Lewis acid dealkylation of aralkyl ethers. Cleavage of C–O bonds in benzylic alcohols is similarly effected as shown in Scheme LX and in examples in Table XXVIII.[181] Activation of the substrate and initiation of hydrogen transfer to the benzylic carbocation appear to be helped by the presence of $AlCl_3$. Simple alkanols are not cleaved under similar conditions. Although reaction times are long (up to 36 h), the small quantity of Lewis acid used makes reduction an attractive alternative to Lewis acid catalyzed hydride transfer reductions employing either $LiAlH_4$ or trialkylsilanes.[282] Benzyl alcohol and diphenylcarbinol are also reduced using refluxing propan-2-ol as hydrogen donor over Raney nickel.[175] The toluene produced from benzyl alcohol is accompanied by 20% benzene.

TABLE XXVI. Heterogeneous Transfer Hydrogenolysis of *O*-Benzyl and Other Derivatives[261]

protected carbohydrate	donor	catalyst	product
2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose	U	a	D-glucose
2,3,5-tri-*O*-benzyl-β-D-arabinofuranose	U	a	D-arabinose
1-*O*-benzoyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose	U	a	1-*O*-benzoyl-α-D-glucopyranose
methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside	U	a	methyl α-D-glucopyranoside
methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-(*tert*-butyldimethylsilyl)-β-D-glucopyranoside	U	a	methyl 4-*O*-mesyl-β-D-glucopyranoside
3-*O*-benzyl-1,2:5,6-di-*O*-isopryopylidene-α-D-glucofuranose	U	a	1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose
methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside	U	a	methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside

TABLE XXVII. Reductive Cleavage of Benzylic and Benzhydrylic Ethers, $PhCR^1R^2(OR^3)$, and Acetals, $PhCR^1(OR^2)_2$[176]

substrate			yield, %	products
R^1	R^2	R^3		
H	H	c-C_6H_{11}	82	c-$C_6H_{11}OH$
H	H	c-C_6H_{15}	94	c-$C_6H_{11}OH$
C_6H_5	H	CH_3	91	CH_3OH
H	H	C_6H_5	87	C_6H_5OH
H	H	CH_3	71	CH_3OH
H	H	$C_6H_5CH_2CH_2$	91	$C_6H_5(CH_2)_2OH$
H	H	*n*-$C_6H_{13}CH(CH_3)$	93	*n*-$C_6H_{13}CH(CH_3)OH$
H	H	cholestanyl	61	cholestanol
H	CH_3		80	CH_3OH
CH_3	CH_3		89	CH_3OH

TABLE XXVIII. Heterogeneous Transfer Hydrogenolysis of C–O Bond in Benzylic Alcohols, $PhCR^1R^2OH$, Using $AlCl_3$ and Pd/C with Cyclohexene as Hydrogen Donor[161]

benzylic alcohol		yield,[a] %
R^1	R^2	
CH_3	$C_6H_5CH(CH_3)$	94
C_6H_5	C_6H_5	90
CH_3	CH_3	84
$(CH_2)_5$		87
C_6H_5	CH_3	84
C_2H_5	c-C_3H_5	81
norbornanediyl		90
C_6H_5	H	92
H	H	74

[a] Yield of hydrocarbon.

Diphenylmethane is obtained in high yield from diphenylcarbinol. A similar reduction of α-tetralol is observed as a step in the conversion of 1-naphthol to tetralin (see section VC on arenes).[175]

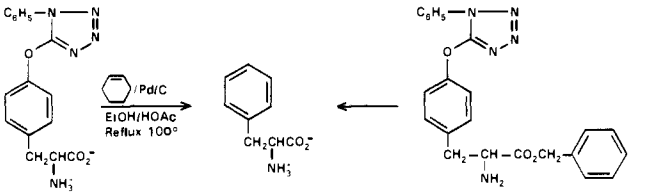
Quaternary ammonium salts of formic acids have been used with palladium (produced in situ from $PdCl_2$ or $Pd(OAc)_2$) to cleave the C–O bond in allylic acetates, $RCH{=}CHCH_2OAc$.[283] During this hydrogenolysis, rearrangement of the alkene bond occurs to give the 1-alkene, $RCH_2CH{=}CH_2$; only small amounts of the 2-alkene, $RCH{=}CHCH_3$, are formed.

