Hydrogenation Methods

Paul N. Rylander

Engelhard Corporation
Edison, New Jersey

1985

ACADEMIC PRESS
(Harcourt Brace Jovanovich, Publishers)

London Orlando San Diego New York
Toronto Montreal Sydney Tokyo

This book is a guide to provide general information concerning its subject matter; it is not a procedural manual. Synthesis of chemicals is a rapidly changing field. The reader should consult current procedural manuals for state-of-the-art instructions and applicable government safety regulations. The Publisher and the authors do not accept responsibility for any misuse of this book, including its use as a procedural manual or as a source of specific instructions.

COPYRIGHT © 1985 BY ACADEMIC PRESS INC. (LONDON) LTD.
ALL RIGHTS RESERVED.
NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS INC. (LONDON) LTD.
24–28 Oval Road
LONDON NW1 7DX

United States Edition published by
ACADEMIC PRESS, INC.
Orlando, Florida 32887

BRITISH LIBRARY CATALOGUING IN PUBLICATION DATA
Rylander, Paul N.
Hydrogenation methods.——(Best synthetic methods)
1. Hydrogenation 2. Chemistry, Organic
I. Title II. Series
547'.23 QD281.H8

LIBRARY OF CONGRESS CATALOGING IN PUBLICATION DATA
Rylander, Paul Nels, Date
Hydrogenation methods.

(Best synthetic methods)
Includes index.
1. Hydrogenation.
QD281.H8R93 1985
ISBN 0-12-605365-0 (alk. paper)

PRINTED IN THE UNITED STATES OF AMERICA

85 86 87 88 9 8 7 6 5 4 3 2 1

Contents

Foreword vii

Preface ix

Detailed Contents xi

Chapter 1. Catalysts, Reactors, and Reaction Parameters 1

Chapter 2. Hydrogenation of Olefins 29

Chapter 3. Hydrogenation of Acetylenes 53

Chapter 4. Hydrogenation of Aldehydes and Ketones 66

Chapter 5. Hydrogenation of Acids, Anhydrides, and Esters 78

Chapter 6. Reductive Alkylation 82

Chapter 7. Hydrogenation of Nitriles and Oximes 94

Chapter 8. Hydrogenation of Nitro Compounds 104

Chapter 9. Hydrogenation of Carbocyclic Aromatic Compounds 117

Chapter 10. Hydrogenation of Anilines, Phenols, and Derivatives 123

Chapter 11. Hydrogenation and Hydrogenolysis of Heterocycles 133

Chapter 12. Catalytic Dehydrohalogenation 148

Chapter 13. Miscellaneous Hydrogenolyses 157

Index of Compounds and Methods 185

Foreword

There is a vast and often bewildering array of synthetic methods and reagents available to organic chemists today. Many chemists have their own favoured methods, old and new, for standard transformations, and these can vary considerably from one laboratory to another. New and unfamiliar methods may well allow a particular synthetic step to be done more readily and in higher yield, but there is always some energy barrier associated with their use for the first time. Furthermore, the very wealth of possibilities creates an information retrieval problem: How can we choose between all the alternatives, and what are their real advantages and limitations? Where can we find the precise experimental details, so often taken for granted by the experts? There is therefore a constant demand for books on synthetic methods, especially the more practical ones like "Organic Syntheses," "Organic Reactions," and "Reagents for Organic Synthesis," which are found in most chemistry laboratories. We are convinced that there is a further need, still largely unfulfilled, for a uniform series of books, each dealing concisely with a particular topic from a *practical* point of view—a need, that is, for books full of preparations, practical hints, and detailed examples, all critically assessed, and giving just the information needed to smooth our way painlessly into the unfamiliar territory. Such books would obviously be a great help to research students as well as to established organic chemists.

We have been very fortunate with the highly experienced and expert organic chemists who, agreeing with our objective, have written the first group of volumes in this series, "Best Synthetic Methods." We would always be pleased to receive comments from readers and suggestions for future volumes.

A.R.K., O.M.-C., C.W.R.

Preface

Hydrogenation is one of the most useful, broad-scoped reactions available to the synthetic organic chemist. The aim of this work is to give the reader ready access to what can be done with hydrogenation and how to do it. Appropriate choices of catalyst, solvent, and reaction conditions are illustrated throughout, and where possible, the influence of these factors has been reduced to working generalities. This volume is heavily documented to support these generalities and to make often difficult to find literature readily available. It is hoped that the reader will find this a useful work.

I wish to express my thanks to the management of Engelhard Corporation for their encouragement in this undertaking.

PAUL N. RYLANDER

Detailed Contents

1. Catalysts, Reactors, and Reaction Parameters

1.1. Introduction 1
1.2. Hydrogenation Catalysts 1
1.3. Choosing a Catalyst 2
1.4. Choosing a Catalyst Support 4
1.5. Choosing a Metal Concentration 4
1.6. Choosing Conditions 5
1.7. Effect of Temperature 5
1.8. Prereduction 6
1.9. Measurement of Selectivity 7
1.10. Catalyst Reuse 7
1.11. Synergism 7
1.12. Solvents 8
1.12.1. Influence of Solvent on Selectivity 8
1.12.2. Effect of Acidity 10
1.12.3. Reactive Solvents 10
1.13. Safety 11
1.13.1. Catalysts 12
1.13.2. Loading a Catalyst 12
1.14. Homogeneous Catalysts 13
1.14.1. Asymmetric Hydrogenation 14
1.14.2. Ligand Synthesis 14
1.14.3. Chiral Homogeneous Hydrogenations 15
1.15. Hydrogen-Transfer Reductions 16
1.16. Hydrogenation Reactors 17
1.16.1. Atmospheric Pressure Reactors 18
1.16.2. Low Pressure Reactors 18
1.16.3. High Pressure Reactors 20
1.16.3.1. Safety 20
1.16.3.2. Materials of Construction 21
1.17. Catalyst Preparation 22
1.17.1. Purchased Catalysts 23
1.18. Economics of Catalyst Use 23
1.18.1. Cost of Catalyst 24
1.18.2. Catalyst Life 24

1.18.3. Space–Time Yield 25
1.18.4. Actual Yield 25
References 25

2. Hydrogenation of Olefins

2.1. Double-Bond Migration 29
2.1.1. Mechanism of Olefin Hydrogenation 29
2.1.2. Effect of Hydrogen Availability 31
2.1.3. Catalysts 31
2.1.4. Effect of Solvent 33
2.2. Consequences of Double-Bond Migration 34
2.3. Selective Reductions of Olefins 36
2.3.1. Dienes and Polyenes 36
2.3.2. Unsaturated Carbonyl Compounds 40
2.4. Vinylic and Allylic Functions 41
2.5. Olefinic Sulfur Compounds 44
2.6. Stereochemistry 45
Asymmetric Hydrogenation of Olefins 47
References 49

3. Hydrogenation of Acetylenes

3.1. Catalysts 53
3.1.1. Catalyst Modifiers 55
3.2. Solvents 56
3.3. Influence of Reaction Variables 57
3.4. Functionalized Acetylenes 58
3.4.1. Acetylenic Carbonyls, Glycols, and Esters 59
3.4.2. Acetylenic Epoxides 60
3.4.3. Progargylamines 61
3.4.4. Acetylenic Aldehydes and Ketones 62
References 62

4. Hydrogenation of Aldehydes and Ketones

4.1. Catalysts 66
4.2. Solvents 67
4.2.1. Alcohol Solvents 68
4.3. Hydrogenolysis 68
4.3.1. Aliphatic Carbonyls 69
4.3.2. Aromatic Carbonyls 69
4.4. Unsaturated Carbonyls 70
4.5. Diketones 71
4.6. Stereochemistry 72
4.6.1. Axial Alcohols 73
4.6.2. Asymmetric Hydrogenation 74
References 75

5. Hydrogenation of Acids, Anhydrides, and Esters

5.1. Acids ... 78
5.2. Anhydrides ... 79
5.3. Esters ... 80
References ... 80

6. Reductive Alkylation

6.1. Introduction ... 82
6.2. Catalysts ... 86
6.3. Solvents ... 86
6.4. Amine and Carbonyl Precursors ... 88
6.5. Stereochemistry ... 91
References ... 91

7. Hydrogenation of Nitriles and Oximes

7.1. Nitriles ... 95
7.1.1. Solvents ... 95
7.1.2. Catalysts ... 97
7.1.3. Cyclizations ... 98
7.2. Oximes ... 99
7.2.1. Catalysts ... 99
7.2.2. Solvents ... 100
7.2.3. Oximino Ketones ... 101
References ... 101

8. Hydrogenation of Nitro Compounds

8.1. Catalysts ... 104
8.2. Solvents ... 104
8.3. Influence of Impurities ... 105
8.4. Aromatic Hydroxylamines ... 106
8.4.1. Cyclic Products ... 107
8.5. Bifunctional Molecules ... 108
8.5.1. Halonitro Aromatics ... 108
8.5.2. Acetylenic and Olefinic Nitro Compounds ... 109
8.5.3. Nitronitriles ... 110
8.5.4. Nitroaldehydes and Nitroketones ... 110
8.5.5. Dinitro Compounds ... 111
8.5.6. Nitroenamines ... 113
References ... 114

9. Hydrogenation of Carbocyclic Aromatic Compounds

9.1. Catalysts ... 117
9.2. Olefin Intermediates ... 118

9.3. Effect of Substrate Structure ... 119
9.3.1. Polycyclic Systems ... 119
9.3.2. Fused Rings ... 120
References ... 121

10. Hydrogenation of Anilines, Phenols, and Derivatives

10.1. Anilines ... 123
10.1.1. Catalysts ... 123
10.1.2. Catalyst Reactivation ... 124
10.1.3. Control of Coupling ... 125
10.1.4. Reductive Hydrolysis ... 126
10.1.5. Synthetic Applications ... 126
10.2. Phenols and Derivatives ... 126
10.2.1. Partial Hydrogenation of Phenols to Cyclohexanones ... 126
10.2.2. Deoxygenation with Ring Saturation ... 127
10.2.3. Deoxygenation without Ring Reduction ... 128
10.2.4. Ring Saturation without Hydrogenolysis ... 129
References ... 130

11. Hydrogenation and Hydrogenolysis of Heterocycles

11.1. Ring Saturation ... 133
11.1.1. Furans ... 133
11.1.2. Pyrroles ... 134
11.1.3. Indoles ... 134
11.1.4. Pyridines and Derivatives ... 135
11.1.4.1. Partial Hydrogenation ... 136
11.1.4.2. Decarboxylation ... 137
11.2. Ring Hydrogenolysis ... 137
11.2.1. Oxiranes ... 137
11.2.1.1. Deoxygenation ... 137
11.2.1.2. Direction of Ring Opening ... 138
11.2.2. Aziridines ... 139
11.2.3. Isoxazoles ... 140
11.2.4. Isoxazolines ... 140
11.2.5. Oxazoles and Oxazolines ... 143
References ... 144

12. Catalytic Dehydrohalogenation

12.1. Catalysts ... 148
12.2. Basic and Acidic Media ... 149
12.3. Polyhalo Compounds ... 151
12.4. Halonitro Compounds ... 153
12.5. Coupling Reactions ... 153
12.6. Rosenmund Reduction ... 153
12.6.1. Regulated Catalysts ... 154
12.6.2. Procedure ... 154
References ... 155

13. Miscellaneous Hydrogenolyses

13.1. Benzyl Groups Attached to Oxygen 157
13.1.1. Effect of Substrate Structure 158
13.1.2. Promoters 158
13.1.3. Stereochemistry of Hydrogenolysis 160
13.1.4. Carbobenzyloxy Compounds 160
13.2. Benzyl Groups Attached to Nitrogen 163
13.2.1. Catalysts 163
13.2.2. Effect of Structure 164
13.2.3. Stereochemistry 164
13.2.4. Reverse Selectivity 165
13.3. Vinyl Functions 165
13.4. Allylic Functions 167
13.4.1. Steric Factors 167
13.4.2. Catalysts and Environment 167
13.4.3. Double-Bond Migration 168
13.5. Hydrogenolysis of the Nitrogen–Nitrogen Bond 168
13.5.1. Hydrazones and Hydrazides 168
13.5.2. Azines 169
13.5.3. Azides 170
13.6. Hydrogenolysis of the Nitrogen–Oxygen Bond 171
13.6.1. Amine Oxides 171
13.6.2. Hydroxylamines 172
13.6.3. *N*-Nitrosoamines 173
13.6.4. *C*-Nitroso Compounds 173
13.7. Hydrogenolysis of the Carbon–Carbon Bond 173
13.7.1. Cyclopropanes 174
13.7.2. Cyclobutanes 175
13.7.3. Aromatization 176
13.8. Hydrogenolysis of the Oxygen–Oxygen Bond 176
References 177

-1-

Catalysts, Reactors, and Reaction Parameters

1.1. Introduction

Catalytic hydrogenation is one of the most powerful weapons in the arsenal of the synthetic organic chemist. Most functional groups can be readily reduced, often under mild conditions, and frequently in high chemo-, regio-, and stereoselectivity. At the conclusion of the reduction, hydrogen is allowed to escape, and the heterogeneous catalyst is filtered from the mixture, to leave a solution free of contaminating reagents. Homogeneous hydrogenation catalysts need to be removed otherwise, a major disadvantage of using this type of catalyst.

In the minds of many, especially those who have not had the opportunity to use it, catalytic hydrogenation has acquired an aura of mystery; the choice of catalyst seems capricious, operating conditions arbitrary, catalyst preparation secret, and the working of the catalyst unfathomable. It is the purpose of this work to meet these objections; to provide rationale for choice of catalyst and conditions; to acquaint the reader with catalysts, equipment, and procedure; and to impart the conviction that hydrogenation is a powerful, readily handled, broad-scoped procedure of general utility for synthesis in both laboratory and industrial plant.

1.2. Hydrogenation Catalysts

Hydrogenation catalysts are of two types, heterogeneous and homogeneous. Heterogeneous catalysts are solids that form a distinct phase in the gas or liquid environment. The great majority of hydrogenations are done with this type of catalyst. Homogeneous catalysts dissolve in the liquid environment, forming only a single phase. Catalysts of this type are of relatively recent

origin; the first example was reported by Calvin in 1939 (*27*), but the area remained dormant until interest was spurred by the classic papers of Wilkinson on chlorotris(triphenylphosphine)rhodium(I), a catalyst that bears his name. Considerable effort has been expended in recent years in "anchoring" homogeneous catalysts to a solid, insoluble support in an effort to capture the best features of both types of catalysts (*9,10,11,23,44*).

Heterogeneous catalysts can be divided into two types; those for use in fixed-bed processing wherein the catalyst is stationary and the reactants pass upward (flooded-bed) or downward (trickle-bed) over it, and those for use in slurry or fluidized-bed processing. Fixed-bed catalysts are relatively large particles, 1/32 to 1/4 inch, in the form of cylinders, spheres, or granules. Slurry or fluidized-bed catalysts are fine powders, which can be suspended readily in a liquid or gas, respectively. Fixed-bed processing is especially suited to large-scale production, and many important bulk chemicals are made in this mode.

However, the vast majority of catalytic hydrogenations are done in a slurry process. Fixed-bed processing demands a dedicated unit, continuous production, invariant feed, large capital investment, and lengthy development to establish optimum conditions and adequate catalyst life. Slurry processes permit variations in the substrate as in hydrogenation of unsaturated triglycerides from a variety of sources, multiuse equipment, easily changed reaction conditions, intermittent operation, and relatively quick development time. Laboratory experiments are scaled up easily to industrial productions.

1.3. Choosing a Catalyst

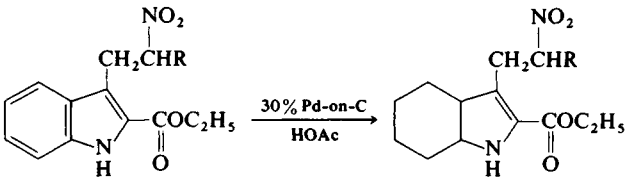
The gross physical form of a catalyst is chosen to conform to the type of process to be used. The chemical and catalytic characteristics are chosen to achieve the desired reaction and, as an important corollary, to avoid undesired reactions.

The literature on catalytic hydrogenation is very extensive, and it is tempting to think that after all this effort there must now exist some sort of cosmic concept that would allow one to select an appropriate catalyst from fundamentals or from detailed knowledge of catalyst functioning. For the synthetic chemist, this approach to catalyst selection bears little fruit. A more reliable, quick, and useful approach to catalyst selection is to treat the catalyst simply as if it were an organic reagent showing characteristic properties in its catalytic behavior toward each functionality. For this purpose, the catalyst is considered to be only the primary catalytic metal present. Support and

catalyst preparation usually have but secondary influences compared to the metal.* Viewed this way, selection of a catalyst is no different than selection of any other reagent. One simply checks the literature to find what type of metal has proved active and selective previously. Many guides to catalyst selection are given throughout this work. Theoretically oriented scientists are apt to feel dissatisfied with this purely empirical approach to catalyst selection, but with the present state of the art no surer means exists short of a catalyst development program.

There is a complication in choosing a catalyst for selective reductions of bifunctional molecules. For a function to be reduced, it must undergo an activated adsorption on a catalytic site, and to be reduced selectively it must occupy preferentially most of the active catalyst sites. The rate at which a function is reduced is a product of the rate constant and the fraction of active sites occupied by the adsorbed function. Regardless of how easily a function can be reduced, no reduction of that function will occur if all of the sites are occupied by something else (a poison, solvent, or other function).

Adsorbability is influenced strongly by steric hindrance, and because of this almost any function can be reduced in the presence of almost any other function in suitably constructed molecules. A case in point is the reduction of the aromatic ring in **1** in preference to reduction of the nitro function, producing **2**. However, when R = CH_3 (**3**) the nitro group was reduced instead, a fact attributed to a less sterically crowded environment (*109*).



(**1**) R = C_2H_5
(**3**) R = CH_3

(**2**) R = C_2H_5

The simplest guide for choosing a catalyst to achieve a selective reduction in a bifunctional molecule is from among those catalysts that are effective for what is to be achieved, avoiding those that are also effective for what is to be avoided. Guides for such a selection may be obtained from the chapters devoted to the chemistry of the functions in question. Selectivity can be influenced further by the reaction environment, solvent, and modifiers; these are discussed in other sections.

* There are, of course, many preparations, some good, some poor, and the statement applies only to preparations yielding good, i.e., active, catalysts.

1.4. Choosing a Catalyst Support

Base metals frequently are used in nonsupported form, but noble metals rarely are, except in laboratory preparations. Supporting the noble metals makes a more efficient catalyst on a weight of metal basis and aids in recovery of the metal. Neither of these factors is of much importance in experimental work, but in industrial processing both have significant impact on economics.

A great many materials have been used as catalyst supports in hydrogenation, but most of these catalyst have been in a quest for an improved system. The majority of catalyst supports are some form of carbon, alumina, or silica–alumina. Supports such as calcium carbonate or barium sulfate may give better yields of B in reactions of the type $A \rightarrow B \rightarrow C$, exemplified by acetylenes → *cis*-olefins, apparently owing to a weaker adsorption of the intermediate B. Large-pore supports that allow ready escape of B may give better selectivities than smaller-pore supports, but other factors may influence selectivity as well.

Materials, such as activated carbons, that are derived from natural products differ greatly in their effectiveness when used as catalyst supports, but it is difficult to delimit the factors present in the carbon that influence performance. Certain broad statements, such as that carbons with excessive sulfur or ash content tend to make inferior catalysts, only begin to touch on the problem. One of the advantages of buying commercial catalysts, instead of using laboratory preparations, is that commercial suppliers have solved this problem already by empirical testing of many carbons. They provide catalysts that are best by test.

1.5. Choosing a Metal Concentration

Metal concentration in hydrogenation catalysts varies from 100% metal to a small fraction of 1%. In laboratory experiments where economics is not a factor, noble-metal blacks (finely divided metal) or metal oxides are sometimes used, but these catalysts are seldom seen in industrial practice. More commonly, noble metals are supported, usually on a high surface material such as carbon or alumina, to facilitate metal dispersion and to aid in metal recovery. The lower the metal concentration the higher the specific rate (rate per unit weight of metal) (Table 1) (*48*). Offsetting the gains in metal efficiency, brought about by low metal concentrations, is the increased cost of making the catalyst. To maintain a certain metal level in the system, increasing amounts of catalysts are required as metal concentration is decreased. Supported noble metal catalysts are most commonly used in the 3–5% metal

TABLE 1

Effect of Platinum Content on Cyclohexene Hydrogenation

% Pt-on-Al_2O_3	Specific rate
1.11	76
0.72	96
0.52	113
0.39	121

concentration range, a range apt to give maximum economy when all factors are considered.

More concentrated metals are sometimes used despite declining metal efficiency. These catalysts are used to decrease loss of valuable products by absorption on the carrier, to minimize the amount of catalyst to be filtered, to aid in settling of the catalyst, and to facilitate difficult reductions.

Base metals are much less active and are generally used in much higher metal concentration ranges up to 100%.

1.6. Choosing Conditions

Some hydrogenations require exacting conditions for optimal results but most do not. There is often a wide range of conditions under which satisfactory results can be obtained, which is one of the great assets of hydrogenation as a synthetic tool. The quickest way to success is simply to choose conditions that experience and literature deem reasonable and proceed. Satisfactory results will be obtained very likely. If satisfactory results are not achieved, the most fruitful approach is to ascertain what went wrong, e.g., poisoning, interaction with the solvent, coupling, poor selectivity, or overhydrogenation. It is very much easier to correct a problem if it can be identified. Frequently, potential problems can be identified in advance and corrective measures incorporated in the initial experiments.

1.7. Effect of Temperature

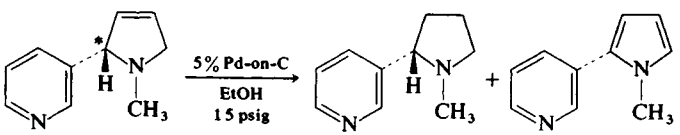
Temperature can have an important influence on rate, selectivity, and catalyst life. In general, the rate of hydrogenation rises with increasing temperature; the rate increase will be much larger when the reaction is

kinetically controlled than when diffusion limited. Catalyst life is often affected adversely by an increased temperature. A 2% palladium-on-carbon catalyst could be reused repeatedly at 69°C without loss in activity in reduction of *o*-nitroaniline to *o*-phenylenediamine in methanol, but at 90°C much activity was lost after one use (*52*).

Most hydrogenations can be achieved satisfactorily near ambient temperature, but in industrial practice the temperature is usually elevated to obtain more economical use of the catalyst and increase the space–time yield of the equipment. In laboratory work, a convenient procedure is to begin at ambient temperature, if reasonable, and raise the temperature gradually within bounds, should the reaction fail to go or if it is proceeding too slowly.

1.8. Prereduction

Prereduction of a catalyst is frequently practiced, that is, the catalyst, solvent, and hydrogen are shaken together before the substrate is added. One purpose of this procedure is to ensure that the measured hydrogen consumption arises only from uptake by the substrate. Another purpose is to activate the catalyst, and another is to eliminate induction periods. At times, selectivity of reduction may be changed by this procedure. For instance, more of the *cis*-β-decalone was formed from hydrogenation of $\Delta^{1,9}$-octal-2-one over palladium when the catalyst was not presaturated than when it was (*8*). See also Ref. *34* for a further example of the hydrogenation of bisenones. Prereductions have been used to suppress unwanted dehydrogenation. Prereduction of 5% Pd-on-C was necessary in the hydrogenation of dehydronicotine to nicotine if formation of the aromatized nicotyrine were to be avoided (*29*).



Prereductions are usually not necessary and may even be detrimental (*85,86*). They are always time-consuming. As a practical matter, prereductions can usually be omitted and reserved only for those catalysts known to require it. Activation by prereduction of a catalyst is more likely to be required if the catalyst is to be used under mild conditions. It is a technique worth resorting to when a system, which literature and experience suggests should work, fails.

1.9. Measurement of Selectivity

There appears now and then in the literature a statement to the effect that the hydrogenation was not selective because there was no break in the hydrogenation rate curve or that the hydrogenation was not selective because absorption did not cease at a discreet number of moles of hydrogen. Statements of this sort arise from a misunderstanding. Neither the rate curve nor the moles absorbed at cessation have necessarily anything to do with selectivity. The only sure way of measuring selectivity is by analysis of the product at or near the theoretical absorption of hydrogen, where usually, but not always, maximal selectivity will occur. Reliance on rate curves as the criterion of selectivity may result in satisfactory reductions being discarded.

1.10. Catalyst Reuse

In commercial hydrogenations, a catalyst should be used as many times as possible consistent with adequate rates and selectivities. Each reuse lowers the cost of operation. Intervening regenerations may or may not be required between reuses. However, in experimental laboratory work the small savings are not worth the uncertainty introduced by reuse.

1.11. Synergism

Two catalysts together sometimes give better results than either separately. The effect may occur when the two catalytic elements are made into a single catalyst and also when two separate catalysts are used together. In the latter case, synergism can be accounted for by the assumption that the reaction involves two or more stages with neither catalyst being optimal for both stages. One could also assume that the second catalyst functions by its superior ability to remove an inhibitor that may form in the reaction. In either case, if one can guess the sequence of steps or the likely inhibitors, one can guess a reasonable second catalyst that, when mixed with the first, will produce synergism (*82*).

1.12. Solvents

Solvents are often used in catalytic hydrogenation (*81*). Solvents may be one of the best means available for markedly altering the selectivity, a fact not sufficiently appreciated. Solvents also help to moderate the heat of hydrogenation, to aid in catalyst handling and recovery, and to permit the use of solid substrates. A convenient solvent may be the product itself or the solvent used in a prior or subsequent step.

Solvents influence rate as well as selectivity. The effect on rate can be very great, and a number of factors contribute to it. In closely related solvents, the rate may be directly proportional to the solubility of hydrogen in the solvent, as was shown to be the case for the hydrogenation of cyclohexene over platinum-on-alumina in cyclohexane, methylcyclohexane, and octane (*48*). Solvents can compete for catalyst sites with the reacting substrates, change viscosity and surface tension (*108*), and alter hydrogen availability at the catalyst surface.

The amount of solvent relative to the amount of total catalyst is usually large, and the amount of solvent relative to the number of active catalyst sites larger still; very small amounts of inhibitors or poisons can have, therefore, large adverse influences on the rate of reduction. Solvent purity per se is of little regard in this connection, for gross amounts of innocuous impurities can be present without untoward effect.

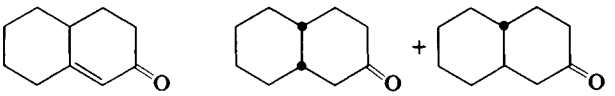
Most workers in exploratory experiments use high grade solvents for it helps avoid complicating factors. Results thus obtained cannot necessarily be extrapolated safely to technical, reused, or reclaimed solvents, and serious errors have been made by doing so. If, in commercial practice, a lower grade solvent is to be used, its effect on the catalyst should be ascertained beforehand.

1.12.1. Influence of Solvent on Selectivity

At times, selectivity changes drastically with a change in solvent, providing one of the best means available for controlling selectivity. The powerful influence of solvent is insufficiently appreciated and its efficacy often overlooked. There are many examples, so many that it is difficult to make encompassing generalities.

One very useful, although fallible, generality is that in a series of solvents the extremes of selectivity will be found at the extremes of the dielectric constant with two provisos; (a) alcohols sometimes should be considered separately,

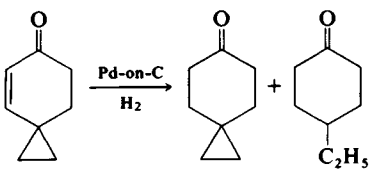
and (b) the charge on the species undergoing hydrogenation should not change. Selected data of Augustine (*7*) on the hydrogenation of β-octalone illustrates appreciable selectivity changes with solvent and the first proviso. The differences in results between methanol and *t*-butanol is particularly striking since these are closely related compounds. Note that in this case selectivity moves with dielectric constant in opposite directions in protic and aprotic solvents. Reasons for these results are discussed by Augustine (*7*).



Solvent	% *cis*-2-Decalone	Dielectric constant
Methanol	41	33.6
t-Butanol	91	10.9
Dimethylformamide	79	38.0
n-Hexane	48	1.89

cis-2-Decalone is obtained in 99.5% yield by palladium-catalyzed hydrogenation of the octalone in tetrahydrofuran containing hydrogen bromide, a solvent system used with much success in the hydrogenation of 3-oxo-4-ene steroids to the 5β compounds (*101*).

Selected data of Wuesthoff and Richborn (*112*) on the hydrogenation of the vinylcyclopropane **4** further illustrates the effect of solvent on selectivity as well as the reason for the second proviso.



(4) **(5)** **(6)**

Solvent	% **5**	% **6**
50 % Aq ethanol	23	77
Hexane	68	32
85% Aq ethanol, 0.1*N* NaOH	84	16

The basic solution, which now contains the enolate ion, gives much different results than those obtained in neutral media. More of the hydrogenolysis product (**6**) is obtained in polar 50% aqueous ethanol than is obtained in the

nonpolar hexane. This latter single bit of data can be used to illustrate a good working generality. One of the most common of competing systems is some sort of hydrogenation versus some sort of hydrogenolysis. The generality is that the hydrogenation product is favored by the less polar solvent, the hydrogenolysis product by the more polar solvent, as illustrated above. The generality applies to a variety of competing reactions including saturation of vinylic, allylic, benzylic, and ring-substituted molecules versus loss of function by hydrogenolysis.

1.12.2. Effect of Acidity

In general, the hydrogenolysis product is also favored by an acidic medium, as illustrated in the hydrogenation over 5% palladium-on-carbon of acetophenone to the hydrogenation product phenylethanol and to the hydrogenolysis product ethylbenzene, with various additives present (*83*).

Moles of additive per mole of acetophenone	Maximum % phenylethanol
None	90
0.20 Acetic acid	60
0.014 Hydrochloric acid	76
0.008 Sodium hydroxide	100

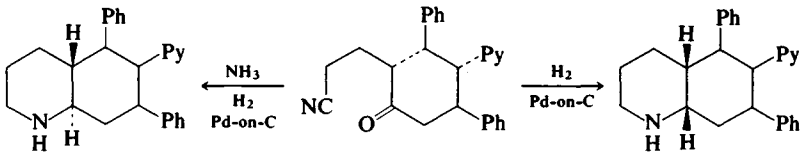
Other workers have obtained higher yields of phenylethanol is absolute methanol; the 90% yield reported above was probably due to traces of residual acid remaining from the catalyst preparation. Note that hydrogenolysis with this catalyst can be prevented completely by traces of base; addition of base is often a useful means of preventing or minimizing unwanted hydrogenolysis in a variety of systems.

Unrecognized traces of residual acids or bases in catalysts is one reason investigators have failed to duplicate the work of others (or their own). On the other hand, this variable often has little or no influence. Acidity of a catalyst can be readily checked by slurring it in water and measuring the pH.

1.12.3. Reactive Solvents

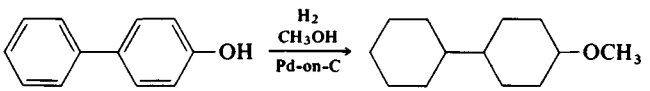
Solvents may enter into the reaction sequence transiently or permanently. Well-known examples of the transient participation of solvent are the use of

ammonia to prevent secondary and tertiary amine formation in the hydrogenation of nitriles, oximes, or anilines. Ammonia enters the product permanently in other reactions such as reductive alkylations with aldehydes or ketones. Ammonia has been used to change stereochemistry as in reduction of **8** to either **7** or **9** (*77*). In the absence of ammonia, the nitrile is reduced to an amine, which undergoes intramolecular reductive alkylation with the carbonyl group; in the presence of ammonia reductive alkylation at the carbonyl group occurs to give the equatorial cyclohexylamine, which in turn reacts with the intermediate aldimine, followed by hydrogenolysis to **7**.



(7) (8) (9)

Solvents sometimes participate in the reduction unexpectedly. For example



84%

This ether formation arises from conversion of the phenol to a cyclohexanone, and ketal formation catalyzed by Pd–H_2 and hydrogenolysis. With Ru-on-C, the alcohol is formed solely (*84*).

1.13. Safety

There are several sources of potential danger in catalytic hydrogenations; these are failure of equipment because of excessive pressures, solvent fires, explosions and fires from mixtures of hydrogen in air, and, with finely divided carbon supports, dust explosions. None of these should cause concern, for all may be avoided easily.

Unlike reactions such as certain oxidations and polymerizations, hydrogenations will not detonate unless the substrate or solvent itself is explosive or undergoes extensive decomposition. Excessive pressures can only come from overpressuring the reaction vessels and from pressures generated by large

exotherms, or by failure of temperature controllers (*94*). Especially active catalysts should be used in smaller concentrations than less active ones to prevent excessive exotherms. It has been suggested, for instance, that in using Raney nickel W-6 above 100°C, the catalyst concentration be kept below 5% (*13*). Dioxane should never be used with any Raney nickel above 200°C; it may decompose almost explosively. Pressure vessels should be charged only to pressures well below the manufacturer's rating, with due allowance made for pressure increases caused by reaction exotherms. Hydrogenations that are proceeding too rapidly are moderated conveniently by cooling, by stopping the agitation, and/or by interrupting hydrogen flow to the vessel.

1.13.1. Catalysts

Some catalysts, such as Raney nickel, are pyrophoric in themselves and will ignite when brought into contact with air. Due care should be taken in handling them. They are best kept wetted.

Metal catalysts on finely divided carbons can undergo dust explosions just as can the carbon itself, flour, or, as recently happened, stearic acid. The problem is circumvented easily by not dusting the catalyst, a poor practice in any case, especially when they contain noble metals. Virgin noble-metal catalysts are nonpyrophoric and can be safely held in the hand. After use, however, all catalysts containing adsorbed hydrogen may ignite when dried. A used, filtered catalyst should be kept wet and out of contact with combustible vapors and solvents.

1.13.2. Loading a Catalyst

Catalysts that in themselves are completely safe may catalyze combustion of hydrogen or of organic vapors or solvents. Compounds that are dehydrogenated readily, such as lower alcohols and cyclohexene, are particularly apt to ignite. Other solvents are ignited with much more difficulty and very rarely, but this should not be relied on, and in all cases due precaution should be taken.

For a catalyst-ignited fire to occur, oxygen must be present; exclusion of oxygen permits completely safe handling. Some workers put the catalyst in the reaction vessel and sweep air from the vessel with a gentle flow of nitrogen or carbon dioxide; argon is ideal if available. The solvent, which may be cooled to diminish its flammability, is then added. Once all of the catalyst has been wet with solvent, fire will not occur. Air can also be removed from the flask by

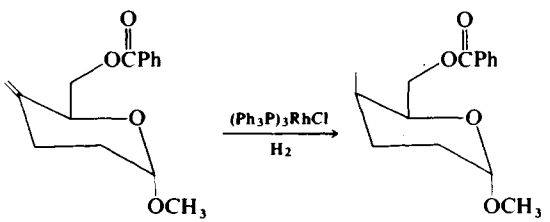
application of vacuum, and solvent is added to the flask from a dropping funnel.

Other workers do the opposite and add catalyst to the solvent (which again may be cooled) after first sweeping the flask with inert gas to remove air. It appears that if catalyst and solvent are mixed without removal of air (which is certainly not advised) fires are more likely to occur when catalyst is added to the solvent. Catalyst particles falling through organic vapor cannot be effectively cooled and may enter the liquid glowing. On the other hand, when solvent is added rapidly to the catalyst, any tendency of the catalyst to heat is limited by quenching with a massive amount of liquid.

Many catalysts are sold as water-wet and are useful when water can be tolerated. These wetted catalysts are much less apt to start fires. Catalysts can be wetted with safety with methylcellosolve (2-ethoxyethanol) before adding them to volatile solvents (*40*).

1.14. Homogeneous Catalysts

Homogeneous hydrogenation catalysts provide a welcome supplement to heterogeneous catalysts although their use has been relatively limited for a single important reason: the more easily handled heterogeneous catalysts are just as or more satisfactory in most cases. Nonetheless, five areas have been identified where homogeneous catalysts may be superior. These are (1) where some aspect of selectivity is involved, (2) where heterogeneous catalysts are poisoned, (3) where disproportionation of incipient aromatic systems is possible, (4) where selective labeling is desired, and (5) where asymmetric hydrogenation is sought (*80*). As with heterogeneous catalysis, selectivity in homogeneous catalysis depends on reaction conditions and solvent. Stereoselectivity in hydrogenation of **10** to generate the axial methyl group over $(Ph_3P)_3RhCl$ depended on both solvent and temperature. At 0°C in benzene, **11** was formed cleanly, but in ethanol as solvent or cosolvent, or at higher temperature, selectivity fell (*76*).



(10) **(11)**

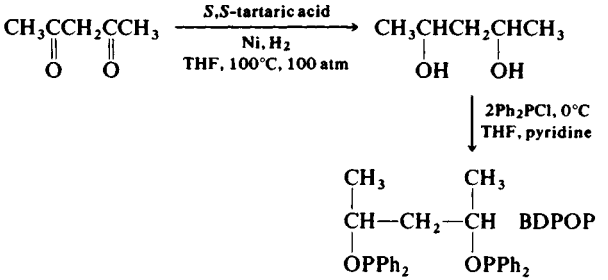
1.14.1 Asymmetric Hydrogenation

One of the most interesting and useful developments in recent years is asymmetric hydrogenation in which chirality is introduced into prochiral molecules in the hydrogenation process through use of chiral catalysts. The catalysts may be homogeneous, heterogeneous (*98*), or a hybrid of the two, an anchored homogeneous complex (*9,10*). An effective catalyst must give both high regioselective and stereoselective yields.

1.14.2. Ligand Synthesis

Four general methods have been used for obtaining chiral ligands: resolution of a racemic mixture, use of a chiral naturally occurring product (*33*), and asymmetric homogeneous or heterogeneous hydrogenation.

The method of Ito *et al.* (*50*) as applied by Bakos *et al.* (*12*) to the reduction of acetylacetone to either (−)-(2*R*,4*R*)- or (+)-(2*S*,4*S*)-2,4-pentanediol will serve to illustrate how a chiral heterogeneous catalyst has been used to prepare a chiral homogeneous ligand precursor.



The chiral catalyst was made from Raney nickel, which was prepared by addition in small portions of 3.9 g Raney nickel alloy to 40 ml water containing 9 g NaOH. The mixture was kept at 100°C for 1 h, and then washed 15 times with 40 ml water. Chirality was introduced by treatment of the Raney nickel for 1 h at 100°C with 178 ml water adjusted to pH 3.2 with NaOH and containing 2 g (*S,S*)-tartaric acid and 20 g NaBr. The solution was then decanted, and the modifying procedure was twice repeated. Hydrogenation over this catalyst of acetylacetone (100 atm, 100°C) in THF containing a small amount of acetic acid gave an isolated yield of chiral pentanediol of 44% (99.6% optical purity).

Chiral heterogeneous hydrogenations have been much studied. The area is not without complication. Results vary widely and depend on a number of

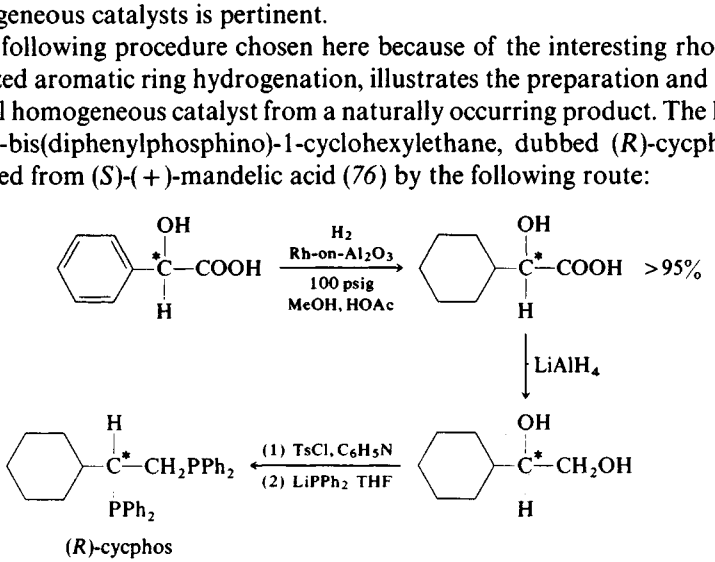
conditions. To use this type of catalyst as a tool, rather than as a research area per se, the most reasonable approach would be to check the literature and then adapt the procedure that was successful for a close analogy. In general, optical yields tend to be higher when using chiral homogeneous catalysts, and they are less sensitive to reaction parameters.

1.14.3. Chiral Homogeneous Hydrogenations

Published reports on homogeneous asymmetric hydrogenations are already voluminous despite the relative newness of the area. Many results are spectacular. For leading references, see, for instance, Koenig *et al.* (*55*), Valentine *et al.* (*103*), Scott *et al.* (*90*), and Amma and Stille (*6*).

An understanding of the factors affecting chiral reductions is unfolding, and it appears that a stereochemically rigid complex is necessary for the highest optical yields, and bidentate ligands accordingly usually give higher optical yields than do monodentate ligands. Optical yields also depend importantly on the ability of the substrate to coordinate at more than one point; great success has been had in the asymmetric hydrogenation of α-(acylamino)acrylic acids (*105*), but compounds lacking either or both a carboxylic acid or an acetoamido group have given much lower optical yields (*51*). Results may depend on minor variations in catalyst structure, and with the present state of the art only by luck could a process be optimized without considerable effort. To apply these catalysts in synthesis, the same advice just given for chiral heterogeneous catalysts is pertinent.

The following procedure chosen here because of the interesting rhodium-catalyzed aromatic ring hydrogenation, illustrates the preparation and use of a chiral homogeneous catalyst from a naturally occurring product. The ligand (*R*)-1,2-bis(diphenylphosphino)-1-cyclohexylethane, dubbed (*R*)-cycphos, is prepared from (*S*)-(+)-mandelic acid (*76*) by the following route:



(*R*)-cycphos

A solution of 76 g (*S*)-(+)-mandelic acid in 400 ml methanol and 5 ml acetic acid was reduced over 5% rhodium-on-alumina under 100 psig for 10 h. The catalyst was removed by filtration through Celite, and the methanol was removed in a rotary evaporator. The white, solid residue was dissolved in 1 l of hot diethyl ether and filtered while hot. After reduction of the volume to 400 ml, 250 ml cyclohexane was added. The remainder of the ether was removed, and the cyclohexane solution was stored for several hours in a refrigerator. The white crystals were filtered and dried *in vacuo* at 40°C; the yield of (*S*)-(+)-hexahydromandelic acid was 71%.

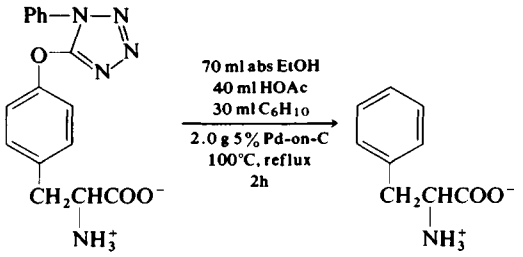
The use of small amounts of acetic acid is important; small amounts have a marked accelerating effect (*95*) larger amounts promote hydrogenolysis of the benzyl oxygen.

The catalyst {[Rh-(*R*)-cycphos] (NBD)} PF_6 (NBD = norbornadiene) is typically prepared by adding 2.2 g $AgPF_6$ to 2.0 g of the Rh dimer, $[Rh(NBD)Cl]_2$ in acetone under a nitrogen blanket. After filtration of the AgCl, 4.1 g of (*R*)-cycphos is slowly added. The solution is reduced to 15 ml and filtered. To the hot solution, 50 ml CH_3OH is added. More solvent is removed *in vacuo*, and, on cooling, an orange precipitate forms, which is washed with ether and dried *in vacuo*. The yield of {[Rh-(*R*)-cycphos] (NBD)}PF_6 is 74%. Many catalysts of this type are sensitive to oxygen and should be handled with rigid exclusion of oxygen.

Good reviews of asymmetric homogeneous hydrogenation catalysts and their syntheses are those of Caplar *et al.* (*28*) and Vineyard *et al.* (*106*).

1.15. Hydrogen-Transfer Reductions

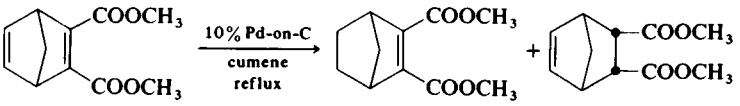
In the presence of hydrogenation catalysts, certain organic compounds can serve as the hydrogen source. The procedure is useful when hydrogen is unavailable or zoned against; only simple equipment is required (*18*). The

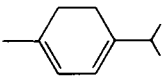


procedure can be carried out in a column (*35*). Suitable donors include materials such as formic acid (*73*), *d*-limonene, α-phellandrene, and cyclohexene (*71,19*). In general, apart from convenience, transfer reductions have no advantage over conventional hydrogenation, but occasionally superior results are obtained (*37*).

A case in point is hydrogenolysis of the 1-phenyltetrazolyl ether of tyrosine, to phenylalanine (*107*).

In hydrogen-transfer hydrogenations, various olefinic hydrogen donors are not necessarily equivalent, neither in selectivity nor in rate. The point is illustrated by selected data of Tabor *et al.* (*97*) on the transfer hydrogenation of dimethyl bicyclo[2.2.1]heptane-2,5-diene-2,3-dicarboxylate.



Donor		% in product
	64	36
	78	2
	12	88

The rate of transfer hydrogenation also varies markedly with donor structure. For cyclohexene, 1-methylcyclohexene, 1-methyl-4-isopropylcyclohexene, and 1-methyl-4-*t*-butylcyclohexene as donor in the above hydrogenations, after 1 min the reduction was 11, 78, 99, and 99% complete, respectively (*97*).

1.16. Hydrogenation Reactors

All hydrogenation reactors serve the purpose of bringing hydrogen, catalyst, and substrate together in the absence of oxygen. Equipment for doing this comes in great variety, ranging from microreactors to huge vessels and

suitable for operation with pressures ranging from atmospheric to thousands of pounds per square inch.

1.16.1. Atmospheric Pressure Reactors

Equipment for use at ambient pressures can be improvised easily in most laboratories. The requirements are that it be provided with some means of removing oxygen from the system, with agitation to ensure hydrogen reaching the catalyst, and with some means of measuring the amount of hydrogen consumed. Agitation can be provided by a stirrer of some sort, by a flow of hydrogen, or by shaking the reaction flask. Many workers use magnetic stirring, which is convenient and usually adequate, but relatively ineffective for mixing, especially when the catalyst is very active. Hydrogen absorption is measured readily with a buret and leveling bulb containing water or mercury (*38,39,60,58*).

There are many descriptions of various microreactors for hydrogenation. Requirements for these reactors are more exacting because of the need to measure accurately small amounts of consumed hydrogen (*22,30,31,36,45,46, 49,59,69,70,91,92,104,111*).

1.16.2. Low-Pressure Reactors

Apparatus for carrying out hydrogenation at several atmospheres can be constructed readily (*1,78,93*), but there seems little point in this exercise since good commercial equipment is available. The most commonly used commercial low-pressure equipment is the Parr hydrogenator (manufactured by Parr Instrument Co., Moline, Illinois). This equipment (Fig. 1) has withstood the test of time; it was first described in 1922 and offered commercially in 1926. It comes in two sizes: one for 500-ml reactor bottles and one for 1000- and 2000-ml reactor bottles. Specially made smaller bottles, down to 50 ml, can be used also but require special holders to compensate for differences in bottle heights. Shaker bottles should not be more than half full to ensure good mixing, a consideration in selection of bottle size.

In operation, the substrate, catalyst, and solvent (if any) are sealed in a reaction bottle and connected to a hydrogen reservoir. Air is removed either by applying vacuum or by flushing with hydrogen. The bottle is then opened to the hydrogen reservoir, and the bottle is shaken vigorously to initiate the reduction. Parr supplies both heating and cooling jackets. After the desired

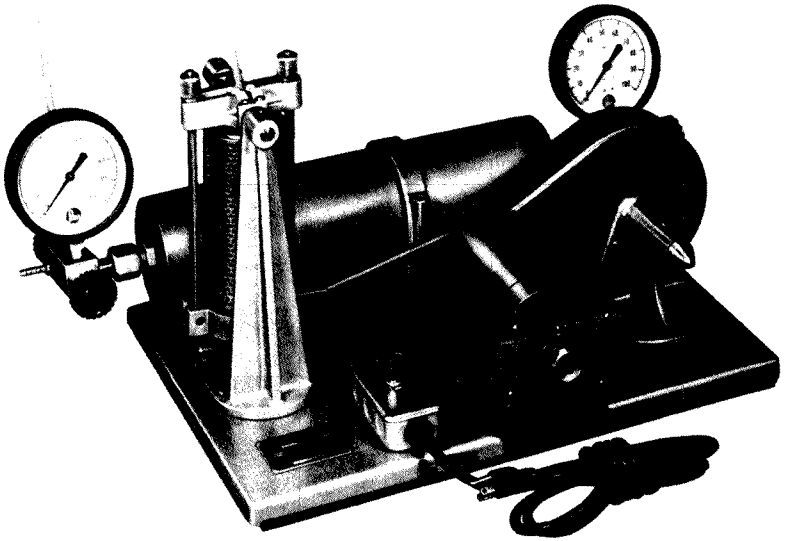


Fig. 1. A Parr shaker type reactor.

hydrogen absorption, the bottle is vented and the product and catalyst are recovered. Hydrogen absorption is determined from the pressure drop in the system. The relationship between pressure drop and moles of hydrogen consumed is determined by hydrogenation of a weighed amount of known compound that unambiguously gives a single product. Parr shaker bottles are made of borosilicate glass, and each is pressure tested at twice its specified maximum pressure, 30–60 psig, depending on size. In operation the bottle is surrounded by a screen to contain glass splinters should the bottle accidently break. Some bottles can be furnished with a tough outer fiberglass coating that usually retains any broken glass and prevents loss of valuable materials should a mishap occur. Parr shakers are commonly operated in the open laboratory without additional barricade, but a glass safety screen is recommended nonetheless. Additional safety requirements are necessary should bottle breakage release a toxic material.

Various workers have suggested modifications of this useful equipment (*26,79*). One such modification, which can be adopted to any reactor, is incorporation of a pressure switch that stops agitation when a predetermined

quantity of hydrogen has been absorbed. This device is useful when overhydrogenation is a possibility and allows operation without constant watching of the equipment (*72*).

1.16.3. High-Pressure Reactors

High-pressure processing requires specially constructed equipment, which is available from a number of manufacturers. Some companies design and build completely packaged units including instrumentation and containment areas. A number of workers have given general descriptions of high-pressure reactors and facilities together with various aspects of safety, design, and control (*3,14,15,16,41,42,56,57,63,74,75,94*). These and other references are well worth consulting before investing in extensive and expensive pressure facilities, to prevent both under- and overdesign. High-pressure equipment is best bought from suppliers rather than made. It is not an area that lends itself easily to amateur work. For this reason no space is taken here for detailed description of reactors since these are given gladly by equipment manufacturers on request.

A useful device to have installed in a stirred autoclave is a liquid sampling tube by which liquid samples are withdrawn under pressure through a filter attached to the lower end of the tube. This device is especially useful for analysis of reaction progress and supplements information obtained from pressure-drop determinations. It is much easier to improve a less than satisfactory yield, if it can be determined what is going wrong and when. For academically orientated persons, a study of the rise and decline of various reaction products, as a function of reaction parameters and catalyst, can be a fertile source of useful publications.

1.16.3.1. Safety

High pressure reactors are frequently called bombs, an unfortunate term indeed. A major aim of any investigation in this area is to make certain that the phrase does not become an apt description. Serious accidents are most likely to happen not as part of the hydrogenation process but as a result of chemistry extrinsic to the hydrogenation, that is, confinement of an unstable material under elevated temperatures. In this regard there is some danger in trying to force a hydrogenation to completion by increasing the reaction temperature excessively. A large-scale destructive, runaway reaction occurred for this reason during hydrogenation of impure 3,4-dichloronitrobenzene, caused by

exothermic disproportionation of intermediate 3,4-dichlorophenylhydroxylamine at its autodecomposition temperature (*100*).

Most reactors are equipped with safety rupture disks to protect the operator and equipment from destructive pressures. The operating pressure in a vessel should never exceed 70% of the range covered by the rupture disk. Similarly, gauges should not be stressed beyond about 70% of full-scale readings for safety and to ensure reliable readings.

1.16.3.2. Materials of Construction

Reactors should not dissolve in the reaction medium. Judging by spectrographic analysis of spent catalysts, some attack of the reactor is more common than is generally supposed. It may be a cause of catalyst failure. Reactors are commonly made of type 316 stainless steel, but other alloys may provide better resistance to specific corrosive agents.

Parr Instrument Company (Moline, Illinois) kindly provided the following general recommendations for this and other alloys. Type 316 stainless steel will handle most organic materials including organic acids. It is not recommended for strong mineral acids and is susceptible to stress corrosion cracking in caustic and chloride solutions. Monel 400* is good for most caustic and chloride solutions and excellent for most fluorine, hydrogen fluoride, and hydrofluoric acid systems. Carpenter 20 Cb-3† is an enriched grade of stainless steel designed specifically for use with dilute sulfuric acid. It can be used also with nitric and phosphoric acids. Inconel 600* offers excellent resistance to caustics and many other materials, particularly at higher temperatures. Hastelloy B-2‡ is about the only alloy with real resistance to hydrochloric acid systems. It is also excellent for sulfuric acid, but sensitive to the presence of ferric or other oxidizing ions. Hastelloy C-276‡ was developed specifically for wet chlorine service. It has perhaps the broadest general corrosion resistance of all commonly used alloys, but it is not intended for use with strong oxidizing acids. Nickel is used generally to handle strong caustic solutions. Titanium offers good resistance to nitric acid and other strong oxidizing acids. It is used also for aqua regia and other mixed acid applications, and offers excellent resistance to chloride ions. Carbon steel is generally used in laboratory apparatus mainly to duplicate available plant equipment. It rusts easily. Stainless steel is much better except for use with caustics. Zirconium offers usable resistance to hydrochloric, sulfuric, nitric, and phosphoric acids as well as to caustics and many salt environments.

* Monel and Inconel are registered trademarks of the International Nickel Co., Inc.

† Carpenter 20 Cb-3 is a registered trademark of Carpenter Technology Corp.

‡ Hastelloy is a registered trademark of the Cabot Corp.

1.17. Catalyst Preparation

It was recommended in Section 1.4 that hydrogenation catalysts be bought rather than made. Nonetheless, for those who wish to make their own catalyst some comments seem in order.

Organic Syntheses describes a number of preparations of palladium, platinum, and nickel catalysts, all of which are, of course, quite usable. Mozingo (*62*) submitted therein preparations for 5% palladium-on-calcium carbonate or barium sulfate, a 5% palladium chloride-on-carbon reduced by alkaline formaldehyde, and a hydrogen-reduced 10% palladium-on-carbon. The advantage of palladium chloride-on-carbon is said to be that there is no loss of activity on storing. In our experience, loss of activity does not occur with any of the catalysts, provided they are kept in tightly closed bottles. The hydrogen-reduced palladium chloride-on-carbon, essentially the development of Hartung (*47*), gives a relatively low-activity catalyst. It is instructive to read comments on the wide variations in activity of samples of this simply prepared catalyst, made in one laboratory with constant ingredients (*110*).

The well-known Adams' platinum oxide can be prepared conveniently by the procedure of Adams *et al.* (*2*). Platinum oxides prepared in this way usually contain some traces of sodium, which in certain reactions can have an adverse effect. The sodium can be removed by washing with dilute acid (*53*). The Nishimuri catalyst (30% Pt, 70% Rh oxides) can be prepared by the same procedure as for platinum oxide or with variations from platinum and rhodium salts (*64,65,66*). This catalyst has much merit. It is usually most useful when hydrogenolysis is to be avoided (*67,85,86*).

A commonly used base metal is some form of Raney nickel. The catalyst is made by treating a nickel–alumina alloy with sodium hydroxide. There are a number of variations that differ in the way the alloy is added, in the washing, in alkali concentration, and in temperature and length of digestion. These catalysts have been compared in activity in the hydrogenation of β-naphthol (*5*). Detailed procedures for Raney nickels W-2, W-3, W-6, and W-7 are given in *Organic Syntheses* (*13*). Other references to various nickel catalyst preparation are available for Raney nickel W-1 and W-4 (*71*), W-5 (*4*), W-8 (*54*), nickel boride P1 (*20*), nickel boride P2 (*21*), nickel boride (*89*), nickel carbide (*24*), nickel-on-graphite (*87,88*), Urushibara nickel (*61,99,102*), nickel-on-kieselguhr (*32*), and Nic catalysts (complex nickel catalysts prepared from sodium hydride) (*25,43*). Many workers routinely use Raney nickel W-2; it is more active than W-1 and has considerable stability. Raney nickels W-3 through W-7 all lose their special activity rather rapidly when stored under water. W-6 and W-7 are very active catalysts; they differ in that W-7 is alkaline and is useful where alkali is beneficial. These active catalysts are effective for

reduction of alkenes, alkynes, aldehydes, ketones, oximes, nitriles, and nitro compounds under mild conditions. Neither catalyst will retain its peak activity very long. The warnings of *Organic Syntheses* (*13*) are worth heeding. It is recommended there that the most active Raney nickel catalysts be used at temperatures lower than 100°C or if at a higher temperature, with a catalyst-to-hydrogen acceptor ratio of less than 5%. Failure to operate within these limits has resulted in violent reactions. Raney nickel W-8 is a low-activity catalysts that has proved useful in deuteration experiments.