2. Aromatic

Replacement of a phenolic hydroxyl group by hydrogen is usually effected by hydrogenolysis of a derivative using a dissolving metal or catalytic hydrogenation. This C–O bond cleavage is most frequently achieved by catalytic hydrogenation of 1-phenyltetrazolyl ethers of phenols.[284] Recently, cleavage of the 1-phenyltetrazolyl ether of tyrosine to give phenylalanine (Scheme LXI)[285] was shown to occur under the hydrogen-transfer conditions described earlier for cleavage of *N*-benzyl and *O*-benzyl groups.

In a more extensive contemporaneous study (Table XXIX), a range of 1-phenyltetrazolyl ethers of phenols was hydrogenolyzed by catalytic hydrogen transfer.[150]

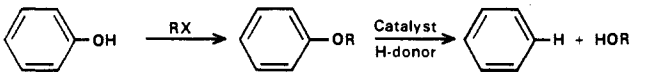
SCHEME LXI



A range of hydrogen donors was studied, the least effective being cyclohexene. The most effective donors were hydrazine and sodium phosphinate. Of the common catalyst metals, only palladium showed significant activity.

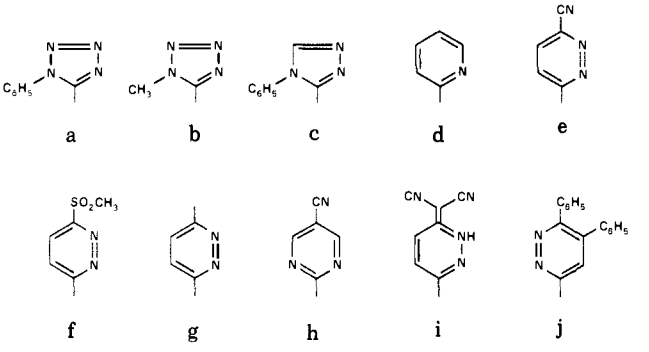
Based on the surmise that the R group in the phenolic ethers (Scheme LXII) needed to be electron

SCHEME LXII



withdrawing, a variety of groups (R) has been examined as alternatives to 1-phenyltetrazolyl. Of these groups (a–j; Scheme LXIII), those containing triazole (c), tetrazole (b), and triazine (j) were effective replacements for the tetrazole (a).

SCHEME LXIII



The 6-cyanopyridazyl group (Scheme LXIIIe) was reduced to 6-(aminomethyl)pyridazyl concomitantly with the required reductive C–O bond cleavage. As 6-(aminomethyl)pyridazyl was not as effective in providing a readily hydrogenolyzed ether, the competitive reduction prevented further C–O bond cleavage. For example, the 6-cyanopyridazyl derivative of 2-naphthol could be cleaved rapidly to give naphthalene in 32% yield after which no further cleavage occurred; the 6-(aminomethyl)pyridazyl ether of 2-naphthol was the only other significant product isolated. Similarly, alkyl ethers of 1-phenyltetrazole were shown to be inert to the cleavage conditions. The failure of other electronegative groups (R) to support ether cleavage suggested that the mechanistic requirement for hydrogenolysis involved more than the presence of an electronegative

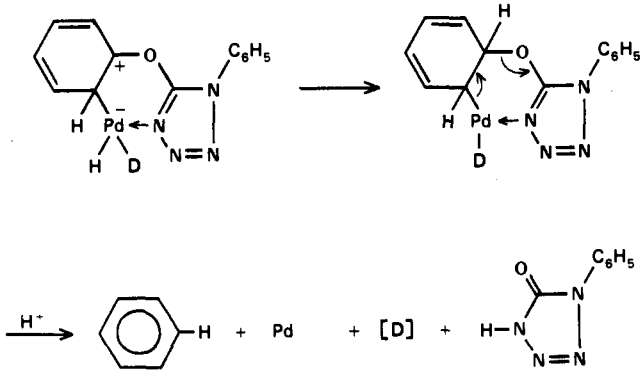
TABLE XXIX. Heterogeneous Transfer Hydrogenolysis of 1-Phenyltetrazolyl Ethers of Phenols (ROH) to give Arenes (RH)[150]