Cobalt boride has been used for reducing unsaturated aldehydes to unsaturated alcohols; improved results are obtained by addition of ferric chloride or chromium chloride (*68*). It is a low-activity catalyst.

1.17.1. Purchased Catalysts

Hydrogenation catalysts in great variety can be purchased from commercial suppliers, and there is some advantage to using them, beyond the time and labor saved. Commercial catalysts are the end result of much empirical testing and represent the best of a type. Supply of large quantities of catalyst is ensured if needed; not all laboratory preprations of catalysts can be conveniently scaled up. Also some suppliers have experience and background in the choice and use of catalysts, which is often available for the asking.

1.18. Economics of Catalyst Use

When hydrogenation reactions cease to be experimental and enter the stage of industrial development, the cost of the hydrogenation process becomes important. Some of the factors that enter into the determination of this cost are considered here.

In general, catalytic hydrogenation is the cheapest possible way to reduce a compound. Exceptions to this generality arise when the yield of hydrogenated product is not comparable to that obtained with other types of reduction or when poisoning of the catalyst causes excessive consumption and unacceptable space–time yields. Often purification of the feed can alleviate economically poisoning difficulties caused by extrinsic materials; poisoning by the substrate is more difficult to correct. Hydrogenation is a mature field, and a great many industrial processes are in operation. The knowledge that a similar type of hydrogenation is already in industrial use should provide the research worker with assurance that a contemplated process is economically viable.

Determination of the actual cost of a hydrogenation process is difficult. Among the factors entering into the determination are catalyst cost, catalyst life, cost of materials, capital investment, actual yield, space–time yield, and purification costs. Considerable data are needed to make an accurate evaluation.

1.18.1. Cost of Catalyst

The purchase price of an initial charge of catalyst is but one factor entering into the cost of using a catalyst. For noble-metal catalysts, which have high reclaim value, this price is in itself relatively unimportant. The number of greater significance is the cost of the catalyst in use, that is, the cost of the catalyst when the value of reclaimed metal has been deducted.

Eventually all catalysts become spent. At this stage they can be discarded, itself sometimes a problem, or returned to a refiner for recovery of metal values. In commercial use, noble-metal catalysts are always returned to a refiner. At the refinery, the catalyst is destroyed and the noble metals are recovered and converted to high-purity metal. In a loop system, the pure metal is converted to a suitable salt and again used for catalyst manufacture. In the entire loop, some metal will be lost and must be replaced with fresh metal. Refining is nowadays very efficient, and most metal loss will occur in the process itself. The total cost of a catalyst used in a loop is accordingly given by:

$$\text{cost of metal} + \text{cost of catalyst manufacture} + \text{cost of refining} + \text{cost of replacing lost metal}$$

When the process is finally terminated, the reclaimed metal can be sold and the investment in it recovered. If metal cost is considered a capital investment that will be later recovered, the cost of using a catalyst is reduced to:

$$\text{cost of catalyst manufacture} + \text{cost of refining} + \text{cost of replacing lost metal}$$

The mistake is sometimes made of estimating catalyst cost based on the price of a small sample of catalyst. This price, which largely reflects the cost of handling, is very much higher than the price of bulk quantities. The price of bulk quantities can be obtained directly from manufacturers.

1.18.2. Catalyst Life

An important determinant in the cost of using a hydrogenation catalyst is catalyst life, i.e., the pounds of product produced per pound of catalyst. In

some reactions the catalyst can be used only once; in many it can be reused repeatedly with or without intervening regenerations. A variety of factors influence catalyst life, which is difficult to estimate without experiment. In general, catalyst activity declines somewhat with each reuse. Reuse may also influence selectivity, either favorably or adversely. The effective life of the catalyst can thus be limited by loss of activity or selectivity or both.

1.18.3. Space–Time Yield

Space-time yield refers to the quantity of product that can be produced in a reactor in a given time. It is a function of both selectivity and activity. Maximum efficiency is reached when this number is high, but if production schedules are not full, lower numbers may be tolerated. Acceptable catalyst life can be extended if space–time yield demands are not heavy. Catalyst cost thus becomes a function of the demands put upon it.

1.18.4. Actual Yield

High actual yields are always desirable. Besides making efficient use of the starting material, a high actual yield lowers purification costs and minimizes disposal problems. Often the saving from a small improvement in yield effected by a change in catalyst completely overshadows the cost of the catalysts.

References

1. R. Adams, and V. Voorhees, *Org. Synth., Coll. Vol.* **1,** 61 (1932).
2. R. Adams, V. Voorhees, and R. L. Shriner, *Org. Synth., Coll. Vol.* **2,** 463 (1941).
3. H. Adkins, "Reactions of Hydrogen." Univ. of Wisconsin Press, Madison, 1937.
4. H. Adkins and H. R. Billica, *J. Am. Chem. Soc.* **70,** 695 (1948).
5. H. Adkins and G. Krsek, *J. Am. Chem. Soc.* **70,** 412 (1948).
6. J. P. Amma and J. K. Stille, *J. Org. Chem.* **47,** 468 (1982).
7. R. L. Augustine, *Adv. Catal.* **25,** 63 (1976).
8. R. L. Augustine and R. W. Warner, *J. Org. Chem.* **46,** 2614 (1981).
9. G. L. Baker, S. J. Fritschell, and J. K. Stille, *J. Org. Chem.* **46,** 2960 (1981).
10. G. L. Baker, S. J. Fritschell, J. R. Stille, and J. K. Stille, *J. Org. Chem.* **46,** 2954 (1981).
11. G. L. Baker, J. F. Scott, and J. K. Stille, *J. Org. Chem.* **46,** 2960 (1981).
12. J. Bakos, K. Toth, and L. Marko, *J. Org. Chem.* **46,** 5427 (1981).

13. H. R. Billica and H. Adkins, *Org. Synth., Coll. Vol.* **3,** 176 (1955).
14. D. W. Blackburn and H. E. Reiff, *Ann. N.Y. Acad. Sci.* **145,** 192 (1967).
15. J. C. Bowen, *Ann. N.Y. Acad. Sci.* **145,** 169 (1967).
16. J. C. Bowen and R. L. Jenkins, *Ind. Eng. Chem.* **49,** 2019 (1957).
17. G. Brieger and T.-H. Fu, *J.C.S. Chem. Commun.* 757 (1976).
18. G. Brieger and T. J. Nestrick, *Chem. Rev.* **74,** 567 (1974).
19. G. Brieger, T. J. Nestrick, and T.-H. Fu, *J. Org. Chem.* **44,** 1876 (1979).
20. C. A. Brown, *J. Org. Chem.* **35,** 1900 (1970).
21. C. A. Brown and V. K. Ahuja, *J.C.S. Chem. Commun.*, 553 (1973).
22. H. C. Brown, K. Sivasankaran, and C. A. Brown, *J. Org. Chem.* **28,** 214 (1963).
23. C. H. Brubaker, Jr., *in* "Catalysis in Organic Synthesis, 1976" (G. V. Smith, ed.), p. 25. Academic Press, New York, 1977.
24. J.-J. Brunet, P. Gallois, and P. Caubere, *Tetrahedron Lett.*, 3955 (1977).
25. J.-J. Brunet, P. Gallois, and P. Caubere, *J. Org. Chem.* **45,** 1937 (1980).
26. J. S. Buck and S. S. Jenkins, *J. Am. Chem. Soc.* **51,** 2163 (1929).
27. M. Calvin, *J. Am. Chem. Soc.* **61,** 2230 (1939).
28. G. Caplar, G. Comisso, and V. Sunjic, *Synthesis*, 85 (1981).
29. C. G. Chavdarian, *J. Org. Chem.* **48,** 1529 (1983).
30. N. D. Cheronis and N. Levin, *J. Chem. Educ.* **21,** 603 (1944).
31. N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.* **1,** 884 (1947).
32. L. W. Covert and H. Adkins, *J. Am. Chem. Soc.* **54,** 4116 (1932).
33. T. P. Dang and H. B. Kagan, *Chem. Commun.* 481 (1971).
34. P. E. Eaton, R. H. Mueller, G. R. Carlson, D. A. Cullison, G. F. Cooper, T. C. Chou, and E. P. Krebs, *J. Am. Chem. Soc.* **99,** 275 (1977).
35. B. El Amin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.* **44,** 3442 (1979).
36. R. M. Engelbrecht, *Anal. Chem.* **29,** 1556 (1957).
37. K. E. Fahrenholtz, *J. Org. Chem.* **37,** 2204 (1972).
38. L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.* **60,** 940 (1938).
39. V. L. Frampton, J. D. Edwards, Jr., and H. R. Henze, *J. Am. Chem. Soc.* **73,** 4432 (1951).
40. M. Freifelder, "Catalytic Hydrogenation in Organic Syntheses. Procedures and Commentary," p. 5. Wiley, New York, 1978.
41. J. P. Friedrich, *Ann. N.Y. Acad. Sci.* **172,** 155 (1970).
42. J. P. Friedrich, CHEMTECH, 52 (1971).
43. P. Gallois, J.-J. Brunet, and P. Caubere, *J. Org. Chem.* **45,** 1946 (1980).
44. O. J. Goodmonson, M. G. Scaros, J. M. Schlatter, and R. H. Mazur, *in* "Catalysis in Organic Syntheses" (W. H. Jones, ed.), p. 35. Academic Press, New York, 1980.
45. C. W. Gould and H. J. Drake, *Anal. Chem.* **23,** 1157 (1951).
46. I. T. Harrison and S. Harrison, *Chem. Ind. (London)*, 834 (1964).
47. W. H. Hartung, *J. Am. Chem. Soc.* **50,** 3373 (1928).
48. A. S. Hussey, G. W. Keulks, G. P. Nowack, and R. H. Baker, *J. Org. Chem.* **33,** 610 (1968).
49. J. F. Hyde and H. W. Scherp, *J. Am. Chem. Soc.* **52,** 3359 (1930).
50. K. Ito, T. Harada, A. Tai, and Y. Izumi, *Chem. Lett.*, 1049 (1979).
51. T. H. Johnson and G. Rangarajan, *J. Org. Chem.* **45,** 63 (1980).
52. P. B. Kalantri and S. B. Chandalla, *Ind. Eng. Chem. Process Res. Dev.* **21,** 186 (1982).
53. C. W. Keenan, B. W. Giesemann, and H. A. Smith, *J. Am. Chem. Soc.* **76,** 229 (1954).
54. N. A. Khan, *J. Am. Chem. Soc.* **74,** 3018 (1952).
55. K. E. Koenig, G. L. Bachman, and B. D. Vineyard, *J. Org. Chem.* **45,** 2362 (1980).
56. V. I. Komarewsky, C. H. Riesz, and F. L. Morritz, *in* "Technique of Organic Chemistry" (A. Weissberger, ed.), 2nd ed., Vol. 11, pp. 18–93. Wiley (Interscience), New York, 1956.

57. E. Lavagnino and J. Campbell, *Ann. N.Y. Acad. Sci.* **214,** 3 (1973).
58. R. W. Meschke and W. H. Hartung, *J. Org. Chem.* **25,** 137 (1960).
59. J. W. Miller and D. D. DeFord, *Anal. Chem.* **30,** 295 (1958).
60. F. L. Morritz, E. Lieber, and R. B. Bernstein, *J. Am. Chem. Soc.* **75,** 3116 (1953).
61. I. Motoyama, *Bull. Chem. Soc. Jpn.* **33,** 232 (1960).
62. R. Mozingo, *Org. Synth., Coll. Vol.* **3,** 685 (1955).
63. C. G. Myers, Jr., *in* "Catalysis in Organic Syntheses" (W. H. Jones, ed.), p. 207. Academic Press, New York, 1980.
64. S. Nishimura, *Bull. Chem. Soc. Jpn.* **33,** 566 (1960).
65. S. Nishimura, *Bull. Chem. Soc. Jpn.* **34,** 32 (1961).
66. S. Nishimura, *Bull. Chem. Soc. Jpn.* **34,** 1544 (1961).
67. S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Jpn.* **36,** 353, 873 (1963).
68. Y. Nitta, T. Imanaka, and S. Teranishi, *Bull. Chem. Soc. Jpn.* **53,** 3154 (1980).
69. C. L. Ogg and F. J. Cooper, *Anal. Chem.* **21,** 1400 (1949).
70. F. C. Pack, R. W. Planck, and F. G. Dollear, *J. Am. Oil Chem. Soc.* **29,** 227 (1952).
71. A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.* **68,** 1471 (1946).
72. W. M. Pearlman, *Ann. N.Y. Acad. Sci.* **158,** 577 (1969).
73. V. S. Rao and A. S. Perlin, *J. Org. Chem.* **47,** 367 (1982).
74. M. A. Rebenstorf, *Ind. Eng. Chem.* **53,** 40A (1961).
75. M. A. Rebenstorf, *Ann. N.Y. Acad. Sci.* **145,** 178 (1967).
76. D. P. Riley and R. E. Shumate, *J. Org. Chem.* **45,** 5187 (1980).
77. M. M. Robinson, B. F. Lambert, L. Dorfman, and W. G. Pierson, *J. Org. Chem.* **31,** 3220 (1966).
78. W. K. Rohwedder, *J. Catal.* **10,** 47 (1968).
79. P. T. Russotto, *Chemist Analyst.* **53**(3), 85 (1964).
80. P. N. Rylander, "Organic Syntheses with Noble Metal Catalysts," p. 60. Academic Press, New York, 1973.
81. P. N. Rylander, *in* "Catalysis in Organic Syntheses, 1978" (W. S. Jones, ed.), p. 155. Academic Press, New York, 1978.
82. P. N. Rylander and G. Cohn, *Actes Congr. Int. Catal. 2nd 1960* **1,** 907 (1961).
83. P. N. Rylander and L. Hasbrouck, *Engelhard Ind. Tech. Bull.* **8,** 148 (1968).
84. P. N. Rylander and X. Vaflor, paper presented at the New York–New England Catalysis Society, Spring Symposium, New Haven, Connecticut, March, 1974.
85. P. N. Rylander, L. Hasbrouck, S. G. Hinden, I. Karpenko, G. Pond, and S. Starrick, *Engelhard Ind. Tech. Bull.* **8,** 25 (1967).
86. P. N. Rylander, L. Hasbrouck, S. G. Hindin, R. Iverson, I. Karpenko, and G. Pond, *Engelhard Ind. Tech. Bull.* **8,** 93 (1967).
87. D. Savoia, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.* **46,** 5340 (1981).
88. D. Savoia, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.* **46,** 5344 (1981).
89. J. A. Schreifels, P. C. Mayburg, and W. E. Swartz, Jr., *J. Org. Chem.* **46,** 1263 (1981).
90. J. W. Scott, D. D. Keith, G. Nix, Jr., D. R. Parrish, S. Remington, G. P. Roth, J. M. Townsend, D. Valentine, Jr., and R. Yang, *J. Org. Chem.* **46,** 5086 (1981).
91. S. Siggia, "Quantitative Organic Analysis," 3rd Ed, pp. 318–341. Wiley, New York, 1963.
92. B. C. Southworth, *Anal. Chem.* **28,** 1611 (1956).
93. J. R. Snyder, P. F. Hagerty, and M. C. Molstad, *Ind. Eng. Chem.* **49,** 689 (1957).
94. J. F. Stenberg, W. E. Pascoe, and J. R. Wesel, *in* "Catalysis in Organic Syntheses" (W. H. Jones, ed.), p. 285. Academic Press, New York, 1980.
95. J. H. Stocker, *J. Org. Chem.* **27,** 2288 (1962).
96. P. E. Sum and L. Weiler, *Can. J. Chem.* **60,** 327 (1982).
97. D. C. Tabor, F. H. White, L. W. Collier, IV, and S. A. Evans, Jr., *J. Org. Chem.* **48,** 1638 (1983).

98. A. Tai, K. Ito, and T. Harada, *Bull. Chem. Soc. Jpn.* **54,** 223 (1981).
99. S. Taira, *Bull. Chem. Soc. Jpn.* **34,** 1294 (1961).
100. W. R. Tong, R. L. Seagraves, and R. Wiederhorn, *Natl. Loss Prev. Symp. A.I.C.h.E. 83rd, Houston, Texas* (1977).
101. N. Tsuji, J. Suzuki, and M. Shiota, *J. Org. Chem.* **45,** 2730 (1980).
102. Y. Urushibara, *Ann. N.Y. Acad. Sci.* **145,** 52 (1967).
103. D. Valentine, Jr., R. C. Sun, and K. Toth, *J. Org. Chem.* **45,** 3703 (1980).
104. F. A. Vandenheuvel, Anal. Chem. **24,** 847 (1952).
105. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. I. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.* **99,** 5946 (1977).
106. B. D. Vineyard, W. S. Knowles, and M. J. Sabacky, *J. Mol. Catal.* **19,** 159 (1983).
107. V. Viswanatha and V. J. Hrudy, *J. Org. Chem.* **45,** 2010 (1980).
108. H.-C. Yao and P. H. Emmett, *J. Am. Chem. Soc.* **83,** 796, 799 (1961).
109. D. V. Young and H. R. Snyder, *J. Am. Chem. Soc.* **83,** 3161 (1961).
110. J. G. Young, W. H. Hartung, and H. H. Daniels, *J. Org. Chem.* **18,** 227 (1953).
111. C. Weygand and A. Werner, *J. Prakt. Chem.* **149,** 330 (1937).
112. M. T. Wuesthoff and B. Richborn, *J. Org. Chem.* **33,** 1311 (1968).

-2-

Hydrogenation of Olefins

Olefins are hydrogenated very easily, unless highly hindered, over a variety of catalysts. With active catalysts, the reaction is apt to be diffusion limited, since hydrogen can be consumed faster than it can be supplied to the catalyst surface. Most problems connected with olefin hydrogenation involve some aspect of regio- or stereoselectivity. Often the course of reduction is influenced greatly by the catalyst, by reaction variables, and by hydrogen availability at the catalyst surface.

2.1. Double-Bond Migration

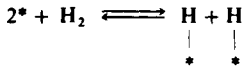
Double-bond migrations during hydrogenation of olefins are common and have a number of consequences (*93*). The extent of migration may be the key to success or failure. It is influenced importantly by the catalyst, substrate, and reaction environment. A consideration of mechanisms of olefin hydrogenation will provide a rationale for the influence of these variables.

2.1.1. Mechanism of Olefin Hydrogenation

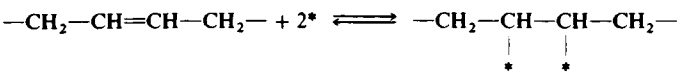
The mechanisms of olefin hydrogenation are complex and many details are still unknown. However, a mechanism proposed long ago by Horiuti and Polanyi (*51*), while lacking insight into subtle problems of present thinking, provides a useful way of accounting for all aspects of olefin hydrogenation that are of interest to the synthetic organic chemist.

Hydrogen is dissociatively adsorbed on two catalyst sites. indicated by an asterisk. Sites need not necessarily be on different atoms.†

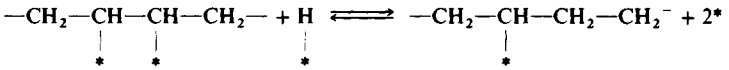
† Recent work has defined more carefully the nature of active sites. Metal surfaces are thought to contain three main types of sites; terraces, ledges (or steps) and kinks, which correspond to one, two, and three coordinatively unsaturated sites of organometallic chemistry. These sites display differing activities toward saturation, isomerization, and exchange (*7,20,68,101,103,104,105*).



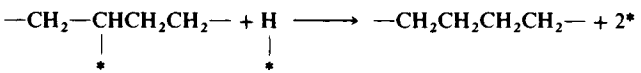
and the olefin is diadsorbed on two adjacent sites.



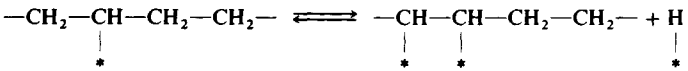
A hydrogen atom adds to one carbon, leaving a monoabsorbed species, often referred to as a half-hydrogenated state.



Addition of a second hydrogen atom forms the paraffin, which is desorbed from the catalyst, and the cycle is repeated. All steps except the last are reversible.



If the half-hydrogenated state undergoes a configurational change before reverting to an olefin, cis–trans isomerization may be effected. Double-bond migration will occur if the half-hydrogenated state returns to a diadsorbed species different than the original.



The extent of migration and isomerization is related to the rate at which the half-hydrogenated species reforms a diadsorbed species relative to the rate at which it adds a second hydrogen. The greater the hydrogen concentration at the catalyst surface, the greater will be the rate of saturation relative to the rate of reversion. Migration and isomerization are favored by a low hydrogen concentration at the surface ("hydrogen-poor catalysts"), and diminished by high hydrogen availability at the surface ("hydrogen-rich catalysts"). This last statement is supported by a huge body of experimental data but the reason for it is less certain. It has been suggested, for instance, and supported with some data, that under conditions of low hydrogen availability on palladium the mechanism changes, that hydrogen is lost to give a syn or anti π-allyl species, and that then through addition of hydrogen the initial π-species or an isomer is reformed.

2.1.2. Effect of Hydrogen Availability

Regardless of detail, the experimental facts are clear; process conditions that favor formation of hydrogen-poor catalysts favor migration and isomerization. Table 1 is a convenient summary of this concept. Hydrogen availability refers to hydrogen concentration at the catalyst surface. Additives that retard the rate of reduction increase hydrogen availability and retard isomerization; they may also block sites with enhanced activity for migration (*53*).

TABLE 1

Influence of Reaction Variables

Increased variable	Effect on H_2 availability	Effect on migration	Effect on isomerization
Pressure	+	−	−
Agitation	+	−	−
Solvent	+	−	−
Inhibitors	+	−	−
Catalyst activity	−	+	+
Temperature	−	+	+
Metal concentration	−	+	+
Catalyst concentration	−	+	+

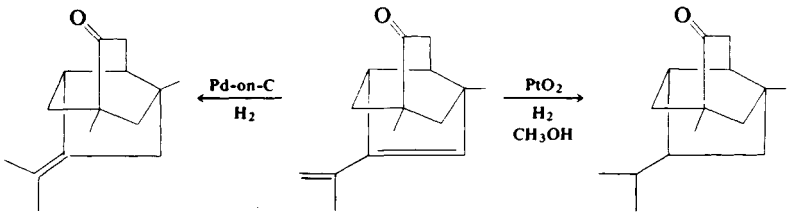
2.1.3. Catalysts

Catalysts have a profound effect on the extent of double-bond migration. The influence is a property of the metal itself and its structure and is little altered by the support (*17,18*). It is related to the relative tendencies of the half-hydrogenated states to reform an unadsorbed olefin. A decreasing ordering of metals for double-bond migration (*46*) is Pd > Ni ≫ Rh ≫ Ru ~ Os > Ir ~ Pt.

In examination of various disubstituted cyclic olefins, the following decreasing isomerization order was adduced Pd ≫ Rh, Ru, Pt > Os > Ir (*84*). At 20% conversion of 1-octene to octane, the ratio of isomerization to hydrogenation in isopropanol for various unsupported metals was Pd (2.05), Rh (0.125), Ru (0.12), Pt (0.025), Ir (0.025), Os (0.009) (*82*). Palladium is used frequently when migration and isomerization are wanted; platinum, when they are to be avoided (*2,124*).

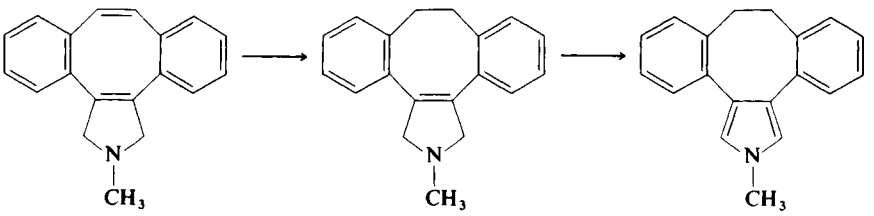
For example, the apparently straightforward saturation of **1** to give pupukeanone (**2**) could not be achieved by hydrogenation over Pd-on-C;

instead, the product was that derived as if by 1,4-addition (**3**). Pupukeanone was obtained smoothly by saturation of **1** over platinum oxide (*96*). Most of **3** was probably formed by isomerization of an initially formed monoene.



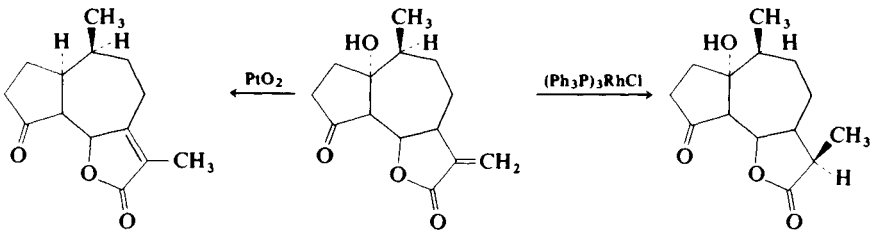
(3) (1) (2)

Conversion of **4** to **6** consumes no hydrogen and appears to be a consequence of double-bond migration. In this case, however, the reaction proceeded in two stages, hydrogen addition (**5**) followed by hydrogen elimination and migration (*28*).



(4) (5) (6)

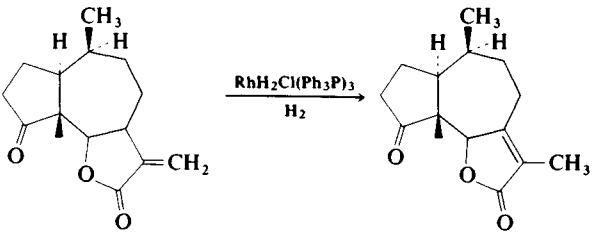
In some cases the tendency of double bond to migration rather than saturation is so large that even platinum does not prevent it. In these cases homogeneous catalysts may be useful. A case in point is coronopilin (**7**), which affords either dihydrocoronopilin (**8**) or the isomerized product isocoronopilin (**9**), depending on the catalysts.



(9) (7) (8)

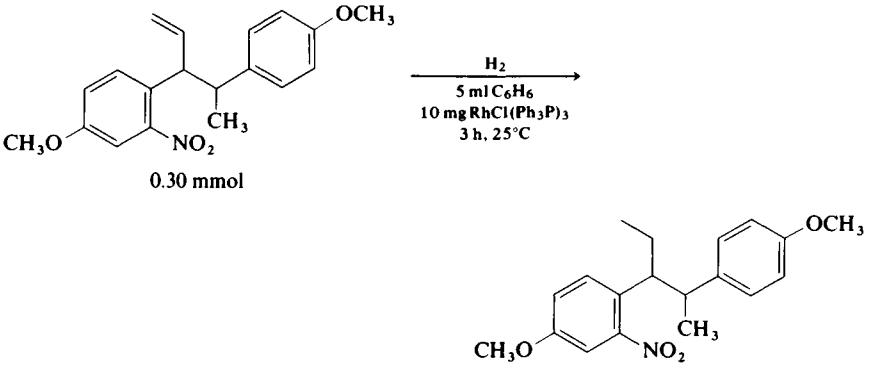
Over platinum oxide the yield of isocoronopilin varied from 63 to 100%, depending on whether or not the catalyst was prehydrogenated (*92*). Minor

structural differences may alter the course of reaction and over $RhH_2Cl(Ph_3P)_3$ [formed from $RhCl(Ph_3P)_3$ by treatment with H_2] damsin (**10**) mainly is isomerized to isodamsin (**11**) rather than undergoing saturation (*14*).



(**10**) (**11**)

The extent of double-bond isomerization over homogeneous catalysts is influenced by choice of solvent. Saturation of the double bond in 4-(4-methoxyphenyl)-3-(2-nitro-4-methoxyphenyl)-1-pentene was achieved smoothly by reduction over $RhCl(Ph_3P)_3$ in benzene without any hydrogenation of the nitro function. If the solvent were benzene–ethanol, isomerization of the double bond to a conjugated position also occurred; this styryl bond was inert to reduction under these conditions (*77*).

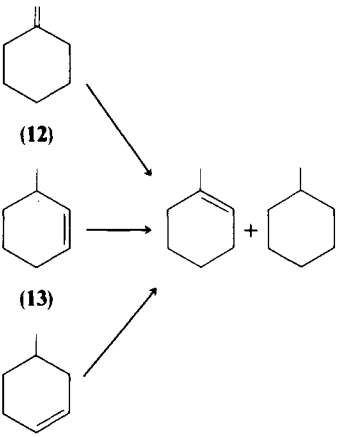


0.30 mmol

2.1.4. Effect of Solvent

Solvents can have a large influence on the extent of double-bond migration (*6*). The factors involved are complex as shown in the hydrogenation of methylenecyclohexane, 3-methylcyclohexene, and 4-methylcyclohexene to methylcyclohexane in benzene–ethanol, in pentane, and in ethanol over 5% Pd, 5% Pt, and 5% Rh-on-carbon. The amount of isomerized 2-methylcyclohexene was measured at 25% completion and, depending on the system,

varied from 73.3 to 0%. Benzene proved to be a strong isomerization inhibitor. Regardless of solvent and catalyst, isomerization fell in the order **12** ≫ **13** ≃ **14**.



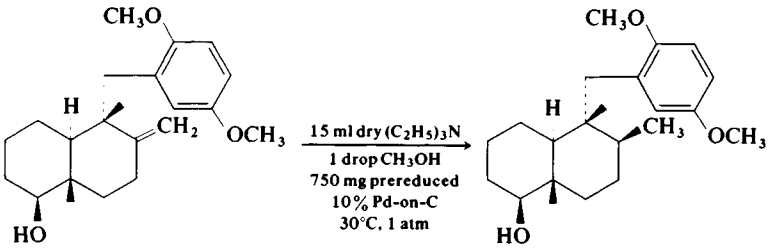
Regardless of substrate and solvent, isomerization fell in the order 5% Pd-on-C ≫ 5% Rh-on-C > 5% Pt-on-C, and, regardless of substrate or catalyst, isomerization fell with solvent in the order ethanol > pentane > 1:1 benzene–ethanol. Benzene is effective as an isomerization inhibitor mixed with other solvents as well; 1:20 benzene–acetone showed marked inhibition. Substituted benzenes are less effective than benzene.

2.2. Consequences of Double-Bond Migration

Double-bond migration often passes unnoticed, for unless tracers are employed, there may be no direct evidence remaining that migration has occurred. Nonetheless, the fact that it does occur can have a number of important consequences. Selective removal of cis homoconjugated dienes and trienes in natural oils, used to make edible hydrogenated fats, depends mainly on prior isomerization of multiple unsaturation into conjugation under hydrogenation conditions (*39*).

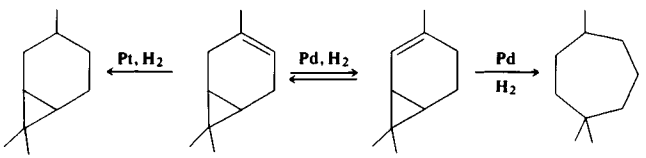
A common consequence of migration in complex molecules is that tetrasubstituted olefins result, which can be hydrogenated only with difficulty, if at all. It is easier to try to prevent hindered olefin formation than it is to correct it. Attempted hydrogenation of the exocyclic methylene group in **15** proved difficult when using an aged 10% Pd-on-C catalyst; there was a

complete isomerization of the exo double bond to the more hindered endocyclic position. The hydrogenation was achieved successfully with a large amount of 10% Pd-on-C in triethylamine containing a small amount of methanol. A quantitative yield of a mixture of epimeric methyl derivatives (**16**) was obtained in 85:15 ratio. The major isomer had the secondary methyl function in the equatorial (β) configuration; hydrogen had added from the less hindered face (*95*).

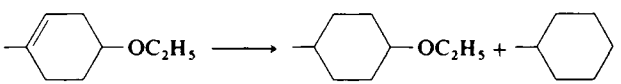


(**15**) (**16**)

Compounds that have no easily hydrogenolyzable function may lose that function, nonetheless, as a consequence of its becoming allylic or vinylic during the hydrogenation. Carene-3, which contains a nonconjugated cyclopropyl ring, gives mainly 1,1,4-trimethylcycloheptane on reduction over palladium, a result of isomerization to the conjugated 2-carene. Platinum, which has a low isomerization activity, gives high yields of carane (*29*).



Another example is the hydrogenation of the homoallylic compound 4-methyl-3-cyclohexenyl ethyl ether to a mixture of 4-methylcyclohexyl ethyl ether and methylcyclohexane. The extent of hydrogenolysis depends on both the isomerizing and the hydrogenolyzing tendencies of the catalysts. With unsupported metals in ethanol, the percent hydrogenolysis decreased in the order palladium (62.6%), rhodium (23.6%), platinum (7.1%), iridium (3.9%), ruthenium (3.0%) (*83*).



The cis ether was always formed in greater amounts than the trans, but the cis–trans ratio varied considerably with the metal [Pd (2.0), Ru (3.0), Rh (4.0), Ir (4.4), Pt (5.2)].

Unsaturated alcohols may be converted to saturated carbonyl compounds as a result of migration (*75*). When migration relative to saturation is high, the isomerization gains synthetic utility (*9,49*).

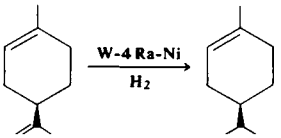
Olefins contained in an incipient aromatic system may be especially prone to migration, aromatization providing the driving force (*87,109*). Aromatization may occur even if a carbon–oxygen (*27*) or a carbon–carbon bond (*8,76*) need be broken in the process. Disproportionation is a special form of migration in which, in essence, a double bond migrates from one molecule to another, producing an aromatic and a hydroaromatic compound from the same olefinic substrate. Palladium is probably always the catalyst of choice when aromatization is wanted (*26,54*). Homogeneous catalysts, $(Ph_3P)_3RhCl$, are useful when aromatization is to be avoided (*11*).

2.3. Selective Reductions of Olefins

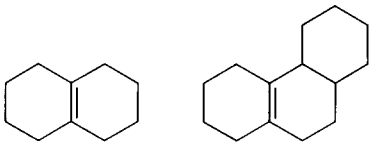
Most problems concerned with olefin hydrogenation involve the competitive hydrogenation of a double bond in the presence of another double bond or other function. There is usually a way of achieving the desired selectivity.

2.3.1. Dienes and Polyenes

Several generalities can be formulated regarding selective reduction of polyolefins. Usually the least hindered double bond is hydrogenated preferentially (*123*), and, with steric hindrance about equal, the most strained bond will be reduced first. Exocyclic olefins are reduced more easily than those in the ring. (*R*)-(+)-Limonene, 190 g, was shaken with W-4 Raney nickel (12 g) under hydrogen at atmospheric pressure. After 31.9 l of hydrogen had been absorbed, the solution was filtered. Essentially, pure (*R*)-(+)-carvomenthene was obtained in 96% yield (*58*).



In judging hindrance, it is useful to view the molecule in its three-dimensional, folded configuration. For instance, **17** can be reduced without undue difficulty, whereas **18** requires extreme conditions (Raney Ni, 200°C, 200 atm) (*1*), a difference not expected from planar representations of the molecule. Saturation of $\Delta^{9,10}$-octalin (**17**) may largely go through a prior isomerization to $\Delta^{1,9}$-octalin, despite an unfavorable equilibrium (*121*).



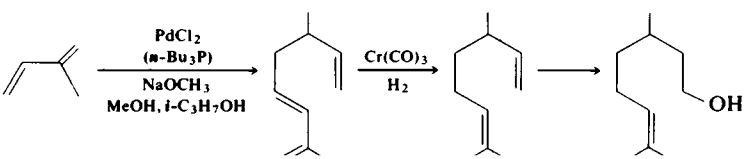
(17) **(18)**

Selectivity depends importantly on the catalytic metal. A number of selectivity series have been determined for simple olefins, and the presumption is that the sequence holds for more complex polyenes as well. Selectivity for the reduction of allene to propylene declined with metal in the order palladium > rhodium ≃ platinum > ruthenium > osmium ≫ iridium (*17*). Allenes with terminal bonds are selectively reduced in the terminal position (*37,45*).

Selective reduction of conjugated diolefins, such as 1,3-pentadiene, falls with metal in the sequence palladium > rhodium > ruthenium ≳ platinum > iridium (*18*). Selective reduction of homoconjugated diolefins, such as found in naturally occurring fatty acids, falls with metal in the order palladium > rhodium > platinum > ruthenium > iridium (*125*). This latter sequence results as a combination of the relative tendencies of metals to induce conjugation through double-bond migration, and of the selectivity order for conjugated dienes.

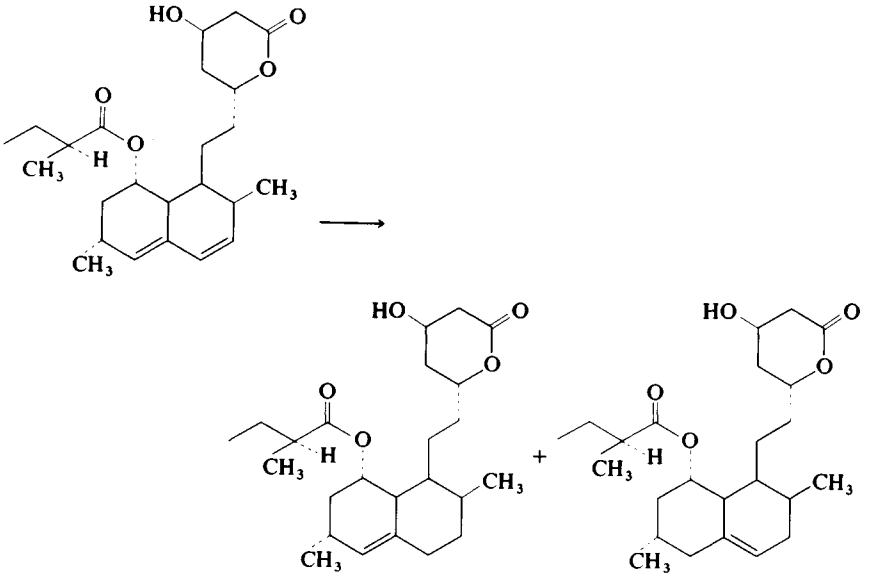
In reductions of dienes to monoenes, it is important to monitor the hydrogen consumed and to stop the reduction at the stoichiometric point; few reductions will stop spontaneously.

Tricarbonylchromium complexes are useful for 1,4-addition of hydrogen to 1,3-dienes to afford monoenes selectively (*40,42,43,44*). With 1,4-dienes, isomerization into conjugation precedes hydrogenation. Isolated double



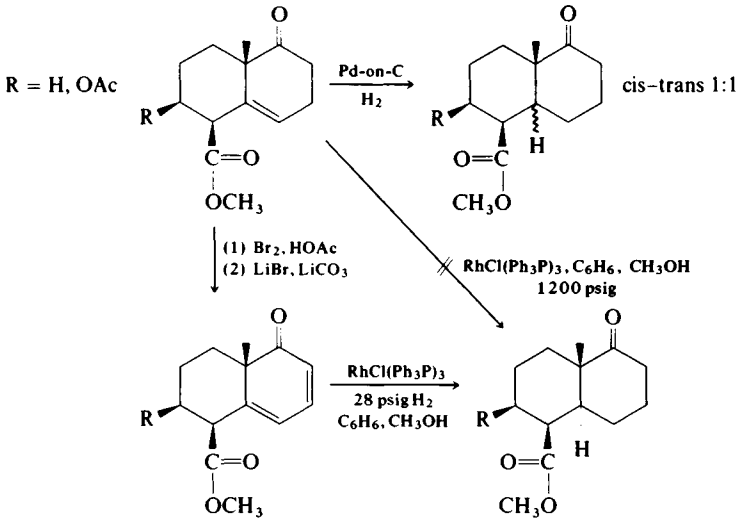
bonds are untouched as illustrated in the synthesis of citronellol from isoprene (*50*). Methyl benzoate–$Cr(CO)_3$, prepared according to King (*62*), was used under elevated pressures (30 atm) and temperatures ($\sim 150°C$). To minimize decomposition of the catalyst, it is important to flush the system with nitrogen and to purge the autoclave repeatedly with hydrogen before heating (*41*).

Appropriate choice of catalyst permitted formation of either of two dihydro derivatives of mevinolin in high yield (*67*). Hydrogenation of mevinolin over platinum oxide in ethyl acetate gave the tetrahydro derivative as a 1:3 mixture of *cis*- and *trans*-decalin isomers.

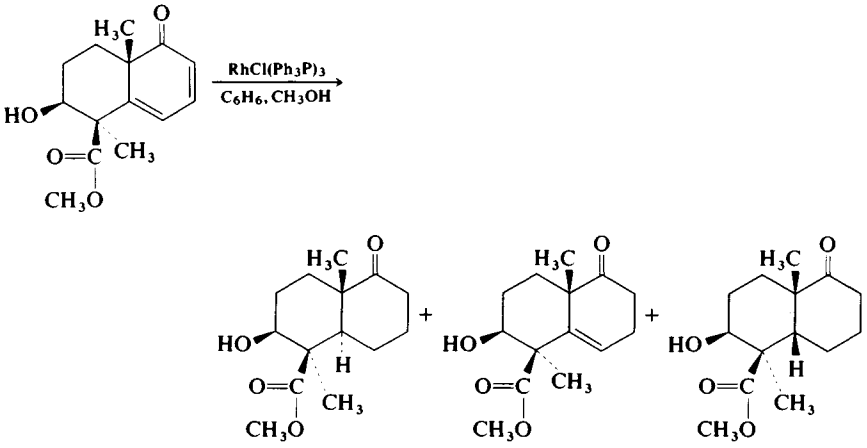


Catalyst and solvent	90% minor	10% major or exclusive
$(Ph_3P)_3RhCl$, $PhCH_3$		
5% Pd-on-$CaCO_3$, EtOH		

Dienes can sometimes be completely saturated under conditions where a monoene is not reduced, as illustrated by the data of Reuvers and deGroot (*91*). In fact, the monoene was still inert at 1200 psig, whereas the diene could be reduced at 28 psig.



In this series both regio- and stereochemistry are markedly influenced by relatively small pressure changes, as illustrated by selected examples (*91*).

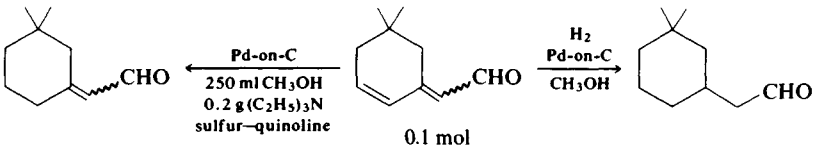


Pressure (psi)	Percentage		
24	37	63	—
60	87	13	—
150	70	20	10
230	30	40	30

2.3.2. Unsaturated Carbonyl Compounds

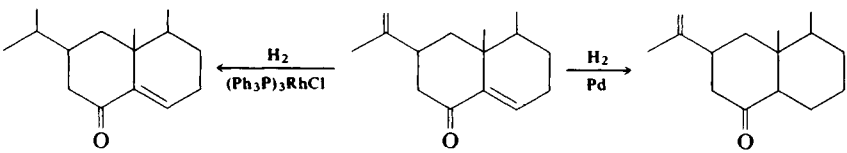
Reduction of unsaturated carbonyl compounds to the saturated carbonyl is achieved readily and in high yield. Over palladium the reduction will come to a near halt except under vigorous conditions (*73*). If an aryl carbonyl compound, or a vinylogous aryl carbonyl, such as in cinnamaldehyde is employed, some reduction of the carbonyl may occur as well. Carbonyl reduction can be diminished or stopped completely by addition of small amounts of potassium acetate (*35*) to palladium catalysts. Other effective inhibitors are ferrous salts, such as ferrous sulfate, at a level of about one atom of iron per atom of palladium. The ferrous salt can be simply added to the hydrogenation solution (*94*). Homogeneous catalysts are not very effective in hydrogenation of unsaturated aldehydes because of the tendencies of these catalysts to promote decarbonylation.

Of greater challenge is the selective hydrogenation of those carbonyl compounds having two or more double bonds. Sometimes conditions can be adjusted so that either or both double bonds can be reduced at will. Quantitative yields of either **19** or **21** could be obtained by hydrogenation of **20** with appropriate use of modifiers (*114*).



(19) **(20)** **(21)**

Homogeneous catalysts are useful in this type problem. The conjugated double bond of eremophilone (**22**) was reduced preferentially over a variety of heterogeneous palladium catalysts to (**23**), whereas 13, 14-dihydroeremophilone (**24**) was obtained on reduction with $(Ph_3P)_3RhCl$ (*23*). A solution of 0.102 g **22** and 0.07 g $(Ph_3P)RhCl$ was stirred in 15 ml benzene for 8 h under 1 atm hydrogen. Yield of **24** was 94%.



(24) **(22)** **(23)**

Selective conversion of 1,4-androstadiene-3,17-dione to 4-androsten-3,17-dione was achieved with $(Ph_3P)_3RuCl_2$ (*81*), prepared by refluxing ruthenium

chloride hydrate in ethanol with triphenylphosphine (*107*). Selectivity to 4-androsten-3,17-dione varied with pressure ranging from 66% at 10 atm to 92% at 162 atm. Reaction virtually ceases after absorption of 1 mol of hydrogen. Ligands carrying *p*-methoxy and *p*-methyl substituents greatly enhance activity, when used in the presence of base (*84*). Other selective homogeneous reductions of 3-oxo-1,4-diene steroids have used $(Ph_3P)_3RhCl$ (*15,32,34*). Heterogeneous catalysts, 10% palladium-on-carbon (*119*) and prereduced ruthenium dioxide (*111*) are also effective in these selective reductions. In dienes of this type, selectivity is influenced by the structure as a whole. For instance, substituents at position 11 may interfere with coordination of the catalysts to the 1,2 double bond and sharply lessen discrimination (*122*).

Selective hydrogenation of 3-oxo-4-ene and -1,4-diene steroids is a convenient and widely used route to 5β-steroids (*4,5*). Palladium catalysts are usually used. Stereoselectivity depends on the reaction solvent; lower alcohols with potassium hydroxide, pyridine, acetic acid, or preferably, tetrahydrofuran with hydrobromic acid have favored formation of 5β-compounds. Pyridine has been generally the most useful, but even it has given poor results. The use of 4-methoxypyridine has given excellent results whenever low yields were obtained in other solvents. It is an excellent solvent for steroids and permits hydrogenation to be done at high concentrations (*115*). After a comparison with other bases, the authors concluded that the nucleophilicity of nitrogen bases, rather than their pK_as, is an important factor in determining 5β-content (*115*). Solvent effects are also influenced by substituents remote from the unsaturation (*85*).

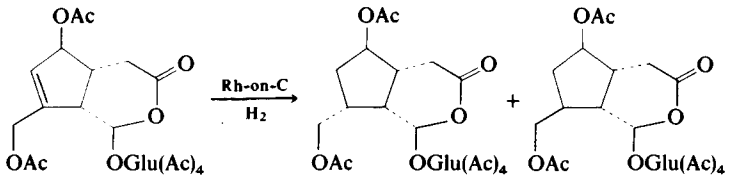
2.4. Vinylic and Allylic Functions

Reduction of vinylic and allylic compounds without hydrogenolysis may present a problem. The ratio of olefin saturation to hydrogenolysis depends importantly on catalyst, temperature, solvent, and pH. In both classes of compounds, hydrogenolysis is favored by polar solvents, acid, and elevated temperatures; hydrogenation, by nonpolar solvents and low temperatures.

In general, hydrogenolysis of vinylic compounds is favored by platinum and hydrogenation by ruthenium and rhodium (*31,55,59,72,106*). In the reduction of 4-methyl-1-cyclohexenyl ether, the order of decreasing hydrogenolysis to give methylcyclohexane was established as Pt $\gg$ Ir > Rh > Os $\gg$ Ru $\simeq$ Pd (*82*).

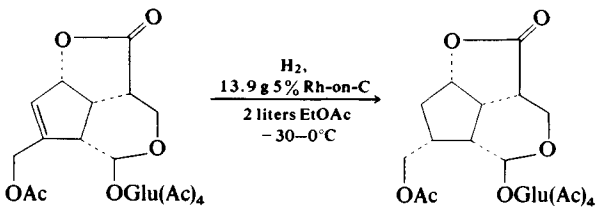
The order for decreasing hydrogenolysis of allylic functions appears to be Pd > Pt $\gg$ Rh $\simeq$ Ru. Hydrogenolysis of allylic functions over palladium may

occur through formation of a π-allyl complex (*3*). Attempted saturation of **25** over PtO_2 or Pd-on-C in acetic acid, ethanol, ethyl acetate, or dioxane–water gave extensive hydrogenolysis of the allylic acetate groups, but over 5% Rh-on-C in ethyl acetate a 1:1 mixture of **26** and **27** was obtained in 95% combined yield (*12*).



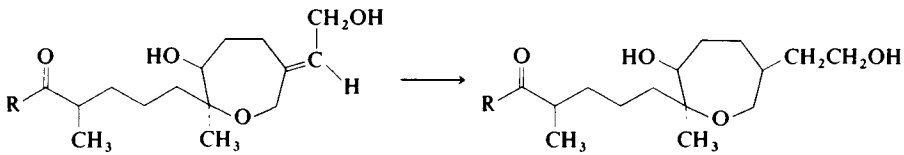
(25) **(26)** **(27)**

Hydrogenolysis can be diminished by reduction at low temperature. Hydrogenation of asperuloside tetraacetate (**28**) over 5% Rh-on-C in ethyl acetate at 25°C gave mainly **29** accompanied by several hydrogenolysis products, but by starting at −30°C and raising the temperature slowly to 0°C over 3 h, **29** was obtained quantitatively. The catalyst was reusable at least three times (*13*).



(28) **(29)**

A difficult reduction was achieved smoothly over an unusual system (PtO_2, $NaNO_2$), following Dart and Henbest (*33*), after many other catalysts had failed (*69*). Reduction of zoapatanol (**30**) over PtO_2–$NaNO_2$ gave **31**, whereas over Pd-on-C, hydrogenolysis of the allylic oxygens was extensive (*70*).

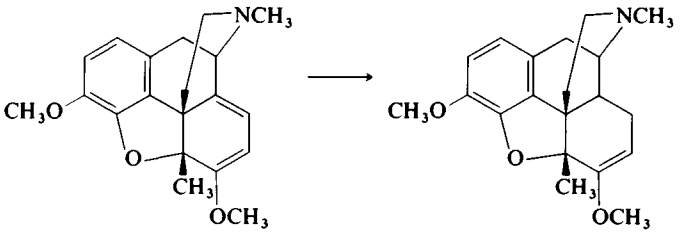


(30) **(31)**

R = $(CH_3)_2C{=}CHCH_2$ R = $(CH_3)_2CHCH_2CH_2$

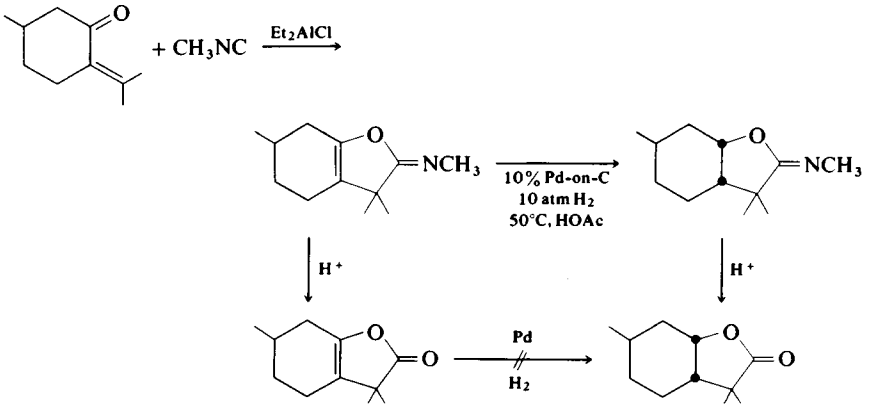
Dart and Henbest (*33*) demonstrated that the amount of salts remaining in platinum oxide catalysts had an important bearing on the hydrogenation–hydrogenolysis ratio of allylic functions. Hydrogenolysis is inhibited by salts remaining from the catalyst preparation or by salts such as sodium nitrite, cyanide, or hydroxide added later.

Steric hindrance around an allylic function will diminish its hydrogenolysis as access of the function to the catalyst surface is impeded. Reduction of 5-methylthebaine (**32**) proceeds smoothly over Pd-on-C in ethanol at 1 atm to afford 5-methyldihydrothebaine (**33**), whereas reduction of thebaine itself is less clean and gives dihydrothebainol, dihydrothebainone, and dihydrothebaine (*16*).

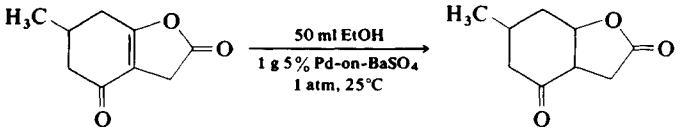


(**32**) (**33**)

Tetrasubstituted double bonds frequently are difficult to reduce, but in the following such a bond was readily reduced even though it contained a vinylic oxygen. A general stereoselective synthesis of γ-butyrolactones involves 1,4-cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides, catalyzed by diethylaluminum chloride, to afford unsaturated N-substituted iminolactones. These are stereoselectively hydrogenated by palladium-on-carbon and then acid hydrolyzed. If hydrolysis precedes hydrogenation, the resulting unsaturated lactone is very difficult to reduce (*57*).



Similar lactones (**34**) have been reduced over Pd-on-$BaSO_4$ to the dihydro derivative (**35**) in high yield (*36*), perhaps facilitated by 1,4-addition.

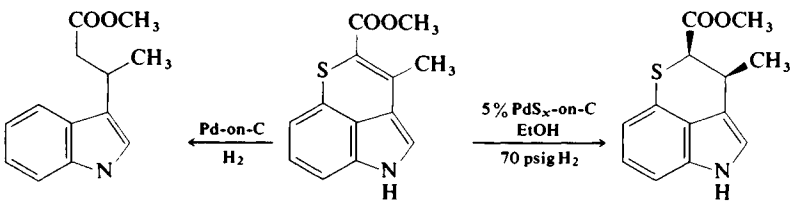


(**34**) (**35**)

2.5. Olefinic Sulfur Compounds

Olefins containing divalent sulfur can be expected to be reduced slowly, since divalent sulfur is a strong inhibitor for hydrogenation catalysts. On the other hand, oxidized sulfur is not, and materials such as sulfuric acid and dimethyl sulfoxide can be excellent solvents for hydrogenation. Olefins with divalent sulfur can be reduced satisfactorily but will require high catalyst loading and lengthy reduction times. Usually palladium-on-carbon is employed in these reductions (*71,80,88,89,98,110*).

A remarkably effective reduction of a complex vinyl sulfide was achieved (*65*) in a synthesis leading to the antibiotic alkaloid chuangxinmycin. Compound **36** would be expected to be converted to **37** only with great difficulty. The double bond is tetrasubstituted and is a vinylogous amide, structures known to be difficult to reduce. The sulfur atom would be expected to inhibit the catalyst and the compound is susceptible to hydrogenolysis. Indeed, a variety of catalysts and reducing agents failed to give any **37**. Palladium-on-carbon gave the desulfurized indole (**38**). However, success was achieved with 5% PdS_x-on-C producing a single product. Under mild conditions, this catalyst has low activity at best, and very high catalyst loadings and patience were required for success. This catalyst, as well as PtS_x-on-C and RhS_x-on-C, have often proved effective when hydrogenolysis was to be avoided.

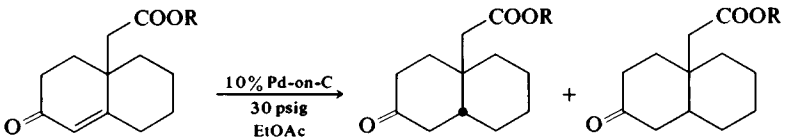


(**38**) (**36**) (**37**)

2.6. Stereochemistry

The stereoisomers of olefin saturation are often those derived by cis addition of hydrogen to the least hindered side of the molecule (*99*). But there are many exceptions and complications (*97*), among which is the difficulty of determining which side of the molecule is the least hindered. Double-bond isomerization frequently occurs, and the hydrogenation product is the resultant of a number of competing reactions. Experimentally, stereochemistry has been found to vary, sometimes to a marked degree, with olefin purity, reaction parameters, solvent, and catalyst (*30,100*). Generalizing, it is expedient, when unwanted products arise as a result of prior isomerization, to avoid those catalysts and conditions that are known to favor isomerization.

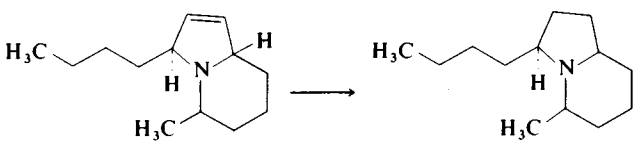
Some olefinic molecules have a second function that anchors itself on the catalyst surface in such a way so as to enforce addition of hydrogen to its own side of the molecule. This anchoring effect, dubbed haptophilicity (*112,113*), has been observed by many investigators (*10,19,74,78,90,120*). An example of Gula and Spencer (*47*) illustrates how the anchoring tendencies of a function remote from the point of saturation may influence the stereochemistry.



R = K	100%	0
R = CH_3	61%	25%

Stereochemistry can be influenced strongly by both catalyst and nonbonded interaction between an oxygen lone pair and nonadjacent π electrons, as illustrated by selected data of Ishiyama *et al.* (*56*) (Table 2).