R	H Donor	reactn time, min	product (RH)	yield, %
2-naphthyl	U	10	naphthalene	85
2-naphthyl	C	180	naphthalene	70
2-naphthyl	U	75	naphthalene	100
2-naphthyl	Y	135	naphthalene	100
2-naphthyl	T	50	naphthalene	85
2-naphthyl	T	90	naphthalene	85
1-naphthyl	Y	45	naphthalene	70
1-naphthyl	T	75	naphthalene	83
phenyl	Y	50	benzene	86
phenyl	U	10	benzene	83
4-methylphenyl	T	210	toluene	100
4-aminophenyl	T	50	aniline	83
4-cyanophenyl	T	275[a]	cyanobenzene	84
4-cyanophenyl	Y	70	cyanobenzene	95
2-methoxyphenyl	T	110	anisole	100
2-methoxyphenyl	Y	95	anisole	94
4-acetylphenyl	T	15	acetophenone azine	54
4-acetylphenyl	T[b]	45	acetophenone	84
4-acetylphenyl	Y	55	acetophenone	84
4-acetylphenyl	U	5	acetophenone (1-phenylethanol)	53
4-formylphenyl	Y	150	benzaldehyde	<10
4-(1,3-dioxolan-2-yl)phenyl	T	395	2-phenyl-1,3-dioxolane	52
4-(phenoxycarbonyl)phenyl	Y	45	phenyl benzoate	61
4-(phenoxycarbonyl)phenyl	Y	200	phenyl benzoate	95
4-(phenoxycarbonyl)phenyl	Y	70	phenyl benzoate	95
4-(phenoxycarbonyl)phenyl	U	10	phenyl benzoate	100
2-chlorophenyl	Y	250	chlorobenzene	5–10
			benzene	90
2-chlorophenyl	C	250	chlorobenzene	0
			benzene	100
3-methyl-4-nitrophenyl	Y	90	2-methylaniline	81
4-carboxyphenyl	Y	50	benzoic acid	80
1-(methylsulfonyl)-7-naphthyl	T	90	1-(methylsulfonyl)naphthalene	75
7-coumarinyl	Y	55	coumarin and 3,4-dihydrocoumarin	91

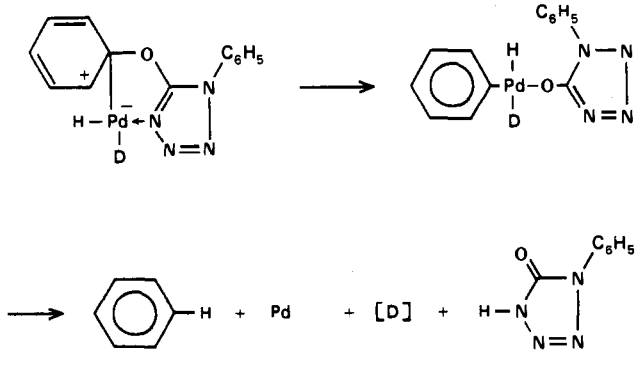
[a] Reaction halted. [b] T plus KOH.

group (R). The prime requirements of two proposed mechanisms[150] (Schemes LXIV and LXV) appear to be

SCHEME LXIV



SCHEME LXV



formation of a σ-complex with an atom of the catalytic metal bonded to the phenolic ring and a ligand (to the same metal atom) supplied by the heterocyclic ring attached to the ether. Stabilization of ortho insertion reactions in homogeneous organometallic chemistry by such ligands is well-known,[286] but are generally effective through five-membered intermediates (Scheme LXV) rather than the six-membered one shown in Scheme LXIV.

A number of hydrogenolyses in differing solvent systems has demonstrated the importance of solvent/donor relationships for these ether cleavages (Table XXIX). Improvements in yields of arenes and reduction in reaction times for cleavage of the 1-phenyltetrazolyl ether of 2-naphthol illustrate the advantages of a two-phase system. Further, the addition of a phase-transfer catalyst improved some reductions. Remarkably, formic acid alone as both hydrogen donor and solvent at about 100 °C provided a poor system for hydrogenolysis but the system, formic acid/benzene/water, cleaved 1-phenyltetrazolyl ethers of phenols in about 10 min at much lower temperatures. Using formic acid as solvent might mean that its adsorption onto the catalyst surface excludes simultaneous adsorption of the phenolic ether; in a two-phase aqueous system, the catalyst would not be saturated by the formic acid so that the adsorption of the phenolic ether can compete with that of the hydrogen donor. Nonselective cleavage and reduction are accepted disadvantages of catalytic hydrogenation with molecular hydrogen. With the wide range of hydrogen donors