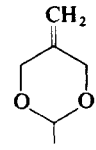
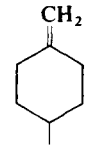
Involvement of a center remote from the point of saturation has also been demonstrated in another connection. Hydrogenation of a stereoisomeric mixture of dehydro alkaloids over PtO_2 in acetic acid produced only a single alkaloid. The phenomenon appears general for related 3,5-dialkyl-$\Delta^{3,4}$-dehydroindolizidine alkaloids.



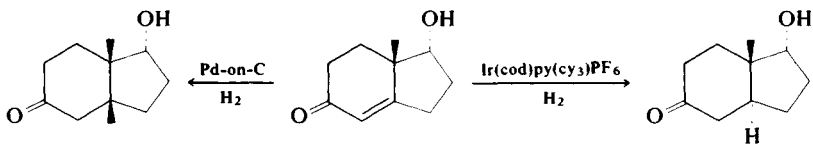
Stork and Kahne (*108*) have demonstrated remarkable stereochemical control in the hydrogenation of a series of cyclohexenols containing allylic

TABLE 2

Percentage cis Isomer Resulting from Hydrogenation

Catalyst		
Raney Co	73	37
Raney Ni	89	45
Ru-on-C	88	77
Rh-on-C	87	61
Pd-on-C	90	26
Ir-on-C	76	66
Pt-on-C	84	64
PtO_2	98	64

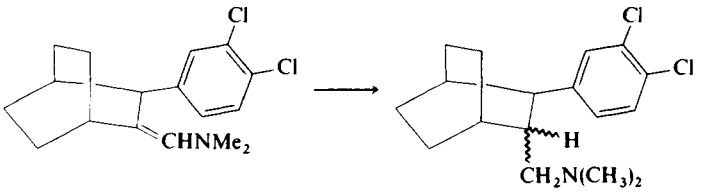
and homoallylic double bonds, using $Ir(cod)py(Pcy_3)PF_6$.* This catalyst was chosen because it has two sites available for coordination with a bidentate substrate and because it was known to reduce trisubstituted double bonds. Reduction of **40** over 5% Pd-on-C gave the *cis*-indanone **39** almost exclusively, a result characteristic of indenones, whereas in reduction over $Ir(cod)py(Pcy_3)PF_6$ the *trans*-indanone **41** formed in high yield, a result attributable to the oppositely placed hydroxy group.



(39) (40) (41)

Solvents and pH may have a marked effect on stereochemistry as was illustrated in Chapter 1, and the generality given there is useful. A further example of the stereochemical influence that may be exerted by proper choice of catalyst and solvent is shown in the hydrogenation of a complex enamine. By proper choice of conditions high yields of either the *cis* or *trans* product could be obtained. Selected results are shown below (*52*) (data used with permission).

* cod = 1,5-cyclooctadiene, cy = cyclohexyl, py = pyridine.



Catalyst	Solvent	Ratio (%) cis	Ratio (%) trans	Isolated yields of amines (%)
5% Pd-on-C	Benzene	0	100	99
5% Pd-on-C	Ethanol	0	100	99
PtO_2	Benzene	0	100	—
PtO_2	Ethanol	92	8	59
PtO_2	Ethyl Acetate	95	5	38
PtO_2	Isopropanol	98	2	39

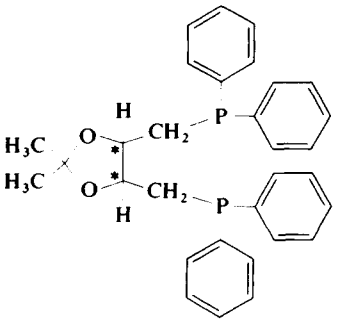
This was the first investigation of stereoselective formation of geometric isomers of tertiary amines. The authors suggested most enamine systems should be subject to considerable stereochemical control.

2.6.1. Asymmetric Hydrogenation of Olefins

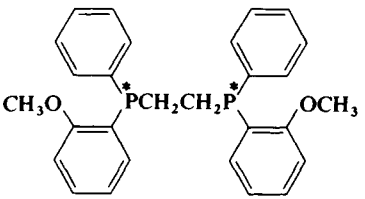
Asymmetric hydrogenation of olefins has not been highly stereoselective except in the synthesis of amino acids and closely related compounds (*21,22,24,38,60,116*), an area in which enantiomeric excesses approaching 100% have been obtained. The medically important compound, L-Dopa (3,4-dihydroxyphenylalanine) is so obtained by hydrogenation over a homogeneous, chiral rhodium–phosphorus complex. Usually the best optical yields are obtained with a chelating diphosphine ligand, where chirality may reside in the coordinating phosphorus atom, such as DIPAMP, or in a substituent or backbone carbon, such as in DIOP and BPPM (*61,63,64,116*).

Wide variations in stereoselectivity are possible between the *E* and *Z* isomers (*79*). In hydrogenation of several (*E*)- and (*Z*)-α-acylaminocinnamic acid derivatives, the *Z* isomers gave greater enantiomeric excesses at 15–100 times the rate of reduction of the *E* isomer, but in all cases the *S* enantiomer was formed in greater excess (*117*). The greater effectiveness of *Z*-olefins is general (*118*).

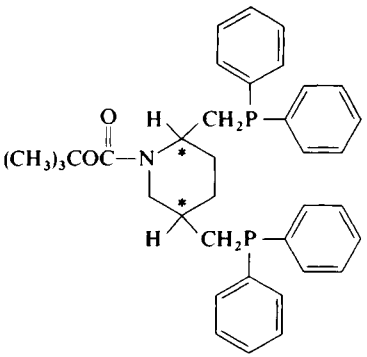
Stereoselectivity may be influenced strongly by both temperature and pressure. In general, the optical yield is decreased with increasing pressure, and at high pressures (50 atm) the predominant product chirality actually has been



DIOP



DIPAMP



BPPM

reversed (*86*). Perhaps running counter to intuition, optical yields may fall with decreasing temperature and increase with increasing temperature (*48*); in one case, optical yield rose from 0 to 60% in going from 0 to 100°C (*102*).

The origin of the remarkable stereoselectivities displayed by chiral homogeneous catalysts has occasioned much interest and speculation. It has been generally assumed, using a lock-and-key concept, that the major product enantiomer arose from a rigid preferred initial binding of the prochiral olefin with the chiral catalyst. Halpren (*48*) on the basis of considerable evidence, reached the opposite conclusion; the predominant product enantiomer arises from the minor, less stable diastereomer of the olefin–catalyst adduct, which frequently does not accumulate in sufficient concentration to be detected. The predominant adduct is in essence a "dead-end" complex for it hydrogenates at a much slower rate than does the minor adduct.

Homogeneous catalysts may also be effective in the hydrogenation of sulfur-containing compounds. (*Z*)-2-Benzamide(acetamido)-3-(2-thienyl)-2-propenoic acid was reduced in 100% yield and 78% enantiomeric excesses over Rh(I)–DIOP catalysts (*25*).

References

1. A. A. Allen and F. Kurzer, *Tetrahedron* **34,** 1261 (1978).
2. M. Ando, A. Akahane, H. Yamaoka, and K. Takase, *J. Org. Chem.* **47,** 3909 (1982).
3. K. Annen, R. Tschesche, and P. Welzel, *Ber. Dtsch. Chem. Ges.* **106** (2), 576 (1973).
4. R. L. Augustine, "Organic Reactions in Steroid Chemistry" (J. Fried and J. A. Edwards, eds.), Vol. 1. Van Nostrand Reinhold, New York, 1972.
5. R. L. Augustine, *Adv. Catal.* **25,** 56 (1976).
6. R. L. Augustine, V. Nocito, J. Van Peppen, R. Warner, and F. Yaghmaie, *in* "Catalysis in Organic Syntheses" (W. H. Jones ed.), p. 173. Academic Press, New York 1980.
7. R. L. Augustine, F. Yaghmaie, and J. F. Van Peppen, *J. Org. Chem.* **49,** 1865 (1984).
8. R. Baird and S. Winstein, *J. Am. Chem. Soc.* **79,** 4238 (1957).
9. M. F. Barnes and J. MacMillian, *J. Chem. Soc.*, 361 (1967).
10. P. Beak and T. L. Chaffin, *J. Org. Chem.* **35,** 2275 (1970).
11. R. A. Benkeser, F. G. Belmonte, and J. Kang, *J. Org. Chem.* **48,** 2796 (1983).
12. W. F. Berkowitz, I. Sasson, P. S. Sampathkumar, J. Hrable, S. C. Choudhry and D. Pierce, *Tetrahedron Lett.*, 1641 (1979).
13. W. F. Berkowitz, S. C. Choudhry, and J. A. Hrabie, *J. Org. Chem.* **47,** 824 (1982).
14. J. F. Biellmann and M. J. Jung, *J. Am. Chem. Soc.* **90,** 1673 (1968).
15. A. J. Birch and K. A. M. Walker, *J. Chem. Soc. C*, 1894 (1966).
16. R. M. Boden, M. Gates, S. P. Ho, and P. Sundararaman, *J. Org. Chem.* **47,** 1347 (1982).
17. G. C. Bond and P. B. Wells, *Adv. Catal.* **15,** 92 (1964).
18. G. C. Bond and J. C. Rank, *Proc. Int. Congr. Catal. 3rd, 1964* **2,** 1225 (1965).
19. B. Bosnich and M. D. Fryzuk, *Top. Stereochem.* **12,** 119 (1981).
20. W. E. Brower, Jr., M. S. Matyjaszczyk, T. L. Pettit, and G. V. Smith, *Nature (London)* **301,** 497 (1983).
21. J. M. Brown and D. Parker, *J. Org. Chem.* **47,** 2722 (1982).
22. J. M. Brown and D. Parker, *Organometallics* **1,** 950 (1982).
23. M. Brown and L. W. Piszkiewicz, *J. Org. Chem.* **32,** 2018 (1967).
24. J. M. Brown, P. A. Chaloner, B. A. Murrer, D. Parker, *A.C.S. Symp. Ser.* **119,** 169–194 (1980).
25. C. Cativiela, J. Fernandez, J. A. Mayoral, E. Melendez, R. Uson, L. A. Oro, and M. J. Fernandez, *J. Mol. Catal.* **16,** 19 (1982).
26. S. A. Cerefice and E. K. Fields, *J. Org. Chem.* **39,** 971 (1974).
27. J. L. Chitwood, P. G. Gott, and J. C. Martin, *J. Org. Chem.* **36,** 2216 (1971).
28. E. Ciganek, *J. Org. Chem.* **45,** 1505 (1980).
29. W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C*, 41 (1966).
30. E. Cooke, T. C. Paradellis, and J. T. Edward, *Can. J. Chem.* **60,** 29 (1982).
31. R. C. Cookson, D. P. G. Hamon, and R. E. Parker, *J. Chem. Soc.*, 5014 (1962).
32. N. S. Crossley and R. Dowell, *J. Chem. Soc. C* 2496 (1971).
33. M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
34. C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.* **88,** 4537 (1966).
35. M. Dunkel, D. J. Eckhardt, and A. Stern, U.S. Patent No. 3,520,934 (1970).
36. T. A. Eggelte, J. J. J. deBoer, H. deKoning, and H. O. Huisman, *Synth. Commun.* **8,** 353 (1978).
37. G. Eglinton, E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 3197 (1954).
38. J. C. Fiaud, A. Hibon deGournay, M. Larcheveque, and H. B. Kagan, *J. Organomet. Chem.* **154,** (2) 175 (1978).

39. E. N. Frankel, *in* "Topics in Lipid Chemistry" (F. D. Gunstone, ed.), p. 6. Logan Press, London 1970.
40. E. N. Frankel, *in* "Catalysis in Organic Syntheses" (W. H. Jones, ed.), p. 185. Academic Press, New York, 1980.
41. E. N. Frankel and R. O. Butterfield, *J. Org. Chem.* **34,** 3930 (1969).
42. E. N. Frankel and F. L. Little, *J. Am. Oil Chem. Soc.* **46,** 256 (1969).
43. E. N. Frankel, E. Selke, and C. A. Glass, *J. Org. Chem.* **34,** 3936 (1969).
44. E. N. Frankel, F. L. Thomas, and J. C. Cowan, *J. Am. Oil Chem. Soc.* **47,** 497 (1970).
45. E. J. Glamkowski, G. Gal, R. Purick, A. J. Davidson, and M. Sletzinger, *J. Org. Chem.* **35,** 3510 (1970).
46. I. V. Gostunskaya, V. S. Petrova, A. I. Leonava, V. A. Mironava, M. Abubaker, and B. A. Kazanski, *Neftekhimiya* **7**(1), 3 (1967).
47. M. J. Gula and T. A. Spencer, *J. Org. Chem.* **45,** 805 (1980).
48. J. Halpren, *Science* **217,** 401 (1982).
49. W. Herz, K. Ueda, and G. Inayama, *Tetrahedron* **19,** 483 (1963).
50. M. Hidai, H. Ishiwatari, H. Yagi, E. Tanaka, K. Onozawa, and Y. Uchida, *J.C.S. Chem. Commun.*, 170 (1975).
51. I. Horiuti and M. Polanyi, *Trans. Faraday Soc.* **30,** 1164 (1934).
52. D. C. Horwell and G. H. Timms, *Synth. Commun.* **9,** 223 (1979).
53. W. D. Huntsman, W. L. Madison, and S. I. Schlesinger, *J. Catal.* **2,** 498 (1963).
54. A. S. Hussey, T. A. Schenach, and R. H. Baker, *J. Org. Chem.* **33,** 3258 (1968).
55. H. H. Inhoffen, G. Stoeck, G. Kolling, and U. Stoech, *Justus Liebigs Ann. Chem.* **568,** 52 (1950).
56. J.-I. Ishiyama, Y. Senda, and S. Imaizumi, *J.C.S. Perkin Trans. 2*, 71 (1982).
57. Y. Ito, H. Kato, and T. Saegusa, *J. Org. Chem.* **47,** 741 (1982).
58. L. M. Jackman, R. L. Webb, and H. C. Yick, *J. Org. Chem.* **47,** 1824 (1982).
59. H. I. Jacobson, M. J. Griffin, S. Preis, E. V. Jensen, *J. Am. Chem. Soc.* **79,** 2608 (1957).
60. H. B. Kagan, *Pure Appl. Chem.* **43,** 401 (1975).
61. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.* **10,** 175 (1978).
62. R. B. King, "Organometallic Syntheses," Vol. I, pp. 123, 136. Academic Press, New York, 1965.
63. W. S. Knowles, B. D. Vineyard, M. I. Sabacky, and B. R. Stults, *in* "Fundamental Research in Homogeneous Catalysis" (M. Tsutsui, ed.), Vol. 3, p. 537. Plenum, New York, 1979.
64. W. E. Koenig, *Ann. N.Y. Acad. Sci.* **333,** 16 (1980).
65. A. P. Kozikowski and M. N. Greco, *J. Am. Chem. Soc.* **102,** 1165 (1980).
66. A. P. Kozikowski, M. N. Greco, and J. P. Springer, *J. Am. Chem. Soc.* **104,** 7622 (1982).
67. C. H. Kuo, A. A. Patchett, and N. L. Wendler, *J. Org. Chem.* **49,** 1991 (1983).
68. M. J. Ledoux and F. G. Gault, *J. Catal.* **60,** 15 (1979).
69. S. D. Levin, personal communication (1980).
70. S. D. Levin, R. E. Adams, R. Chen, M. L. Cotter, A. F. Hirsch, V. V. Kane, R. M. Kanojia, C. Shaw, M. P. Wachter, E. Chin, M. Huettemann, P. Ostrowski, J. L. Mateos, L. Noriega, A. Guzman, A. Mijarez and L. Tovar, *J. Am. Chem. Soc.* **101,** 3404 (1979).
71. J. H. Markgraf, B. A. Hess, Jr., C. W. Nichols, and R. W. King, *J. Org. Chem.* **29,** 1499 (1964).
72. J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *J. Org. Chem.* **31,** 943 (1966).
73. T. C. McMorris, P. H. Le, M. W. Preus, S. R. Schow, and G. R. Weihe, *J. Org. Chem.* **48,** 3370 (1983).
74. J. E. McMurry, *Tetrahedron Lett.*, 3731 (1970).
75. F. J. McQuillin, *Tech. Org. Chem.* **9,** 498 (1963).
76. B. Miller and L. Lewis, *J. Org. Chem.* **39,** 2605 (1974).
77. R. Mohan and J. A. Katzenellenbogen, *J. Org. Chem.* **49,** 1238 (1984).

78. K. Mori, K. Abe, M. Washida, S. Nishimura, and M. Shiota, *J. Org. Chem.* **36,** 231 (1971).
79. J. D. Morrison, W. F. Masler, and M. K. Neuberg, *Adv. Catal.* **25,** 81 (1976).
80. R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, Jr., N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.* **67,** 2092 (1945).
81. S. Nishimura and K. Tsuneda, *Bull. Chem. Soc. Jpn.* **42,** 852 (1969).
82. S. Nishimura, M. Katagiri, T. Watanabe and M. Uramoto, *Bull. Chem. Soc. Jpn.* **44,** 166 (1971).
83. S. Nishimura, M. Uramoto, and T. Watanabe, *Bull. Chem. Soc. Jpn.* **45,** 216 (1972).
84. S. Nishimura, T. Ichino, A. Akimoto, and K. Tsuneda, *Bull. Chem. Soc. Jpn.* **46,** 279 (1973).
85. S. Nishimura, Y. Momma, H. Kawamura, and M. Shiota, *Bull. Chem. Soc. Jpn.* **56,** 780 (1983).
86. I. Ojima, T. Kogure, and N. Yoda, *J. Org. Chem.* **45,** 4728 (1980).
87. I. J. Pachter, R. F. Raffauf, G. E. Ullyot, and O. Ribeiro, *J. Am. Chem. Soc.* **82,** 5187 (1960).
88. W. E. Parham and S. H. Groen, *J. Org. Chem.* **29,** 2214 (1964).
89. W. E. Parham, T. M. Roder, and W. R. Hasek, *J. Am. Chem. Soc.* **75,** 1647 (1953).
90. R. G. Powell, R. V. Madrigal, C. R. Smith, Jr., and K. L. Mikolajczak, *J. Org. Chem.* **39,** 676 (1974).
91. J. T. A., Reuvers and A. deGroot, *J. Org. Chem.* **49,** 1110 (1984).
92. H. Ruesch and T. J. Mabry, *Tetrahedron* **25,** 805 (1969).
93. P. N. Rylander, *Adv. Chem. Ser.* **98,** 150 (1971).
94. P. N. Rylander and N. Himelstein, *Engelhard Ind. Tech. Bull.* **4,** 131 (1964).
95. A. S. Sarma and P. Chattopadhyay, *J. Org. Chem.* **47,** 1727 (1982).
96. G. A. Schiehser and J. D. White, *J. Org. Chem.* **45,** 1864 (1980).
97. R. K. Sehgal, R. U. Koenigsberger, and T. J. Howard, *J. Org. Chem.* **40,** 3073 (1975).
98. J. C. Sheehan and C. W. Beck, *J. Am. Chem. Soc.* **77,** 4875 (1955).
99. S. Siegel, *Adv. Catal.* **16,** 123 (1966).
100. S. Siegel and J. R. Cozort, *J. Org. Chem.* **40,** 3594 (1975).
101. S. Siegel, J. Outlaw, Jr., and N. Garti, *J. Catal.* **60,** 15 (1979).
102. D. Sinou, *Tetrahedron Lett.* **22,** 2987 (1981).
103. G. A. Somorjai, *Acc. Chem. Res.* **9,** 248 (1976).
104. G. V. Smith, W. E. Brower, M. S. Matyjaszczyk, and T. L. Pettit, *Proc. Int. Congr. Catal. 7th 1980* (1980).
105. G. V. Smith, O. Zahraa, A. Molnar, M. M. Khan, B. Rihter, and W. E. Brower, *J. Catal.* **83,** 238 (1983).
106. P. Z. Smyrniotis, H. T. Miles, and E. R. Stadman, *J. Am. Chem. Soc.* **82,** 1417 (1960).
107. T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.* **28,** 945 (1966).
108. G. Stork and D. E. Kahne, *J. Am. Chem. Soc.* **105,** 1072 (1983).
109. H. H. Takimoto, G. C. Denault, and L. D. Krbechek, *J. Org. Chem.* **29,** 1899 (1964).
110. D. S. Tarbell and M. A. McCall, *J. Am. Chem. Soc.* **74,** 48 (1952).
111. B. D. Tiffany and M. A. Rebenstorf, *Ann. N.Y. Acad. Sci.* **172,** 253 (1970).
112. H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.* **95,** 6379 (1973).
113. H. W. Thompson, E. McPherson, and B. L. Lences, *J. Org. Chem.* **41,** 2903 (1976).
114. P. C. Traas, H. Boelens, and H. J. Takken, *Synth. Commun.* **6,** 489 (1976).
115. N. Tsuji, J. Suzuki, and M. Shiota, *J. Org. Chem.* **45,** 2729 (1980).
116. D. Valentine, Jr., and J. W. Scott, *Synthesis,* 329 (1978).
117. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.* **99,** 5946 (1977).
118. B. D. Vineyard, W. S. Knowles, and M. J. Sabacky, *J. Mol. Catal.* **19,** 159 (1983).
119. R. Vitali, G. Caccia, and R. Gardi, *J. Org. Chem.* **37,** 3745 (1972).

120. E. J. Warawa and J. R. Campbell, *J. Org. Chem.* **39,** 3511 (1974).
121. A. W. Weitkamp, *Adv. Catal.* **18,** 1 (1968).
122. P. Wieland and G. Anner, *Helv. Chim. Acta* **51,** 1698 (1968).
123. J. R. Williams, J. F. Callahan, and C. Lin, *J. Org. Chem.* **48,** 3162 (1983).
124. P. Yates and J. H. Hoare, *Can. J. Chem.* **61,** 1397 (1983).
125. M. Zajcew, *J. Am. Oil Chem. Soc.* **37,** 473 (1960).

- 3 -

Hydrogenation of Acetylenes

Acetylenes have high synthetic utility, and hydrogenation of the triple bond occurs in many reaction sequences (*1*). Often the goal of this reduction is formation of the cis olefin, which usually can be achieved in very high yields (for an exception, see Ref. *10*). Continued reduction gives the paraffin. Experimentally, both the relative and absolute rates of acetylene and olefin hydrogenation have been found to depend on the catalyst, substrate, solvent, reaction conditions, and hydrogen availability at the catalyst surface. Despite these complexities, high yields of desired product usually can be obtained without difficulty.

Acetylenes are, in general, much more strongly adsorbed than the corresponding olefin, and as long as the acetylene is present, it will occupy most of the catalyst sites and be reduced preferentially, regardless of the relative rates of the acetylene and olefin hydrogenation when not in competition for sites. The reduction

$$\text{acetylene} \longrightarrow \text{olefin} \longrightarrow \text{paraffin}$$

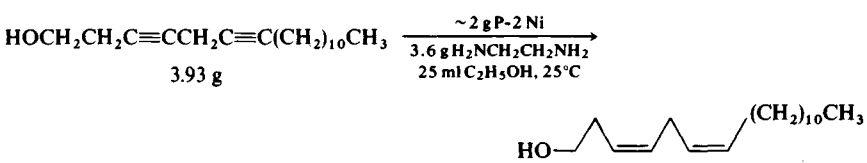
is, over selective metals, very largely sequential. The term molecular queuing has been used to describe the operation of a hierarchy of adsorbabilities (*19*).

3.1. Catalysts

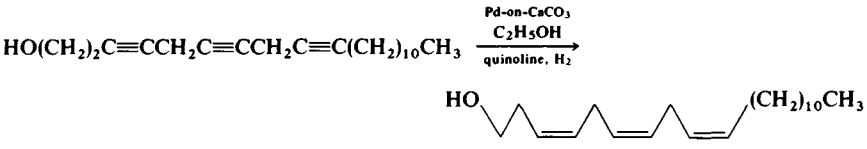
Many workers (*5,6,7,87*) have compared various metals for the selective hydrogenation of lower acetylenes to olefins, and it was always found that palladium was by far the most selective. This conclusion concurs with the usual synthetic experience, but under special circumstances other metals, such as platinum, may prove more useful (*35,63*). The catalyst support may also have an influence (*21,65*). Carbon, calcium carbonate, and barium sulfate are frequently used supports. Examples of some differences are noted later.

Highly stereospecific hydrogenations of acetylenes to cis olefins have been achieved also with nickel (P-2) catalysts in the presence of ethylenediamine as promoter (*37,38,55,58,72*). The catalyst is prepared by reduction of nickel acetate in ethanol with sodium borohydride (*9*). Despite successes (*44*), the use of nickel is relatively infrequent (*51*).

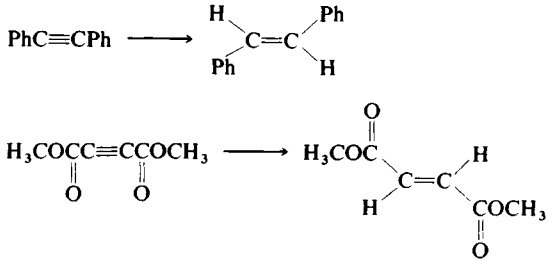
An a priori choice of an optimum acetylene hydrogenation catalyst is not always easy. For instance, hydrogenation of octadeca-3,6-diynol over P-2 nickel gave the corresponding (*Z,Z*)-dienol satisfactorily (*37*), but when the



catalyst system was applied to hydrogenation of the similar 3,6,9-heneicosatriynol, selectivity was poor; the reduction product contained at least four components in comparable amounts. Palladium-on-barium sulfate in methanol containing quinoline (*16*), or palladium-on-calcium carbonate in hexane containing triethylamine (*14*) gave almost the same results as P-2 nickel, but the classical Lindlar catalyst (*45*) gave (*Z,Z,Z*)-3,6,9-heneicosatrienol smoothly (*34*).



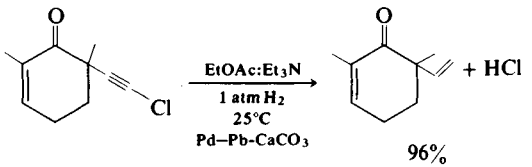
Homogeneous catalysts rarely are used for hydrogenation of acetylenes, but workable systems have been described (*78*). A solution of $PdCl_2$ in CH_2Cl_2 containing polyethylene glycol was more selective in hydrogenation of diphenylethyne to diphenylethylene than 10% Pd-on-C. A remarkable trans hydrogenation of alkynes has been achieved with the homogeneous catalyst, $RhH_2(O_2COH)[P(i\text{-}Pr)_3]_2$ (*88*).



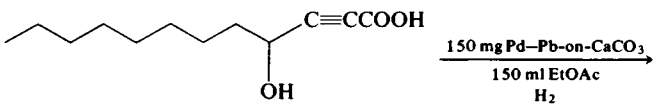
Heretofore, most homogeneous and all heterogeneous catalysts have given cis hydrogenation.

3.1.1. Catalyst Modifiers

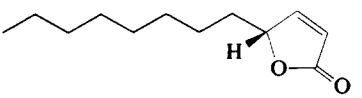
A variety of modifiers have been used in hydrogenation of acetylenes to improve selectivity (*4*). The modifiers have been incorporated during preparation of the catalyst and also added subsequently to preformed catalysts at the time of use. Among the metal salts used for this purpose are those of zinc, cadmium, zirconium, ruthenium, gold, silver, lead, and tin. A function that many modifiers may have in common is to increase hydrogen availability at the catalyst surface, by decreasing the rate of hydrogen consumption relative to the rate of hydrogen supply. They may also cause rearrangement of the palladium surface (*46,47*). The best known of these promoted catalysts is the Lindlar catalyst, palladium–lead-on-calcium carbonate (*45*), which has been used successfully by many workers (*17,25,26,32,36,53,54,66,77,79,80,83,85*) with and without additional modifiers. Selective hydrogenation of alkynes over Lindlar catalysts has proved very useful in syntheses of pheromones (*67*) and prostaglandins (*15,76*). A general route to synthetically useful α-vinyl carbonyl compounds involves semihydrogenation of the corresponding α-chloroethynyl compounds, over Pd–Pb-$CaCO_3$ (Lindlar catalyst) in 10:1 ethyl acetate:triethylamine at atmospheric pressure. Yields are uniformly in the high nineties (*41*).



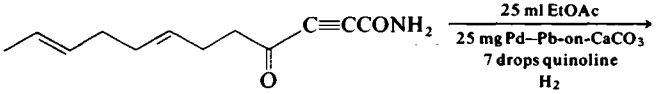
Hydrogenations with Lindlar catalysts frequently slow down or stop after absorption of 1 mol of hydrogen. Reduction of 4-hydroxydodec-2-ynoic acid stopped spontaneously when about 95% of the theoretical hydrogen had been absorbed (*39*).