TABLE XXX. Heterogeneous Transfer Hydrogenolysis of Aromatic Halides Using Trimethylammonium Formate[261]

substituted benzene	catalyst	temp, °C	reactn time, h	product, % yield
1-CN-4-Cl	d	100	23.5	C_6H_5CN, 80
1-CO_2CH_3-4-Cl	d	100	42	$C_6H_5CO_2CH_3$, 93
1-CH=$CHCO_2CH_3$-4-Cl	d	100	1.5	C_6H_5CH=$CHCO_2CH_3$, 22 $C_6H_5CH_2CH_2CO_2CH_3$, 55
1-NO_2-4-Cl	d	100	1	$C_6H_5NO_2$, 91
			6	$C_6H_5NO_2$, 83 $C_6H_5NH_2$, 3
			48	$C_6H_5NH_2$, 85
1-NH_2-4-Cl	d	100	<1	$C_6H_5NH_2$, 87
1-CO_2CH_3-4-Cl	d	100	29	1-CO_2CH_3-4-DC_6H_4, 90
1-CN-4-Br	e	50	20	C_6H_5CN, 53
1-CH=$CHCO_2CH_3$-4-Br	d	100	7	C_6H_5CH=$CHCO_2CH_3$, 93
1-NO_2-3-Br	d	50	1.5	$C_6H_5NO_2$, 46 $C_6H_5NH_2$, 15
1-NO_2-2-Br	d	50	48	$C_6H_5NO_2$, 78 $C_6H_5NH_2$, 8
1-NH_2-2,4-Br_2	d	50	0.5	$C_6H_5NH_2$, 50 2-$BrC_6H_4NH_2$, 10 4-$BrC_6H_4NH_2$, 4
1-CHO-2-Br	d	50	20	C_6H_5CHO, 44
CH=CHBr	d	50	19.5	C_6H_5CH=CH_2, 34 $C_6H_5CH_2CH_3$, 31
1-Br-4-I	d	100	1.5	C_6H_5Br, 58
1-CO_2CH_3-4-I	d	100	48	$C_6H_5CO_2CH_3$, 91

available, such problems may be resolved more readily using hydrogen-transfer techniques. For example, the partial catalyst poisoning observed in the cleavage of the 1-phenyltetrazolyl ether of 4-cyanophenol using hydrazine as hydrogen donor is readily overcome by using sodium phosphinate as donor instead (Table XXIX).

C. C–S Bonds

The removal of *S*-benzyl protecting groups in peptides has been reported as being incomplete with 5% aqueous formic acid as hydrogen donor and a palladium black catalyst.[168] This result is not surprising, in view of the known propensity of divalent sulfur compounds for poisoning many catalyst systems. In a study to find effective means of desulfurizing industrial processes, hydrogen transfer between cyclohexane (donor) and thiophene (acceptor) over $Co/Mo/Al_2O_3$ catalysts at 400 °C was investigated.[165] Most of the hydrogen transfer was found to be indirect, i.e., the cyclohexane was dehydrogenated to give hydrogen which was then transferred to thiophene. However, in the presence of promotors, such as Ti, Zr, Zn, Sn, Cr, and V, direct hydrogen transfer was observed.

D. C–Halogen Bonds

C–F bonds appear to be resistant to hydrogenolysis under the usual conditions of catalytic transfer reduction. Previous results[128] have shown that cleavage of C–Cl bonds during reduction of halonitroarenes could be minimized by use of sodium phosphinate as hydrogen donor. However, cleavage of the 1-phenyltetrazolyl ether of 2-chlorophenol under all conditions yielded mostly benzene and little or no chlorobenzene. Further investigation of this reaction would be desirable because of the proposed mechanisms of these hydrogenolyses (Schemes LXIV and LX). In particular, it would be informative to know whether the 1-phenyltetrazolyl ethers of 3-chlorophenol and 4-chlorophenol also gave only benzene and not chlorobenzene.