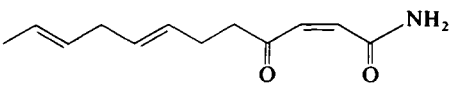
6.3 g



However, this behavior cannot be depended on. It is safer to monitor hydrogen uptake. Reduction of 4-oxo-*trans,trans*-7,10-dodecadiene-2-ynamide (**1**) to **2** neither stopped nor slowed down at the ethylene stage; although in other compounds, the same catalyst did give spontaneously selective reductions.



(1)



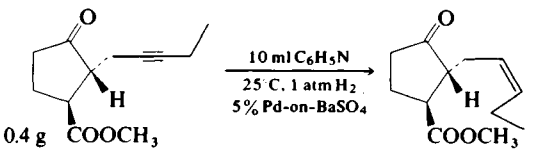
(2)

Beside metal salts, a variety of other modifiers, which include amines, chlorobenzene, hydroxides (*82,82a*), and sulfur compounds, have been used. Among amines used are quinoline (*8,20,57,84*), pyridine (*29,33,50,60,64*), piperidine, aniline, and diethylaniline. The reduction may be quite sensitive to these modifiers; for instance, one drop of quinoline was sufficient to cause hydrogenation to come to an abrupt stop after absorption of 1 mol of hydrogen (*2a*).

3.2. Solvents

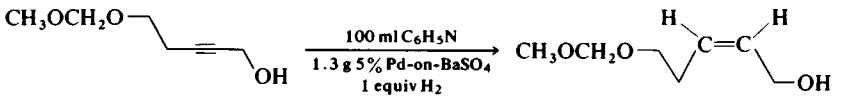
Many solvents have been used successfully. Some workers have expressed preference for nonpolar solvents, such as pentane or hexane, over alcohols (*3,27a,32,45*).

Amines (*7a,12a*), especially pyridine (*73*), have also been used as solvents in the hydrogenation of acetylenes. Hydrogenation of **3** over 5% Pd-on-$BaSO_4$ in pyridine gave *dl-cis*-jasmanate (**4**) quantitatively (*40*). The authors comment that this combination for reduction of acetylenes was superior to the Lindlar catalyst in all cases examined. (See also Refs. *12* and *24* for similar conclusions.)



(3) (4)

A convenient synthesis of 5-(methoxymethoxy)-2-pentenal was accomplished by selective reduction of **5** to **6**, followed by oxidation with pyridinium chlorochromate (*59*).



(5)
13.3 g

(6)

A useful self-terminating catalyst system (*11*), employs a Pd catalyst [prepared from $Pd(OAc)_2$, NaH, and *t*-AmOH in THF]. The solvent required for the hydrogenation depends on the acetylene structure; monosubstituted acetylenes require solvents such as hexane or octane, whereas disubstituted acetylenes need ethanol, ethanol–hydrocarbon, or ethanol–THF mixtures. In all cases it was necessary to use quinoline as a catalyst modifier. The authors consider this system one of the best for achieving both high yield and stereoselectivity.

3.3. Influence of Reaction Variables

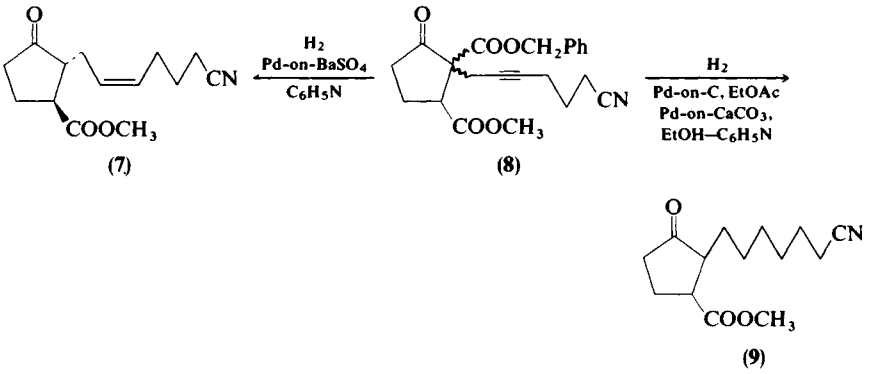
Selectivity of acetylene hydrogenation to the cis olefin has been found to depend on temperature, catalyst loading (*21,26a*), catalyst support (*21*), agitation (*22a*), modifiers, and solvent. Many of these effects can be rationalized by the influence the variable has on hydrogen availability at the catalyst surface. Over palladium, the metal most often used, double-bond migration and cis–trans isomerization tend to be faster than saturation, especially so, as the catalyst becomes hydrogen poor. Hydrogenations proceeding beyond 1 mol of hydrogen absorbed will result, therefore, in the loss of more initially formed cis isomer than calculated from the stoichiometry of the excess absorption. It is sometimes advisable to stop the hydrogenation before stoichiometric hydrogen is absorbed (*2,78*).

High thermodynamic selectivity (*7*) demands that the initially formed cis olefin be displaced rapidly relative to its saturation or to its isomerization. As the reaction nears completion and the acetylene concentration diminishes, its effectiveness in displacing olefin will diminish and selectivity will fall. Displacement by acetylene is also impeded through depletion of acetylene in the vicinity of the catalyst owing to intra- or interpartile diffusion resistance (*53a*). A change in a reaction parameter thus can have different influences

depending on whether or not the reaction is at the transition into the range of external mass transfer (*12b*).

Support has been shown to influence selectivity and some workers have obtained higher yields of cis isomer over palladium-on-calcium carbonate or palladium-on-barium sulfate (*21*), whereas others find carbon satisfactory. In general, carbon support makes the more active catalyst and it is, therefore, more prone to become hydrogen poor.

Choice of catalyst and solvent allowed considerable flexibility in hydrogenation of **8**. With calcium carbonate in ethanol–pyridine, the sole product was the trans isomer **9**, but with barium sulfate in pure pyridine the reaction came to a virtual halt after absorption of 2 equiv of hydrogen and *trans*-2-[6-cyanohex-2(*Z*)-enyl]-3-(methoxycarbonyl)cyclopentanone (**7**) was obtained in 90% yield together with 10% of the dihydro compound. When palladium-on-carbon was used in ethyl acetate, a 1:1 mixture of cis and trans **9** was obtained on exhaustive hydrogenation (*86*). It is noteworthy that in preparation of **7** debenzylation took precedence over double-bond saturation.



(**7**) (**8**) (**9**)

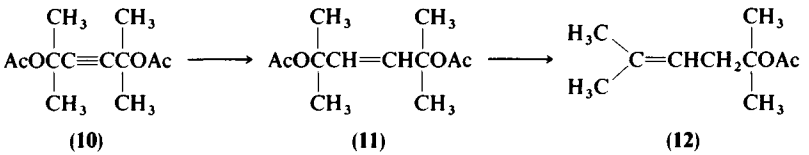
3.4. Functionalized Acetylenes

A frequent problem is selective reduction of an acetylene to the olefin in the presence of other easily reducible functions. Usually the reaction can be done without difficulty because of the relatively strong and preferential adsorption of the acetylenic function on the catalyst. Functions adjacent to the triple bond may cause special problems if the resulting allylic compound is itself susceptible to facile hydrogenolysis (*18,23*). The product composition is, as expected, sensitive to steric effects (*82*).

3.4.1. Acetylenic Carbinols, Glycols, and Esters

Acetylenic carbinols and glycols appear frequently in synthetic work. They are often hydrogenated to either the olefinic or paraffinic hydroxy compounds, usually without difficulty. The glycols are more sensitive to catalysts and conditions than are the carbinols, for they undergo hydrogenolysis more readily, as well as, in the presence of acids, cyclization to furans (*82a*). The preferred metal usually is palladium. A good technique for full or partial hydrogenation of hydroxyacetylenes is use of palladium promoted with small amounts of potassium hydroxide (*82b*). Large amounts of alkali may promote cis–trans isomerization (*46a*). Reduction of acetylenic glycols and carbinols in general seems less stereospecific than that of nonsubstituted acetylenes (*42*). Another technique for minimizing hydrogenolysis (*8a*) and cis–trans isomerization is to operate at subambient temperature (*32,68*).

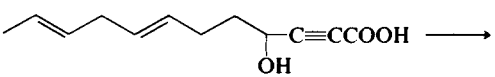
Hydrogenation of 2,5-diacetoxy-2,5-dimethyl-3-hexyne **10** over 10% palladium-on-carbon is exceptionally complex. Seven different products are formed together with acetic acid. All are hydrogenolysis products arising from the initially formed 2,5-diacetoxy-2,5-dimethyl-3-hexene **11**. One of these, 2,5-dimethyl-2-acetoxy-4-hexene **12** forms in as much as 48% yield.



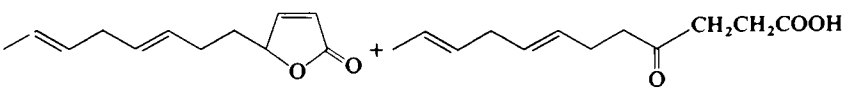
(10) **(11)** **(12)**

The authors suggested a concerted addition of hydrogen via a six-centered transition state that would produce **12** directly from the olefin (**11**) (*61*). Addition of pyridine or quinoline alters the reaction, but it remains complex.

Hydrogenation of acetylenic carbinols is sometimes accompanied by isomerization to the ketone. In the case of **13**, the isomerization to **15** was most pronounced when hydrogenations proceeded very slowly as when impure **13** was used (*39*).

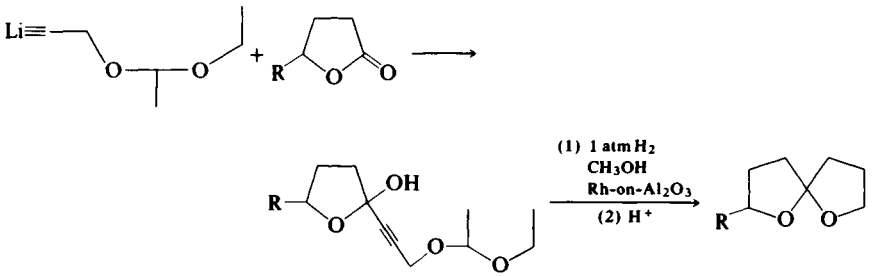


(13)



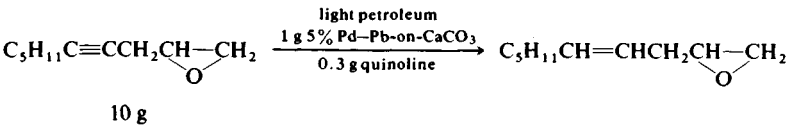
(14) **(15)**

Although palladium is usually the catalyst of choice, other metals have at times given an equal or better performance. A variety of 1,6-dioxaspiro[4.4]nonanes and 1,6-dioxaspiro[4.5]decanes can be prepared conveniently by reaction of the lithium salts of protected alkynols with equimolar amounts of lactones, followed by hydrogenation and acid-catalyzed deprotection and cyclization. Platinum oxide, Pd-on-C, and Rh-on-Al_2O_3 were compared as hydrogenation catalysts and Rh-on-Al_2O_3 was found to give the cleanest reaction and most reproducible yields (*62*). Nickel (P-2) is said to saturate propargylic hydroxy compounds without hydrogenolysis (*9*). Rhodium-on-carbon has been used effectively in similar reductions (*75*).

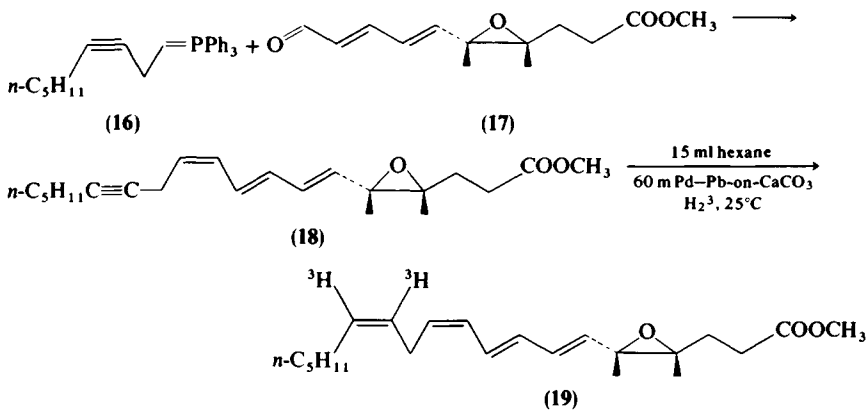


3.4.2. Acetylenic Epoxides

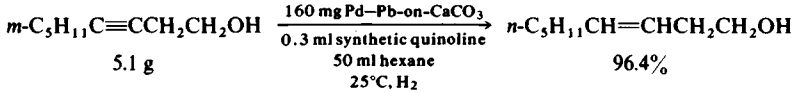
Acetylenic epoxides are reduced readily to the olefinic epoxide, provided the resulting epoxide is not allylic (*27*). In the latter case, one might surmise that hydrogenolysis could best be avoided by use of rhodium in a neutral nonpolar solvent (*81*) or a Lindlar catalyst (*13*). Reduction of 1,2-epoxydec-4-yne over Lindlar catalyst gave (*Z*)-1,2-epoxydec-4-ene in 95% yield (*69*). Hydrogenation ceased spontaneously.



Another example of this preference is found in the enantiospecific syntheses of tritium-labeled leukotrienes (*13*). Commercially available 3-nonyn-1-ol was converted to its phosphorane (**16**) and Wittig-coupled with the unsaturated aldehyde (**17**) to afford **18**, which was reduced over Lindlar catalyst to give **19**.

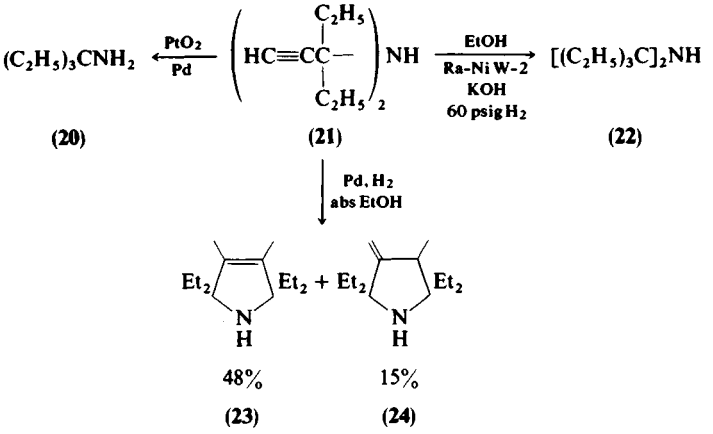


The unlabeled ester is made conveniently by reducing the C_9 acetylene to the olefin before coupling.



3.4.3. Propagargylamines

Hydrogenolysis may be an important side reaction accompanying reduction of propagargylamines. The extent of hydrogenolysis is sensitive to substrate structure (*31a*). Hydrogenolysis has been minimized by employing platinum instead of palladium and by reduction of an amine salt instead of the free amine (*22,48,49,56*). Considerable control can be exercised over the reaction course by appropriate choice of catalyst and conditions as illustrated by hydrogenation of **21**. Reduction of **21** over platinum oxide in a variety of solvents or over palladium in aprotic solvents gave the hydrogenolysis product **20** in high yield. In absolute ethanol over palladium, the cyclized products **23** and **24** formed, whereas over W-2 Raney nickel the saturated product **22** was obtained in 72% yield, when potassium hydroxide was added to suppress hydrogenolysis (*43*). In related problems, potassium hydroxide was found to be less of a rate inhibitor than sodium hydroxide (*82*). Other examples of carbon–carbon bond formation, which may be intramolecular (*74*) or intermolecular (*28*), have been reported in the hydrogenation of acetylenes.



3.4.4. Acetylenic Aldehydes and Ketones

Selective reduction of acetylenes containing carbonyl functions seems to present no difficulties if the groups are not conjugated.

Reduction of enynones to dienones is structure sensitive and is often unsatisfactory if the acetylenic bond is attached directly to the carbonyl (*30,31,52*). Selectivity is improved if the acetylenic bond is terminal (*52,70,71*).

References

1. M. M. Abelman, R. L. Funk, and J. D. Munger, Jr., *J. Am. Chem. Soc.* **104,** 4030 (1982).
2. A. E. Asato, A. Kini, M. Denny, R. S. H. Liu, *J. Am. Chem. Soc.* **105,** 2923 (1983).
2a. W. F. Berkowitz, *J. Org. Chem.* **37,** 341 (1972).
3. R. B. Boar, S. L. Jones, and A. C. Patel, *J.C.S. Perkin Trans. 1,* 513 (1982).
4. J. P. Boitiaux, J. Cosyns, and G. Martino, *in* "Metal Support and Metal Additive Effects in Catalysis" (B. Imelik, G. Naccache, G. Coudurier, H. Praliaud, P. Mesiaudeux, P. Gallezot, G. A. Martin, and I. C. Vedrine, eds.), pp. 355–368. Elsevier, Amsterdam, 1982.
5. G. C. Bond and P. B. Wells, *J. Catal.* **5,** 419 (1966).
6. G. C. Bond, D. A. Dowden, and N. Mackenzie, *Trans. Faraday Soc.* **54,** 1537 (1958).
7. G. C. Bond, G. Webb, P. B. Wells, and J. B. Winterbottom, *J. Catal.* **1,** 74 (1962).
7a. A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.* **80,** 6115 (1958).
8. R. Brettle and I. A. Jafri, *J.C.S. Perkin Trans. 2,* 387 (1983).
8a. C. A. Brown, *J. Am. Chem. Soc.* **91,** 5901 (1969).
9. C. A. Brown and V. K. Ahuja, *JCS Chem. Commun.,* 553 (1973).
10. T. M. Brown, W. Carruthers, and M. G. Pellatt, *J.C.S. Perkin Trans. 1,* 483 (1982).
11. J.-J. Brunet and P. Caubere, *J. Org. Chem.* **49,** 4060 (1984).

12. A. W. Burgstahler and G. N. Widiger, *J. Org. Chem.* **38,** 3652 (1973).
12a. G. O. Chase and J. Galender, U.S. Patent 2,883,431 (1959).
12b. P. Chuchvalec, M. Havlicek, and J. Horak, *J. Chem. Prum.* **21** (10), 488 (1971); *CA* **76,** 7039 (1972).
13. N. Cohen, B. L. Banner, R. J. Lopresti, F. Wong, M. Rosenberger, Y. Y. Liu, E. Thom, and A. A. Liebman, *J. Am. Chem. Soc.* **105,** 3661 (1983).
14. E. J. Corey and J. Kang, *J. Am. Chem. Soc.* **103,** 4618 (1981).
15. E. J. Corey, G. W. J. Fleet, and M. Kato, *Tetrahedron Lett.*, 3963 (1973).
16. D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.* **78,** 2518 (1956).
17. L. Crombie, *J. Chem. Soc.*, 3510 (1955).
18. L. Crombie, and A. G. Jacklin, *J. Chem. Soc.*, 1622 (1957).
19. L. Crombie and R. A. Jenkins, *Chem. Commun.*, 394 (1969).
20. F. Derguini, C. G. Caldwell, M. G. Motto, V. Balogh-Nair, and K. Nakanishi, *J. Am. Chem. Soc.* **105,** 646 (1983).
21. N. A. Dobson, G. Eglinton, M. Krishnamurti, R. A. Raphael, and R. G. Willis, *Tetrahedron* **16,** 16(1961).
22. N. R. Easton, R. D. Dillard, W. J. Doran, M. Livezey, and D. E. Morrison, *J. Org. Chem.* **26,** 3772 (1961).
22a. S. N. Ege, R. Wolovsky, and W. J. Gensler, *J. Am. Chem. Soc.* **83,** 3080 (1961).
23. R. J. D. Evans, S. R. Landor, and R. T. Smith, *J. Chem. Soc.*, 1506 (1963).
24. H. P. Figeys and M. Gelbeke, *Tetrahedron Lett.*, 5139 (1970).
25. M. Freifelder, *J. Pharm. Sci.* **56** (7), 903 (1967).
26. R. I. Fryer, N. W. Gilman, and B. C. Holland, *J. Org. Chem.* **40,** 348 (1975).
26a. W. J. Gensler and G. R. Thomas, *J. Am. Chem. Soc.* **73,** 4601 (1951).
27. E. Ghera, M. Gibson, and F. Sondheimer, *J. Am. Chem. Soc.* **84,** 2953 (1962).
27a. H. Gutmann and H. Lindlar, *in* "Chemistry of Acetylenes" (H. G. Viehe, ed.), p. 355. Dekker, New York, 1969.
28. H. K. Hall, Jr., and M. J. Steuck, *Chem. Ind. (London)*, 545 (1971).
29. S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.* **48,** 4430 (1983).
30. I. Heilbron, E. R. H. Jones, R. W. Richardson, and F. Sondheimer, *J. Chem. Soc.*, 737 (1949).
31. I. Heilbron, E. R. H. Jones, J. B. Toogood, and B. C. L. Weedon, *J. Chem. Soc.*, 1827, 2028 (1949).
31a. G. F. Hennion and A. C. Perriono, *J. Org. Chem.* **26,** 1073 (1961).
32. C. A. Henrick, *Tetrahedron* **33,** 1845 (1977).
33. E. B. Hershberg, E. P. Oliveto, C. Gerald, and L. Johnson, *J. Am. Chem. Soc.* **73,** 5073 (1951).
34. W. Huang, S. P. Pulaski, and J. Meinwald, *J. Org. Chem.* **48,** 2270 (1983).
35. M. Jacobson, M. Beroza, and W. A. Jones, *J. Am. Chem. Soc.* **83,** 4819 (1961).
36. M. Jacobson, R. E. Redfern, W. A. Jones, and M. H. Aldridge, *Science* **170,** 542 (1970).
37. S. C. Jain, D. E. Dussourd, W. E. Conner, T. Eisner, A. Guerrero, and J. Meinwald, *J. Org. Chem.* **48,** 2266 (1983).
38. S. C. Jain, W. L. Roelofs, and J. Meinwald, *J. Org. Chem.* **48,** 2274 (1983).
39. A. A. Jakubowski, F. S. Guziec, Jr., M. Sugiura, C. C. Tam., M. Tishler, and S. Omura, *J. Org. Chem.* **47,** 1221 (1982).
40. F. Johnson, K. G. Paul, and D. Favara, *J. Org. Chem.* **47,** 4254 (1982).
41. A. S. Kende, P. Fludzinski, J. H. Hill, W. Swenson, and J. Clardy, *J. Am. Chem. Soc.* **106,** 3551 (1984).
42. S. S. Klioze and F. P. Darmory, *J. Org. Chem.* **40,** 1588 (1975).
43. I. E. Kopka, Z. A. Fataftah, and M. W. Rathke, *J. Org. Chem.* **45,** 4616 (1980).
44. G. L. Lange and T. W. Hall, *J. Org. Chem.* **39,** 3819 (1974).
45. H. Lindlar and R. Dubuis, *Org. Synth.* **46,** 89 (1966).

46. A. B. McEwen, M. J. Guttieri, W. F. Maier, R. M. Laine, and Y. Shvo, *J. Org. Chem.* **48,** 4436 (1983).
46a. K. J. McQuillin and W. O. Ord, *J. Chem. Soc.*, 2902 (1959).
47. W. F. Maier, *Chem. Eng. News*, 24 (1983).
48. J. Marszak and A. Marszak-Fleury, *C. R. Acad. Sci. Ser. C* **228,** 1501 (1949).
49. J. Marszak and A. Marszak-Fleury, *Bull. Soc. Chim. Fr.* **17,** 1305 (1950).
50. J. Martel, E. Toromanoff, and C. Huynh, *J. Org. Chem.* **30,** 1752 (1965).
51. E. N. Marvell and T. H. Li, *Synthesis*, **8,** 457 (1973).
52. E. N. Marvell, T. Gosink, P. Churchley and T. H. Li, *J. Org. Chem.* **37,** 2989 (1972).
53. E. N. Marvell, C. Hilton, and M. Cleary, *J. Org. Chem.* **48,** 4272 (1983).
53a. S. Matsumoto, H. Fukui, T. Imanaka, and S. Teranishi, *Nippon Kagaku Kaishi* No. 8, 1527 (1972); *CA* **77,** 128572 (1972).
54. A. I. Meyer, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.* **38,** 36 (1973).
55. K. Mori, M. Tominaga, and M. Matsui, *Tetrahedron* **31,** 1846 (1975).
56. D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.* **30,** 579 (1965).
57. Y. Murata, K. Inomata, H. Kinoshita, and H. Kotake, *Bull. Chem. Soc. Jpn.* **56,** 2539 (1983).
58. A. C. Oehschlager, J. W. Wong, V. G. Verigin, and H. D. Pierce, Jr., *J. Org. Chem.* **48,** 5009 (1983).
59. L. E. Overman, D. Lesuisse, and M. Hashimoto, *J. Am. Chem. Soc.* **105,** 5373 (1983).
60. D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.* **76,** 4446 (1954).
61. D. R. Paulson, L. S. Gillian, V. O. Terry, S. M. Farr, E. J. Parker, F. Y. N. Tang, R. Ullman, and G. Ribar, *J. Org. Chem.* **43,** 1782 (1978).
62. C. Phillips, R. Jacobson, B. Abrahams, H. J. Williams, and L. R. Smith, *J. Org. Chem.* **45,** 1920 (1980).
63. A. F. Plate and V. I. Stanko, *Izv. Akad Nauk SSSR, Otd. Khim. Nauk*, 1481 (1960).
64. K. Pramod, H. Ramanathan, and G. S. R. Subba Rao, *J.C.S. Perkin Trans. 1*, 7 (1983).
65. A. Rieche, A. Grimm, and H. Albrecht, *Brenns. Chem.* **42** 177 (1961).
66. M. Rosenberger, C. Newkom, E. R. Aig, *J. Am. Chem. Soc.* **105,** 3661 (1983).
67. R. Rossi, *Synthesis*, 817 (1977).
68. R. Rossi, P. A. Salvadori, A. Carpita, and A. Niccoli, *Tetrahedron* **35,** 2039 (1979).
69. S. W. Russell and H. J. J. Pabon, *J.C.S. Perkin Trans. 1*, 545 (1982).
70. P. Schiess and H. L. Chia, *Helv. Chim. Acta* **53,** 485 (1970).
71. P. Schiess, R. Seeger, and C. Suter, *Helv. Chim. Acta* **53,** 1713 (1970).
72. R. G. Smith, G. D. Daves, Jr., and G. E. Daterman, *J. Org. Chem.* **40,** 1593 (1975).
73. A. B. Smith, III, M. A. Guaciaro, S. R. Schow, P. M. Wovkulich, B. H. Toder, and T. W. Hall, *J. Am. Chem. Soc.* **103,** 219 (1981).
74. H. A. Staab and J. Ipaktschi, *Chem. Ber.* **104,** 1170 (1971).
75. G. Stork and E. Nakamura, *J. Am. Chem. Soc.* **105,** 5510 (1983).
76. G. Stork, C. Kowalski, and G. Garcia, *J. Am. Chem. Soc.* **97,** 3258 (1975).
77. H. C. F. Su and P. G. Manhany, *J. Econ. Entomol.* **67,** 319 (1974).
78. N. Suzuki, Y. Ayaguchi, T. Tsukanaka, Y. Izawa, *Bull. Chem. Soc. Jpn.* **56,** 353 (1983).
79. A. Tai, F. Matsumura, and H. C. Coppel, *J. Org. Chem.* **34,** 2180 (1969).
80. Y. Tamaki, H. Noguchi, and T. Yushima, *Appl. Entomol. Zool.* **8,** 200 (1973).
81. D. S. Tarbell, R. M. Carman, D. D. Chapman, S. E. Cremer, A. D. Cross, K. R. Huffman, M. Kuntsmann, N. J. McCorkindale, J. G. McNally, Jr., A. Rosowsky, F. H. L. Varino, and R. L. West, *J. Am. Chem. Soc.* **83,** 3096 (1961).
82. R. J. Tedeschi, *J. Org. Chem.* **27,** 2398 (1962).
82a. R. J. Tedeschi and G. Clark, Jr. *J. Org. Chem.* **27,** 4232 (1962).

82b. R. J. Tedeschi, H. C. McMahon, and M. S. Pawlak, *Ann. N.Y. Acad. Sci.* **145,** 91 (1967).
83. J. H. Tumlinson, D. E. Hendricks, E. R. Mitchell, R. E. Doolittle, and M. M. Brennan, *J. Chem. Ecol.* **1,** 203 (1975).
84. J. P. Vigneron and J. M. Blanchard, *Tetrahedron Lett.*, 1739 (1980).
85. S. Voerman, A. K. Minks, and N. W. H. Houx, *Environ. Entomol.* **3,** 701 (1974).
86. W. L. White, P. B. Anzeveno, and F. Johnson, *J. Org. Chem.* **47,** 2379 (1982).
87. N. Yoshida and K. Hirota, *Bull. Chem. Soc. Jpn.* **48,** 184 (1975).
88. T. Yoshida, W. F. Youngs, T. Sakaeda, T. Ueda, S. Otsuka, and J. A. Ibers, *J. Am. Chem. Soc.* **105,** 6273 (1983).