Hydrogenolysis of carbon–halogen bonds is usually a reaction to be avoided rather than encouraged. Generally, reductive C–F bond cleavage does not appear to have been reported in contrast to C–Cl, C–Br, and C–I functional groups for which hydrogenolysis becomes increasingly easy.

Avoidance of dehalogenation during catalytic reduction of haloarenes has led to the development of special catalysts. Observations that loss of halogen can be avoided during catalytic hydrogen-transfer reductions by utilizing sodium phosphinate have been made.[128] Where C–halogen cleavage is actually desired, a number of donors has been reported to be effective.[4] In refluxing cyclohexene,[2] halogens other than fluorine were reductively eliminated during reduction of nitroaryl groups. A further wider study (Table XXX) has been made of reductive elimination of halogen from haloarenes using triethylammonium formate as hydrogen donor.[261] By using 5% Pd/C as catalyst, removal of halogen was achieved even in the presence of nitro, cyano, or CO_2CH_3 groups. The order of ease of halogen removal was I > Br > Cl. Removal of halogen from arylaldehydes and cinnamates was inefficient, due to secondary reduction of the carbonyl and olefinic bonds, respectively. The practical use of a hydrogen-transfer reduction which removes halogen depends largely on whether this removal is complete. Many catalyst/donor combinations have been noted which effect only partial hydrogenolysis of arene–halogen bonds, and so need to be avoided when either complete removal or retention of halogen is desired. Low-yield conversions of chlorobenzene, benzyl chloride, and 4-chlorophenol to benzene, toluene, and phenol, respectively, have been reported using Raney nickel and propan-2-ol as hydrogen donor.[175]

Loss of halogen from aryl compounds has been utilized to advantage in the formation of symmetrical biphenyls.[180] Conditions previously reported for reduction of nitroarenes in aqueous alkaline sodium formate, when applied to haloarenes not having a nitro substituent, resulted in moderate yields of biphenyls (Table XXXI).

TABLE XXXI. Preparation of Biaryls from Aryl Halides (ArX) Using Sodium Formate and Pd/C Plus a Surfactant in 32% Sodium Hydroxide Liquor[160]

starting material, ArX	product, ArAr	yield, %
bromobenzene	biphenyl	65
bromobenzene	biphenyl	60
bromobenzene	biphenyl	65
bromobenzene	biphenyl	30
bromobenzene	biphenyl	51
chlorobenzene	biphenyl	48
2-chloropyridine	2,2′-bipyridyl	52
4-chloropyridine	4,4′-bipyridyl	46
4-bromo-2,6-dimethyl-aniline	3,3′,5,5′-tetramethylbenzidine	63
4-bromoanisole	4,4′-dimethoxybiphenyl	49
4-chlorotoluene	4,4′-dimethylbiphenyl	55
3-chlorotoluene	3,3′-dimethylbiphenyl	36
4-bromobiphenyl	quaterphenyl	48
2-bromotoluene	2,2′-dimethylbiphenyl	33
4-bromoacetophenone	4,4′-diacetylbiphenyl	41
4-bromo-2,6-difluoroaniline	3,3′,5,5′-tetrafluorobenzidine	42

The presence of a large amount of sodium hydroxide solution prevents applications of the reaction to many arenes. Yields are reported to be dependent on the choice of surfactant.

E. N–N Bonds

As discussed in section VE, transfer reduction of azobenzene leads to the formation of anilines through initial reduction to hydrazobenzenes followed by hydrogenolysis of the N–N bond.

That N–N bonds are hydrogenolyzed easily was demonstrated by the failure to stop the reduction of *N*-nitrosoamines, R^1R^2NNO, at the hydrazine stage, $R^1R^2NNH_2$.[287] A variety of catalysts and hydrogen donors yielded only the secondary amine, R^1R^2NH.

The nitro group in *N*-nitroarginyl residues of peptides is lost by cleavage of the N–N bond during transfer hydrogenation (see Table XXIV).

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(311) The group notation is being changed in accord with recent actions by the IUPAC and ACS nomenclature committees. A and B notation is being eliminated because of wide confusion. Group I becomes groups 1 and 11, group II becomes groups 2 and 12, group III becomes groups 3 and 13, etc.