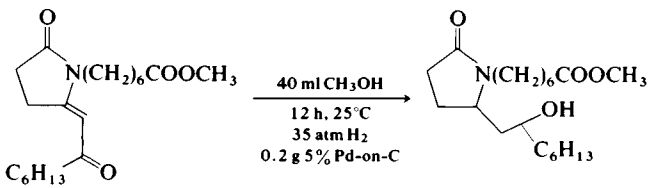
- 4 -

Hydrogenation of Aldehydes and Ketones

Aldehydes and ketones are similar in their response to hydrogenation catalysis, and an ordering of catalyst activities usually applies to both functions. But the difference between aliphatic and aromatic carbonyls is marked, and preferred catalysts differ. In hydrogenation of aliphatic carbonyls, hydrogenolysis seldom occurs, unless special structural features are present, but with aryl carbonyls either reduction to the alcohol or loss of the hydroxy group can be achieved at will.

4.1. Catalysts

A variety of catalysts including copper, nickel, cobalt, and the platinum metals group have been used successfully in carbonyl reduction. Palladium, an excellent catalyst for hydrogenation of aromatic carbonyls is relatively ineffective for aliphatic carbonyls; this latter group has a low strength of adsorption on palladium relative to other metals (*72,91*). Nonetheless, palladium can be used very well with aliphatic carbonyls with sufficient patience, as illustrated by the difficult-to-reduce vinylogous amide **1** to **2** (*9*).

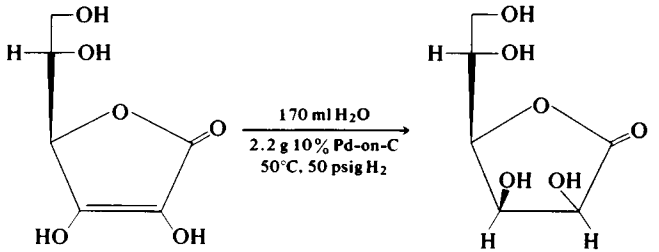


(1)
1.75 g

(2)

In ketones existing largely as the enol, palladium may prove effective in minimizing hydrogenolysis. Hydrogen was added stereoselectively to the least hindered side of L-ascorbic acid (**3**) to give L-gulono-1,4-lactone (**4**)

quantitatively. Raney nickel was inactive under mild conditions and platinum oxide gave a mixture of products (*7*).



(3)
23 g

(4)

Ruthenium is excellent for hydrogenation of aliphatic carbonyl compounds (*92*), and it, as well as nickel, is used industrially for conversion of glucose to sorbitol (*14,15,29,75,100*). Nickel usually requires vigorous conditions unless large amounts of catalyst are used (*11,20,27,37,60*), or the catalyst is very active, such as W-6 Raney nickel (*6*). Copper chromite is always used at elevated temperatures and pressures and may be useful if aromatic-ring saturation is to be avoided. Rhodium has given excellent results under mild conditions when other catalysts have failed (*4,5,66*). It is useful in reduction of aliphatic carbonyls in molecules susceptible to hydrogenolysis.

Platinum, especially platinum oxide, has been used by many investigators (*5*). Platinum oxide, when used with aldehydes is apt to be deactivated before reduction is completed. Deactivation is inhibited by small amounts of ferrous or stannous chlorides (*59,82*). This type of promoter can also sharply curtail hydrogenolysis if it is a troublesome reaction (Rylander and Starrick, 1966). Deactivated systems can often be regenerated by shaking the reaction mixture with air (*2,8,21,23,96*). The usefulness of this regenerative technique transcends aldehyde reductions; it frequently is worth resorting to.

Osmium makes a sluggish carbonyl hydrogenation catalyst but has the unusual property of reducing α,β-unsaturated aldehydes to the unsaturated alcohol in good yield (*85*). The system has proved erratic; high selectivity can only be obtained through prereduction of the catalyst just before use.

4.2. Solvents

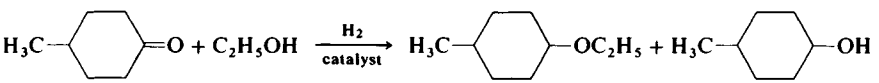
Solvents have a marked effect on the rate of reduction of carbonyls (*16*), in

Small quantities of acid or base may have major effects on both rate and product. Many reasons have been advanced to account for these promotional effects (*65*), and many examples have been cited (*31,32,41,79,80*). The effects of pH are very worthwhile exploring in reductions that somehow are less than satisfactory. Catalysts themselves may contain sufficient acid or base to alter the course of reduction (*25*).

4.2.1. Alcohol Solvents

Hydrogenation of carbonyls, or incipient carbonyls such as phenols (*86*), in lower alcohol solvents may result in the formation of ethers. The ether arises through formation of acetals or ketals with subsequent hydrogenolysis. The reaction has been made the basis of certain ether syntheses (*45,97*). Reaction of alcohols with carbonyls may be promoted by trace contamination, such as iron in platinum oxide (*22,53*), but it is also a property of the hydrogenation catalyst itself. So strong is the tendency of palladium–hydrogen to promote acetal formation that acetals may form even in basic media (*61*).

The data of Nishimura *et al.* (*68*) emphasize how strongly ether formation depends on the catalyst.



Pd	96.6%, 89.8% cis	74.7%, 83.3% cis
Pt		70.1%, 83.0% cis
Rh		100%, 69.0% cis
Ru		

Hydrogenation of the constrained 4-*t*-butylcyclohexanone gives 99% ether (97% cis) in ethanol over palladium (*68*). High yields of methyl ethers are formed by reduction of 5α- and 5β-cholestan-3-ones in methanol over palladium.

4.3. Hydrogenolysis

Hydrogenolysis of aliphatic carbonyls usually does not occur readily unless certain types of structures prevail (*78*), but hydrogenolysis of an aromatic carbonyl will occur easily, mostly via an intermediate benzyl alcohol.

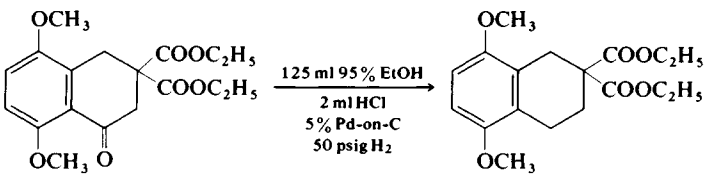
4.3.1. Aliphatic Carbonyls

The stability of aliphatic alcohols to hydrogenolysis is demonstrated by their widespread use as hydrogenation solvents, a fact that effectively rules out the alcohol as a major intermediate in deoxygenation. In certain cases the ability to enolize has been shown to be a prerequisite for hydrogenolysis (*48*), and, indeed, compounds such as β-keto esters (*83,98*), β-keto amides (*48*), and β-diketones (*84,98*) may undergo extensive hydrogenolysis. Hydrogenolysis occurs also with 1,4- and 1,5-diketones, because of their tendency to cyclize. Certain β-amino ketones also undergo extensive hydrogenolysis in acidic media (*78*).

The influence of reaction variables and catalyst is complex (*19,62,83,84*). It is difficult to formulate generalities from available data; suffice it to note that much can be done to alter the extent of hydrogenolysis in compounds susceptible to this reaction.

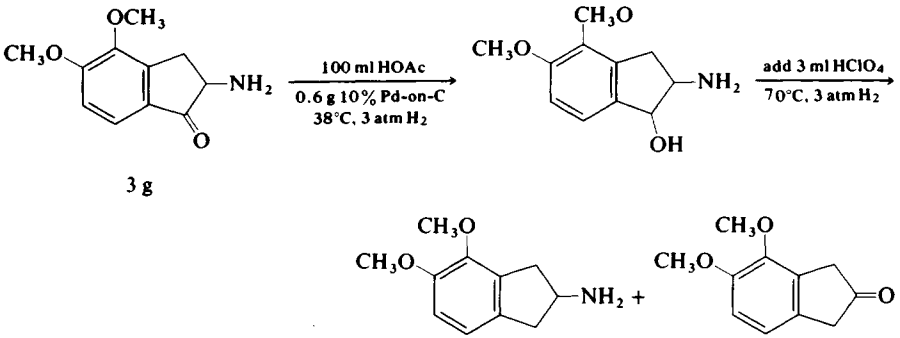
4.3.2. Aromatic Carbonyls

Hydrogenolysis of aromatic carbonyls occurs mainly by conversion to the benzyl alcohol and its subsequent loss. If hydrogenolysis is desired, the usual catalyst is palladium (*38*). Hydrogenolysis is facilitated by polar solvent and by acid (*58*). For instance, hydrogenation of 3,3-dicarbethoxy-5,8-dimethoxy-1-tetralone (**5**) over 5% Pd-on-C gave **6** quantitatively (*54*) when hydrogen absorption ceased spontaneously.

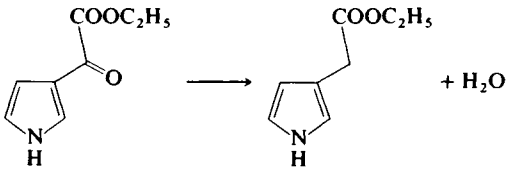


(5) (6)

An unusual by-product was obtained in small yield in palladium-catalyzed reduction of 2-amino-4,5-dimethoxyindanone hydrochloride. The reduction was done in two stages: first, a rapid absorption of 1 mol of hydrogen at 38°C to give the amino alcohol, and then a much slower reduction in the presence of $HClO_4$ at 70°C. The rearranged by-product was shown to arise from attack of acid on the amino alcohol (*50*). Resistance to hydrogenolysis is characteristic of β-amino aromatic alcohols (*56*), a fact that makes reduction of aromatic oximino ketones to amino benzyl alcohols a useful synthetic reaction.



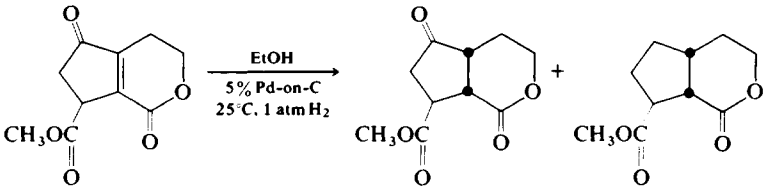
A special technique was necessary to obtain good yields of ethyl pyrrole-3-acetate from ethyl pyrrole-3-glyoxalate. Reduction over W-7 Raney Ni in 50% aq ethanol was accompanied by major ring reduction and tarring. By use of a two-phase system, toluene and 50% aq ethanol, these side reactions could be curtailed. Apparently the desired product was removed effectively from the aqueous layer into the toluene as soon as it was formed (*26*).



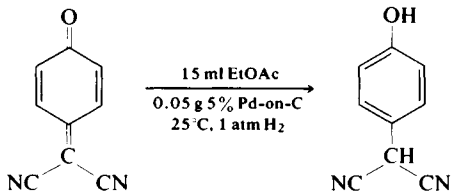
4.4. Unsaturated Carbonyls

Either or both functions in an unsaturated carbonyl compound may be reduced, the products depending in large measure on substrate structure and catalyst. In general, the olefinic function, whether conjugated or not, is easily reduced preferentially if the olefin is not hindered (*3,5,16,18*). The preferred catalyst is palladium if carbonyl reduction is to be minimal. Some industrial processes that can tolerate a mixture use nickel. In compounds of this type, the catalyst plays a large role in shaping product composition. Distillation of available data suggests that olefin reduction is favored by palladium, and carbonyl reduction by platinum or ruthenium.

Carbonyl reduction begins to compete with olefin saturation when the double bond is hindered or the carbonyl is aromatic or an aromatic vinylog. In conjugated systems, deoxygenation may occur via an intermediate allylic alcohol (*51*).



Ketones contained in easily aromatized systems are apt to be converted to phenols on hydrogenation (*46*).



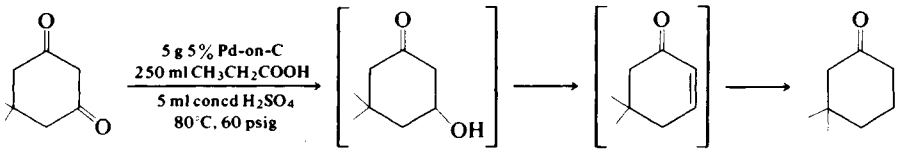
0.5 g

Reduction of unsaturated aldehydes seems more influenced by the catalyst than is that of unsaturated ketones, probably because of the less hindered nature of the aldehydic function. A variety of special catalysts, such as unsupported (*96*), or supported (*81*) platinum–iron–zinc, platinum–nickel–iron (*47*), platinum–cobalt (*90*), nickel–cobalt–iron (*42–44*), osmium (*85*), rhenium heptoxide (*74*), or iridium–on–carbon (*49*), have been developed for selective hydrogenation of the carbonyl group in unsaturated aldehydes. None of these catalysts appears to reduce an α,β-unsaturated ketonic carbonyl selectively.

4.5. Diketones

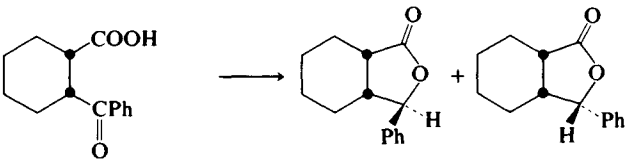
Diketones can be reduced usually in high selectivity to either an intermediate ketol or the diol (*12*). Selectivity to the ketol depends in large measure on both catalyst and solvent. In cyclohexane solvent, the maximal yield of ketol obtained on partial hydrogenation of biacetyl fell in the order 5% Pd-on-C (99%), 5% Rh-on-C (92%), 5% Pt-on-C (88%), 5% Ru-on-C (63%); from acetylacetone the descending order was 5% Pd-on-C (86%), 5% Rh-on-C (60%), 5% Ru-on-C (35%), 5% Pt-on-C (27%) (*86*); from 1,4-cyclohexanedione in isopropanol initial selectivity to the ketol fell in the sequence 5% Pd-on-SiO_2 (96%), 5% Ir-on-C (95%), 5% Ru-on-C (92%), 5% Pt-on-C (67%) (*13*). Generalizing from these data, it appears palladium is a good first choice to achieve maximal selectivity.

A convenient synthesis of 3,3-dimethylcyclohexanone, a compound obtained otherwise with difficulty, involves hydrogenolysis of 5,5-dimethyl-1,3-cyclohexanedione (*88*). The reduction is believed to go through 3,3-dimethylcyclohexenone (*24*). Hydrogenation virtually ceases after absorption of 2 mol of hydrogen.



4.6. Stereochemistry

A great deal of control can be exerted over the stereochemistry of ketone hydrogenation, and it serves as a complement to other reducing systems (*76*).

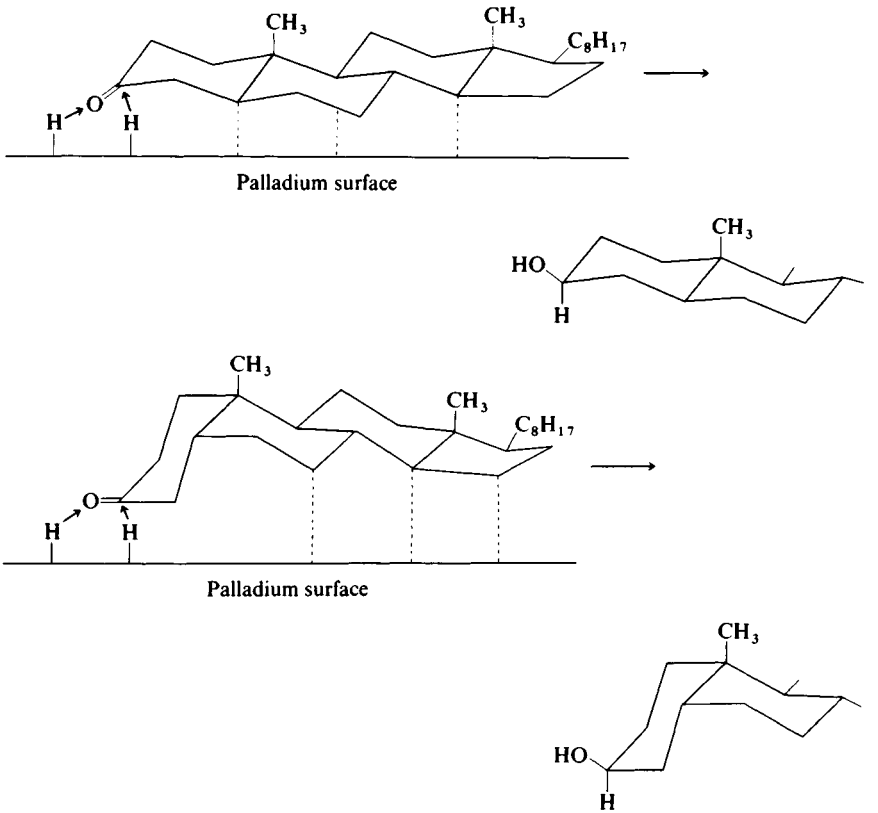


PtO_2, H_2, EtOAc 40 psig	26%	74%
$Li(i\text{-}Bu)_3BH$	95%	5%

Various rules have been devised with partial success (*10,30,99*), but it is difficult to formulate encompassing generalities in a reaction subject to the influence of so many reaction parameters. The stereochemistry can be affected importantly by the catalyst (*35,36,64,65,77,89,94*), solvent (*63*), substrate structure, and haptophilic effects (*77*).

A remarkable example of haptophilicity and effect of metal has been reported by Nishimura *et al.* (*72*). Catalytic hydrogenation of 5α-cholestan-3-one over palladium gives the equatorial 3β-ol in high yield, whereas 5β-cholestan-3-one gives high yields of the axial 3β-ol. Platinum shows this selectivity to a much smaller extent and other noble metals give the same mixture of isomers from both ketones (*70*). The extraordinary and unique selectivity exhibited by palladium has been attributed, on the basis of competition experiments, to a strong adsorption of the α face of the steroids on palladium, a preferential adsorption not shown by other metals. The same explanation has been advanced to account for the unusually high reactivities of Δ^5 steroids in palladium-catalyzed hydrogenation (*73*). Haptophilic effects

have been invoked previously by many investigators but heretofore always involving a preferential adsorption of a functional group. Nishimura *et al.* (*72*) represented interaction of the α faces of 5α- and 5β-cholestan-3-ones as follows:

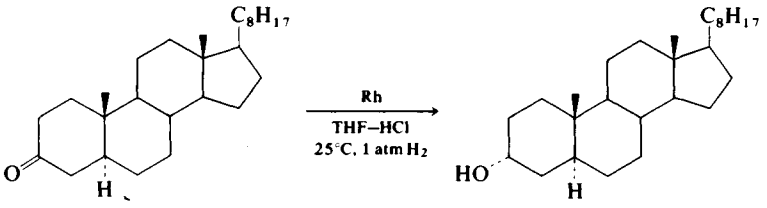


4.6.1. Axial Alcohols

The conclusion was reached in a study of hydrogenation of alkylcyclohexanone that rhodium-on-carbon is generally the most effective for producing axial alcohols, platinum oxide the least (*65,94*). Traces of alkali may produce marked changes in the percentage of axial alcohol, the direction of change being itself a function of the catalyst. Solvents too may have a large influence (*69,71*).

A useful method for the synthesis of axial alcohols from unhindered cyclohexanones is by hydrogenation over rhodium in THF–HCl. Reduction

of 4-*t*-butylcyclohexanone gives the cyclohexanol quantitatively with 99.3% cis isomer (*70,71*). Reduction of 5α-cholestan-3-one (**7**) in the same system gives the axial alcohol **8** in 97.5% yield. Similarly 5β-cholestan-3-one is reduced to the corresponding 3β-ol in 96.6%. Reduction of **7** over platinum in *t*-butanol give predominantly the equatorial alcohol 5α-cholestan-3β-ol (*69*).

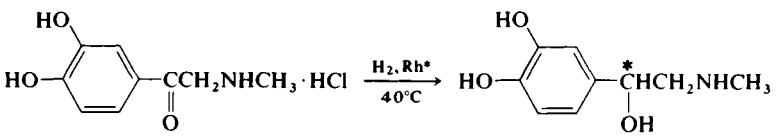


(**7**) (**8**)

Iridium-catalyzed hydrogen transfer from aqueous phosphite esters or phosphorous acid is an effective way of producing axial alcohols (*17,28,34,40,57*).

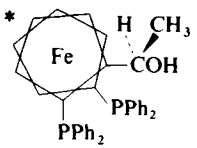
4.6.2. Asymmetric Hydrogenation

Asymmetric hydrogenation of ketones by chiral homogeneous catalysts and by heterogeneous catalysts modified by chiral additives has been the subject of much interest (*1,33,55,93,95*). A single example of each type must suffice to illustrate the area. High optical yields of 2-amino-1-arylethanol have been achieved by asymmetric hydrogenation employing (*R*)-(*S*)-BPPFOH rhodium complex. The chiral ligand is (*R*)-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol. Epinephrine hydrochloride (**10**) was obtained from **9** in 95% enantioselectivity (*39*). Excellent optical yields of

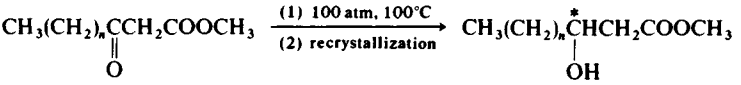


(**9**) (**10**)

100% yield
95% ee



methyl 3-hydroxyalkanoates have been obtained by an enantioface differentiating hydrogenation of methyl 3-oxoalkanoate over an asymmetrically modified nickel, followed by preferential crystallization of an optically pure substance from the mixture (*67*). The catalyst was prepared by soaking a Raney nickel catalyst in an aqueous solution of tartaric acid and sodium bromide at 100°C.



References

1. K. Achiwa, T. Kogure, and I. Ojima, *Tetrahedron Lett.*, 4431 (1977).
2. R. Adams and B. S. Garvey, *J. Am. Chem. Soc.* **48,** 477 (1926).
3. R. Adams and M. Gianturco, *J. Am. Chem. Soc.* **79,** 166 (1957).
4. R. Adams, S. Miyano, and D. Fles, *J. Am. Chem. Soc.* **82,** 1466 (1960).
5. R. Adams, S. Miyano, and M. D. Nair, *J. Am. Chem. Soc.* **83,** 3323 (1961).
6. H. Adkins, and H. R. Billica, *J. Am. Chem. Soc.* **70,** 695 (1948).
7. G. C. Andrews, T. C. Crawford, and B. E. Bacon, *J. Org. Chem.* **46,** 2997 (1981).
8. R. Baltzly, *J. Org. Chem.* **41,** 933 (1976).
9. A. Barco, S. Bennetti, G. P. Pollini, B. Veronessi, P. G. Baraldi, M. Guarnesi, and C. B. Vicentini, *Synth. Commun.* **8,** 219 (1978).
10. D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
11. R. R. Blance and D. T. Gibson, *J. Chem. Soc.*, 2487 (1954).
12. A. T. Blomquist and J. Wolinsky, *J. Am. Chem. Soc.* **77,** 5423 (1955).
13. M. Bonnet, P. Geneste, and M. Rodriquez, *J. Org. Chem.* **45,** 40 (1980).
14. G. G. Boyers, U.S. Patent No. 2,868,847 (1959).
15. P. H. Brahme and L. K. Doraiswamy, *Ind. Eng. Chem. Process Res. Dev.* **15,** 130 (1976).
16. E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.* **24,** 1855 (1959).
17. P. A. Browne and D. N. Kirk, *J. Chem. Soc. C*, 1653 (1969).
18. D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron* **20,** 597 (1964).
19. J. S. Burton and R. Stevens, *J. Chem. Soc.*, 4382 (1963).
20. N. R. Campbell and J. Hunt, *J. Chem. Soc.*, 1379 (1950).
21. W. H. Carothers and R. Adams, *J. Am. Chem. Soc.* **45,** 1071 (1923).
22. W. H. Carothers and R. Adams, *J. Am. Chem. Soc.* **46,** 1675 (1924).
23. W. H. Carothers and R. Adams, *J. Am. Chem. Soc.* **47,** 1047 (1925).
24. R. A. Cormier, *Synth. Commun.* **11,** 295 (1981).
25. M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
26. B. J. Demopoulos, H. J. Anderson, C. E. Loader, and K. Faber, *Can. J. Chem.* **61,** 2415 (1983).
27. R. C. Ebersole and F. C. Chang, *J. Org. Chem.* **38,** 2713 (1973).
28. W. I. Fanta and W. F. Erman, *J. Org. Chem.* **36,** 358 (1971).
29. W. S. Fedor, J. Millar, and A. J. Accola, Jr., *Ind. Eng. Chem.* **52,** 282 (1960).
30. S. P. Findlay, *J. Org. Chem.* **24,** 1540 (1959).

31. J. Forrest and S. H. Tucker, *J. Chem. Soc.*, 1137 (1948).
32. M. Freifelder, T. Anderson, Y. H. Ng, and V. Papendick, *J. Pharm. Soc.* **53,** 967 (1964).
33. L. H. Gross and P. Rys, *J. Org. Chem.* **39,** 2429 (1974).
34. Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, *Proc. Chem. Soc.*, 361 (1964).
35. K. Hanaya, *Nippon Kagaku Zasshi* **87,** 745, 991 (1966).
36. K. Hanaya, *Nippon Kagaku Zasshi* **90,** 314 (1969).
37. M. Harnik, *J. Org. Chem.* **28,** 3386 (1963).
38. W. H. Hartung and R. Simonoff, *Org. Reactions* **7,** 263 (1953).
39. T. Hayashi, A. Katsumara, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, 425 (1979).
40. H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc.* C, 785 (1970).
41. G. P. Hennian and E. J. Watson, *J. Org. Chem.* **23,** 656 (1958).
42. K. Hotta and T. Kubomatsu, *Bull. Chem. Soc. Jpn.* **42,** 1447 (1969).
42a. K. Hotta and T. Kubomatsu, *Bull. Chem. Soc. Jpn.* **44,** 1348 (1971).
43. K. Hotta and T. Kubomatsu, *Bull. Chem. Soc. Jpn.* **45,** 3118 (1972).
44. K. Hotta and T. Kubomatsu, *Bull. Chem. Soc. Jpn.* **46,** 3566 (1973).
45. W. L. Howard and J. H. Brown, Jr., *J. Org. Chem.* **26,** 1026 (1961).
46. J. A. Hyatt, *J. Org. Chem.* **48,** 129 (1983).
47. Y. Ichikawa, T. Yamaji, and T. Sawaki, Jpn. Patent 77 46,008, (1977); *CA* **87,** 136052 (1977).
48. P. L. Julian, J. Pikl, and F. E. Wantz, *J. Am. Chem. Soc.* **57,** 2026 (1935).
49. M. L. Khidekel, E. N. Bakhanova, A. S. Astakhova, K. A. Brikenshtein, V. I. Savchenko, I. S. Monakhova, and V. G. Dorokhov, *Izv. Akad. Nauk SSSR, Ser. Chem.*, 499 (1970).
50. J. C. Kim, *Bull. Chem. Soc. Jpn.* **54,** 3197 (1981).
51. H. Kimura, H. Obara, and S. Takahashi, *Bull. Chem. Soc. Jpn.* **55,** 3661 (1982).
52. S. Kishida and S. Teranishi, *J. Catal.* **12,** 90 (1968).
53. B. O. Lindgren, *Acta Chem. Scand.* **4,** 1365 (1950); **45,** 6602 (1951).
54. J. W. Lown, S. M. Sondhi, S. B. Mandal, and J. Murphy, *J. Org. Chem.* **47,** 4304 (1982).
55. F. J. McQuillin, "Homogeneous Hydrogenations in Organic Chemistry." Reidel, Boston, Massachusetts, 1976.
56. F.-H. Marquardt, *Ann. N.Y. Acad. Sci.* **214,** 110 (1973).
57. I. W. Mathison and P. H. Morgan, *J. Org. Chem.* **39,** 3210 (1974).
58. T. Matsumoto, Y. Endo, and M. Okimoto, *Bull. Chem. Soc. Jpn.* **56,** 2018 (1983).
59. E. B. Maxted and S. Akhtar, *J. Chem. Soc.*, 3130 (1959).
60. J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.* **82,** 5235 (1960).
61. W. S. Millman and G. V. Smith, *in* "Catalysis in Organic Syntheses, 1977" (G. V. Smith, ed.), p. 48. Academic Press, New York, 1979.
62. F. Misani, J. Speers, and A. M. Lyon, *J. Am. Chem. Soc.* **78,** 2801 (1956).
63. E. A. Mistryakov. and G. T. Katvalyan, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **3,** 702 (1969); CA **71,** 38159 (1969).
64. S. Mitsui, Y. Senda, and H. Saito, *Bull. Chem. Soc. Jpn.* **39,** 694 (1966).
65. S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga, and Y. Senda, *Tetrahedron* **29,** 1531 (1973).
66. M. D. Nair and R. Adams, *J. Org. Chem.* **27,** 3059 (1961).
67. M. Nakahata, M. Imaida, H. Ozaki, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.* **55,** 2186 (1982).
68. S. Nishimura, T. Itaya, and M. Shiota, *Chem. Commun.*, 422 (1967).
69. S. Nishimura, M. Katagiri, and Y. Kunikata, *Chem. Lett.*, 1235 (1975).
70. S. Nishimura, M. Katagiri, and Y. Kunikata, *Chem. Lett.*, 963 (1977).
71. S. Nishimura, M. Ishige, and M. Shiota, *Chem. Lett.*, 535 (1977).
72. S. Nishimura, M. Murai, and M. Shiota, *Chem. Lett.*, 1239 (1980).
73. S. Nishimura, I. Takahashi, M. Shiota, and M. Ishige, *Chem. Lett.*, 877 (1981).

74. W. E. Pascoe and J. F. Stenberg, *in* "Catalysis in Organic Syntheses, 1978" (W. H. Jones, ed.), p. 1. Academic Press, New York, 1979.
75. M. A. Phillips, *Br. Chem. Eng.* **8,** 767 (1963).
76. N. Pourahmady and E. J. Eisenbraun, *J. Org. Chem.* **48,** 3067 (1983).
77. C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr. and H. S. Aaron, *J. Org. Chem.* **29,** 2252 (1964).
78. L. P. Reiff and H. S. Aaron, *Tetrahedron Lett.*, 2329 (1967).
79. D. R. Roberts, *J. Org. Chem.* **30,** 4375 (1965).
80. S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).
81. P. N. Rylander and N. Himelstein, *Engelhard Ind. Tech. Bull.* **4,** 131 (1964).
82. P. N. Rylander and J. Kaplan, *Engelhard Ind. Tech. Bull.* **2,** 48 (1961).
83. P. N. Rylander and S. Starrick, *Engelhard Ind. Tech. Bull.*, **7,** 106 (1966).
84. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **5,** 113 (1965).
85. P. N. Rylander and D. R. Steele, *Tetrahedron Lett.*, 1579 (1969).
86. P. N. Rylander and X. Vaflor, Am. Chem. Soc. Cent. Reg. Meeting, Morgantown, West Virginia, No. 12, 1975.
88. R. L. Shriner and H. R. Todd, *Org. Synth. Coll. Vol.* **2,** 200 (1943).
89. A. Sohma and S. Mitsui, *Bull. Chem. Soc. Jpn.* **42,** 1451 (1969).
90. K. Steiner, U.S. Patent No. 3,953,524, (1976).
91. C. Sungbom and K. Tanaka., *Bull. Chem. Soc. Jpn.* **55,** 2275 (1982).
92. W. A. Szarek, B. M. Pinto, and A. H. Haines, *Can. J. Chem.* **60,** 390 (1982).
93. A. Tai, T. Harada, Y. Hiraki, and S. Murakami, *Bull. Chem. Soc. Jpn.* **56,** 1414 (1983).
94. Y. Takagi, S. Tetratani, and K. Tanaka, *in* "Catalysis" (J. W. Hightower, ed.), p. 757. Elsevier, New York, 1973.
95. T. Tanabe, K. Okuda, and Y. Izumi, *Bull. Chem. Soc. Jpn.* **46,** 514 (1973).
96. W. F. Tuley and R. Adams, *J. Am. Chem. Soc.* **47,** 3061 (1925).
97. M. Verzele, M. Acke, and M. Anteunis, *J. Chem. Soc.*, 5598 (1963).
98. G. N. Walker, *J. Org. Chem.* **23,** 133 (1958).
99. R. J. Wicker, *J. Chem. Soc.*, 2165 (1965).
100. L. W. Wright, *CHEMTECH*, 42 (1974).

- 5 -

Hydrogenation of Acids, Anhydrides, and Esters

Acids, anhydrides, and esters are considered together because of their structural similarities and common characteristics on catalytic hydrogenation. None is reduced easily and often vigorous conditions are required.

5.1. Acids

Acids require vigorous conditions for successful reductions on a synthetic scale, but they can be reduced to the alcohol in small yield over rhodium even at ambient conditions. This fractional reduction is without utility but it is sufficient to cause errors in absorption measurements when a carboxylic acid is used as a solvent. At 150°C and 2000 psig, Rh_2O_3 becomes a useful catalyst for carboxylic acid hydrogenation (*13*).

Ruthenium dioxide or ruthenium-on-carbon are effective catalysts for hydrogenation of mono- and dicarboxylic acids to the alcohol or glycol. High pressures (5,000–10,000 psig) and elevated temperatures (130–225°C) have been used in these hydrogenations (*8,12,24*). Yields of alcohol tend to be less than perfect because of esterification of the alcohol. Near quantitative yields of alcohol can be obtained by mixing ruthenium and copper chromite catalysts so as to reduce the ester as formed.

$$RCOOH + 2\,H_2 \xrightarrow{Ru} RCH_2OH + H_2O$$

$$RCH_2OH + RCOOH \longrightarrow RCH_2OCOR + H_2O$$

$$RCH_2OCOR + 2\,H_2 \xrightarrow{CuCr} 2RCH_2OH$$

Rhenium oxides are also useful in reduction of carboxylic acids (~170°C, 3500 psig). Aromatic acids can be reduced to alcohols without ring saturation (*3,4,5,6*). Strongly synergistic effects were found on substituting half of the Re_2O_7 with ruthenium-on-carbon, and excellent results can be obtained at

part attributable to competition of substrate, hydrogen, and solvent for catalyst sites (*52*).

200°C and 600 psig. Hydrocarbon by-products increase if the catalyst is reused and with increased temperature but decrease with increased pressure. Rhodium or palladium with rhenium also shows synergistic effects (*27*). A catalyst made from Re_2O_7 and $Pd(NO_3)_2$-on-carbon gave a 97% yield of 1,6-hexanediol from adipic acid (*10*).

Copper chromite (*14*) and barium-promoted copper chromite (*15,17*) have been used for acid reductions but very high temperatures (300°C) are required. The necessary temperature is sufficiently higher than that required for esters to permit selective reduction of half-acid esters to the hydroxy acid (*23*). The reverse selectivity can be achieved by reduction over $H_4Ru_4(CO)_8(PBu_3)_4$ at 100–200°C and 1500–3000 psig. This homogeneous catalyst will reduce acids and anhydrides, but not esters (*2*).

5.2. Anhydrides

Anhydrides are reduced with relative ease. McAlees and McCrindle (*20*) established the following increasing order of difficulty for various carbonyls: acid chlorides > aldehydes, ketones > anhydrides > esters > carboxylic acids > amides. Reduction may proceed by 1,2-addition of hydrogen or by cleavage of an oxygen–carbonyl bond. If 1,2-addition to the carbonyl occurs, as in the presence of strong protic acids over palladium, 1,1-diesters are formed by acylation (*26*).

$$(CH_3CO)_2O \xrightarrow[70°C]{Pd,\,HCl} CH_3CH(OCOCH_3)_2$$

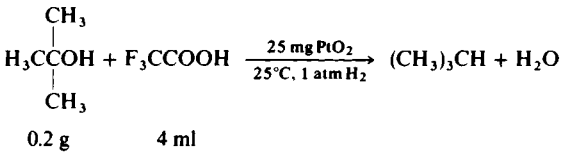
The course of reduction of a variety of anhydrides with platinum and palladium under mild conditions have been discussed in detail (*16,20*). Products vary with substrate structure, reaction conditions, and solvent (*11,20a,25*).

The most studied reaction of this type is hydrogenation of maleic and succinic anhydrides as precursors of butyrolactone, tetrahydrofuran, and 1,4-butanediol, any of which may be made the major product of reduction. The equilibrium ratio of butyrolactone and 1,4-butanediol depends markedly on pressure. At 1 atm and 270°C, butyrolactone is highly favored; at 300 atmospheres the ratio is 6:94, favoring the diol. Tetrahydrofuran can be obtained in 98% selectivity from vapor-phase hydrogenation of maleic anhydride over Cu–Cr–Zn-on-Al_2O_3 (230°C, 25 atm) (*21*). Unsymmetrical anhydrides are reduced preferentially at the carbonyl group having the least

5.3. Esters

Hydrogenation of esters may give alcohols, acids, ethers, or hydrocarbons; the product composition seems to depend largely on the structure of the substrate.

Acids are expected to form when an R—O bond has been weakened as when R = benzyl, vinyl, or allyl. Certain bromo esters (*7,9,19*) form acids and undergo facile debromination, perhaps by elimination with formation of an intermediate olefin. Tertiary esters in the presence of a strong acid also undergo hydrogenolysis readily with formation of a carboxylic acid, perhaps arising through an intermediate alkene (*22*). Tertiary alcohols also undergo facile hydrogenolysis in trifluoroacetic acid, probably through conversion to the trifluoroacetate. The reaction might be useful in selectively removing a tertiary oxygen in a polyfunctional molecule or removal of a *t*-butyl protecting group from an ether or ester.



Alcohols are the most frequently formed products of ester hydrogenolysis. The hydrogenation of esters to alcohols is a reversible reaction with alcohol formation favored at high pressure, ester at low pressure (*1*). Copper chromite is usually the catalyst of choice. Details for the preparation of this catalyst (*17*) and a detailed procedure for hydrogenation of ethyl adipate to hexamethylene glycol (*18*) are given in *Organic Syntheses.*

References

1. H. Adkins and R. E. Burke, Jr., *J. Am. Chem. Soc.* **70,** 4174 (1948).
2. M. Bianchi, G. Menchi, F. Francalanci, F. Fiacenti, U. Matteoli, P. Frediani, and C. Botteghi, *J. Organomet. Chem.* **188,** 109–119 (1980).
3. H. S. Broadbent and W. J. Bartley, *J. Org. Chem.* **28,** 2345 (1963).
4. H. S. Broadbent and T. G. Selin, *J. Org. Chem.* **28,** 2343 (1963).
5. H. S. Broadbent, G. C. Campbell, W. J. Bartley, and J. H. Johnson, *J. Org. Chem.* **24,** 1847 (1959).
6. H. S. Broadbent, V. L. Mylroie, and W. R. Dixon, *Ann. N.Y. Acad. Sci.* **172,** 194 (1970).
7. J. S. Campbell and C. Kemball, *Trans. Faraday Soc.* **59,** 2583 (1963).
8. J. E. Carnahan, T. A. Ford, W. F. Gresham, W. E. Grisby, and G. F. Hager, *J. Am. Chem. Soc.* **77,** 3766 (1955).

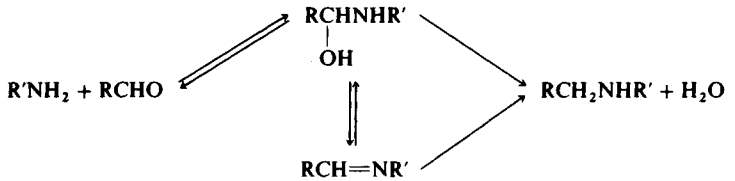
9. D. A. Denton, F. J. McQuillin, and P. L. Simpson, *Proc. Chem. Soc., London*, 297 (1964).
10. J. Disteldorf, W. Huebel, R. Wessendrof, and J. Broschinski, Ger. Offen 2,605,107 (1977).
11. T. A. Eggelte, H. Dekonning, and H. O. Huisman, *Tetrahedron* **29,** 2445 (1973).
12. T. A. Ford, U.S. Patent No. 2,607,807 (1952).
13. R. A. Grimm, A. J. Scirton, and J. K. Well, *J. Am. Oil Chem. Soc.* **46,** 118 (1969).
14. A. Guyer, A. Bieler, and K. Jaberg, *Helv. Chim. Acta* **30,** 39 (1947).
15. A. Guyer, A. Bieler, and M. Sommaruga, *Helv. Chim. Acta* **38,** 976 (1955).
16. R. Kuhn and I. Butala, *Justus Liebigs Ann. Chem.* **718,** 50 (1968).
17. W. A. Lazier and H. R. Arnold, *Org. Synth., Coll. Vol.* **2,** 142 (1943).
18. W. A. Lazier, J. W. Hill, and W. J. Amend, *Org. Synth., Coll. Vol.* **2,** 325 (1943).
19. S. G. Levine and M. E. Wall, *J. Am. Chem. Soc.* **81,** 2829 (1959).
20. A. J. McAlees and R. McCrindle, *J. Chem. Soc. C*, 2425 (1969).
20a. R. McCrindle, K. H. Overton, and R. A. Raphael, *Proc. Chem. Soc.*, 313 (1961).
21. B. Miya, F. Hoshino, and T. Ono, *Am. Chem. Soc., Div. Pet. Chem.* (1973); *CA* **82,** 43112 (1975).
22. P. E. Peterson and C. Casey, *J. Org. Chem.* **29,** 2325 (1964).
23. D. C. Sayles and D. F. Degering, *J. Am. Chem. Soc.* **71,** 3161 (1949).
24. R. C. Schreyer, U.S. Patent No. 2,862,977 (1958).
25. J. Sicher, F. Sipos, and J. Jonas, *Coll. Czech. Chem. Commun.* **26,** 262 (1961).
26. S. Suzuki, Belg. Patent 879,178 (1980); *CA* **93,** 7669 (1980).
27. B. C. Trivedi, D. Grote, and T. O. Mason, *J. Am. Oil. Chem. Soc.* **58,** 19 (1981).

-6-

Reductive Alkylation

6.1. Introduction

Reductive alkylation is the term applied to the process of introducing alkyl groups to ammonia, or a primary or secondary amine by means of an aldehyde or ketone in the presence of a reducing agent (*16*). The term is also applied to those compounds that are not amines or carbonyls per se but that are converted to them in the course of the reaction. Reductive alkylation is a two-step process. The carbonyl compound and amine first undergo an addition reaction to give an intermediate that can undergo hydrogenolysis directly or dehydration to an imine that is then reduced.



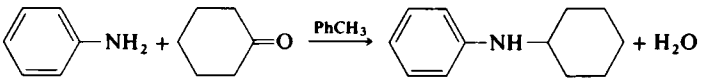
Primary or secondary amines arising from this reaction are themselves suitable reactants that may undergo further alkylation.

$$RCH_2NHR' + RCHO \longrightarrow (RCH_2)_2NR' + H_2O$$

Product composition can be controlled to a considerable extent by the molar ratio of reactants; alkylation tends to become more extensive as the molar ratio of carbonyl to amine increases. Product distribution is influenced also by the catalyst and by steric hindrance with the amount of higher alkylate formed being inversely proportional to the steric hindrance in the neighborhood of the function (*60,62*). Cyclic ketones tend to alkylate ammonia or amines to a further extent than do linear ketones of comparable carbon number (*36*).

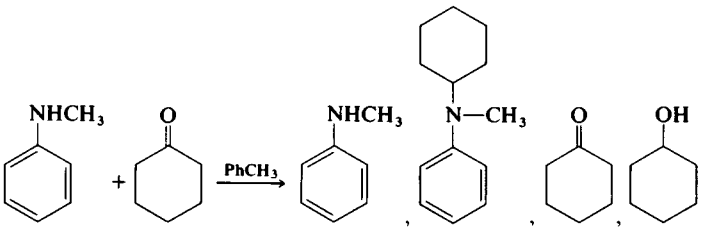
The work of Greenfield and Malz (*25*) on the preparation of arylamines illustrates the sensitivity of yield to hindrance and an influence of catalyst.

Sulfided catalysts are used to minimize reduction of the carbonyl to an alcohol.



0.5 mol 0.5 mol ~98%

5% PtS_x-on-C (10% loading), 25°C, 280–495 psig
5% RhS_x-on-C (10% loading), 80°C, 320–545 psig

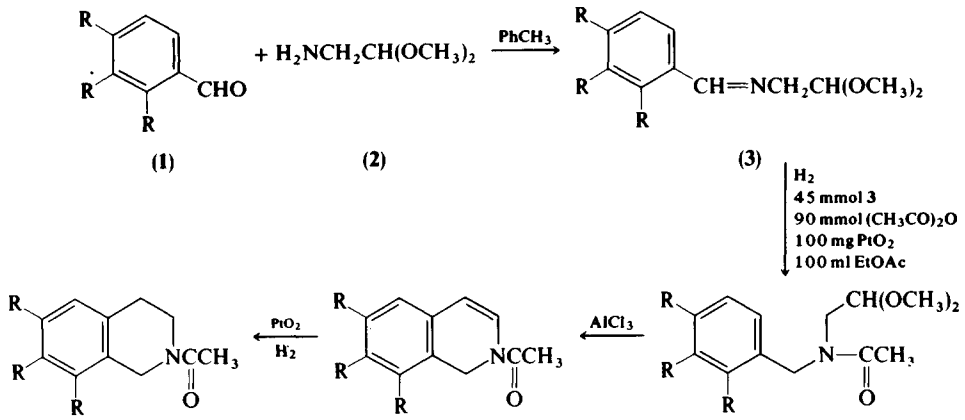


0.5 mol	0.5 mol	20	81	2	14
5% PtS_x-on-C (10% loading) 80°C, 345–505 psi		58	41	40	12
5% RhS_x-on-C (10% loading) 80°C, 445–565 psi					

Platinum was more efficient than rhodium in these experiments. These catalysts give excellent yields of tertiary amines in reductive alkylation of aliphatic secondary amines with ketones (*46*).

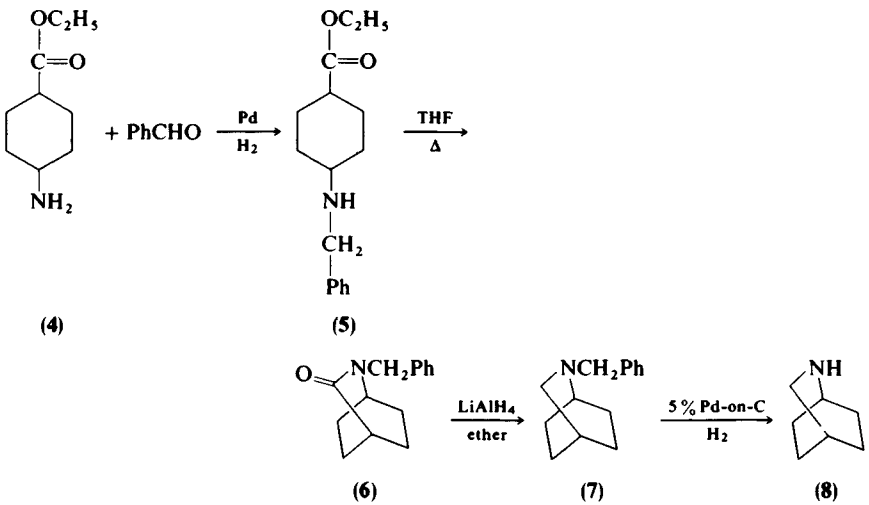
Alkylation to yield a tertiary amine may occur easily if the formation involves cyclization (*53*). Catalysts may have a marked influence. In reductive alkylation of ammonia with cyclohexanones, more primary amine was formed over Ru and Rh and more secondary amine over Pd and Pt. Reduction of the ketone to an alcohol is an important side reaction over ruthenium.

Sometimes the intermediate imine is isolated, but generally it is not and may even be inferior to direct alkylation (*54,63*). Isolation of the Schiff's base was necessary in the following sequence for it was desired to acetylate the alkylated product as formed. A solution of 50 mmol of an aromatic aldehyde (**1**) and 50 mmol of aminoacetaldehyde dimethylacetal (**2**), refluxed 1.5 h in toluene under nitrogen, gave after distillation nearly quantitative yields of the Schiff's base **3** (*56*).



For similar entries into a variety of tetrahydroisoquinolines, see Bobbitt *et al.* (*8*), Bobbitt and Moore (*6*), Gensler *et al.* (*24*), Bobbitt and Shibuya (*7*), and Coomes *et al.* (*12*).

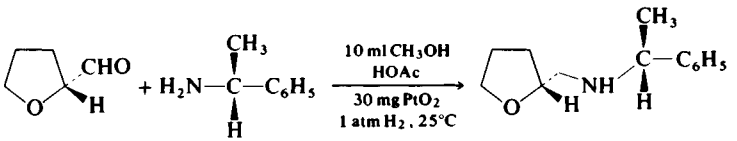
Some workers allow the amine and carbonyl compound to stand together some time before hydrogenation (*3,59*), but this procedure is not always necessary nor even desirable (*33*). The delay technique is illustrated by reductive alkylation of ethyl-4-aminocyclohexane carboxylate (**4**) with benzaldehyde to **5**, a route that permitted an important improvement in the production of isoquinuclidine (**8**) (*59*).



Cyclization of **4** at 258°C in boiling Dowtherm A gives isoquinuclidone in 81–84% yield (*55*), but the temperature is inconvenient on a large scale. By

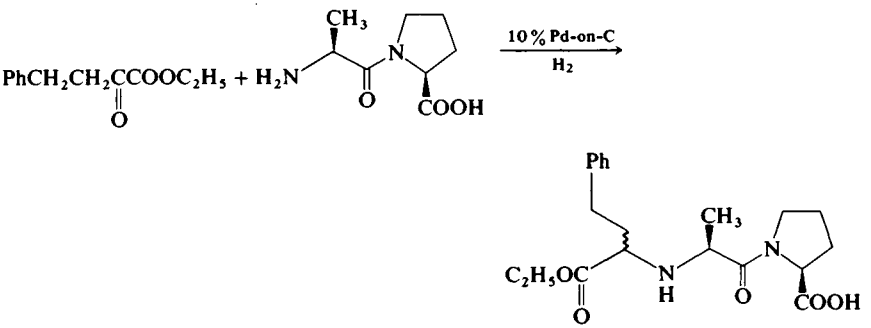
first making the benzyl derivative **5**, cyclization occurs readily in refluxing tetrahydrofuran containing sodium *t*-butoxide. Both cis and trans isomers are useable. The reductive alkylation of **4** is carried out in a solution of triethylamine, acetic acid, and ethanol, which has stood for 2 h. A 10% loading of 5% Pd-on-C is added, and the mixture is hydrogenated at ambient conditions to afford **5** in quantitative yield.

In a further example, reductive alkylation of (*S*)-α-methylbenzylamine with (*R*)-tetrahydrofuran-2-carboxaldehyde over PtO_2 to give **11** was achieved without significant racemization. A mixture of **9** and **10** in methanol containing a few drops of acetic acid was let stand at room temperature before PtO_2 was added (*5*).



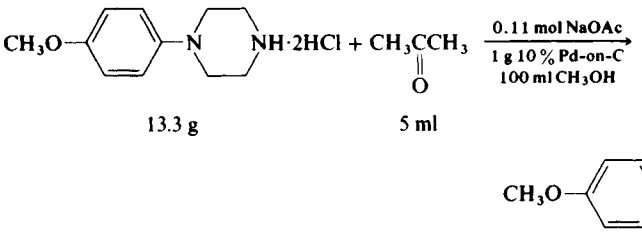
(9) 265 mg **(10)** 322 mg **(11)**

Some workers avoid delay. Palladium-on-carbon was used effectively for the reductive amination of ethyl 2-oxo-4-phenyl butanoate with L-alanyl-L-proline in a synthesis of the antihypertensive, enalapril maleate. Schiff's base formation and reduction were carried out in a single step as Schiff bases of α-amino acids and esters are known to be susceptible to racemization. To a solution of 4.54 g ethyl 2-oxo-4-phenylbutanoate and 1.86 g L-alanyl-L-proline was added 16 g 4A molecular sieve and 1.0 g 10% Pd-on-C. The mixture was hydrogenated for 15 hr at room temperature and 40 psig H_2. Excess α-keto ester was required as reduction to the α-hydroxy ester was a serious side reaction. The yield was 77% with a diastereomeric ratio of 62:38 (SSS:RSS) (*68*).



6.2. Catalysts

Nickel, rhodium, palladium, platinum, and Raney cobalt (*43*) have all been used successfully in reductive alkylations. Platinum is the most used by far (*16*). With small carbonyl molecules, such as acetone, palladium is about as effective as platinum, but as the molecular weight increases, platinum is apt to be more effective (*30*).



Platinum and rhodium sulfided catalysts are very effective for reductive alkylation. They are more resistant to poisoning than are nonsulfided catalysts, have little tendency to reduce the carbonyl to an alcohol, and are effective for avoidance of dehydrohalogenation in reductive alkylation of chloronitroaromatics and chloroanilines (*14,15*). Sulfided catalysts are very much less active than nonsulfided and require, for economical use, elevated temperatures and pressures (300–2000 psig, 50–180°C). Most industrial reductive alkylations, regardless of catalyst, are used at elevated temperatures and pressures to maximize space–time yields and for most economical use of catalysts.

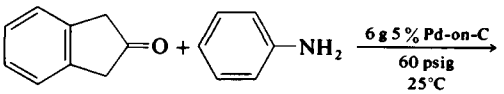
Platinum oxide may show induction periods (*13*) in reductive alkylation and prereduction has been recommended (*37,47*), but it is not always necessary (*19*).

Both steps of the reductive alkylation, i.e., imine formation and the hydrogenation per se, can be catalyzed. A variety of catalysts have been used for the condensation, including basic materials such as tertiary amines (*32*) or pyrrolidine (*63*), acids such as hydrochloric (*1*) or acetic (*61*), acidic carbons, and drying agents (*31*). Acids catalyze also the hydrogenation step by neutralizing the inhibiting effects of the more strongly basic amine products (*22*).

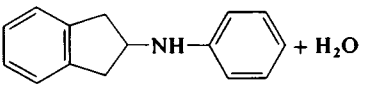
6.3. Solvents

A variety of solvents have been used in reductive alkylations. In industrial practice, excess carbonyl compound is often used as both reactant and solvent.

This common technique, and many others, failed in reductive alkylation of **13** by **12** to **14**, and, in an unusual variation, Campbell and Lavagnino (*10*) obtained satisfactory results only with an excess of aniline serving as both reactant and solvent. Normal procedures were satisfactory when the more basic cyclohexylamine was the reactant.

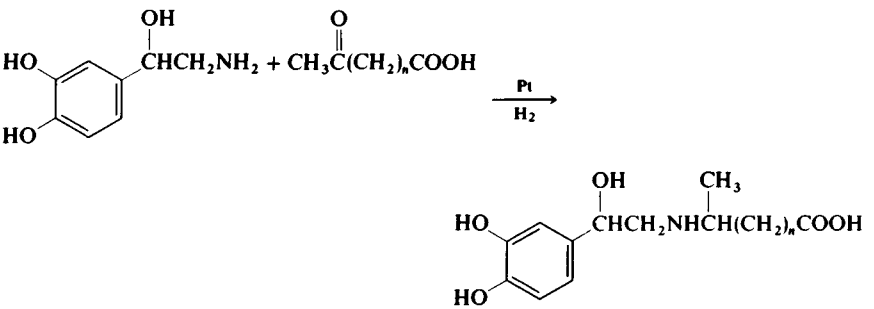


13.2 g (12) 180 ml (13)

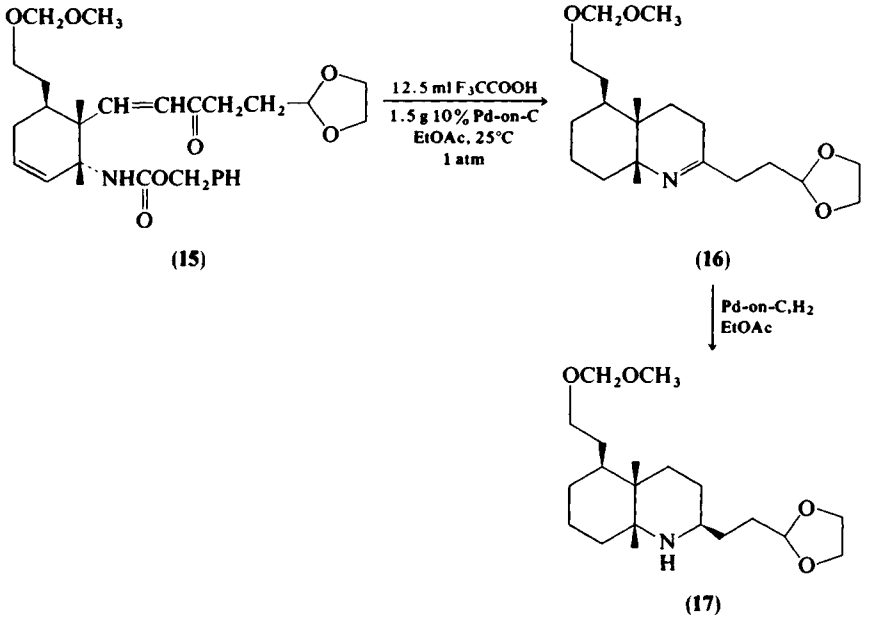


(14)

The solubility of the resulting product may dictate the choice of solvent. Reductive alkylation of norepinephrine with a series of keto acids proceeded smoothly over platinum oxide in methanol–acetic acid mixtures. However, when $n = 4$ or 5, the product tended to precipitate from solution, making catalyst separation difficult. The problem was circumvented by using glacial acetic acid as solvent (*38*).

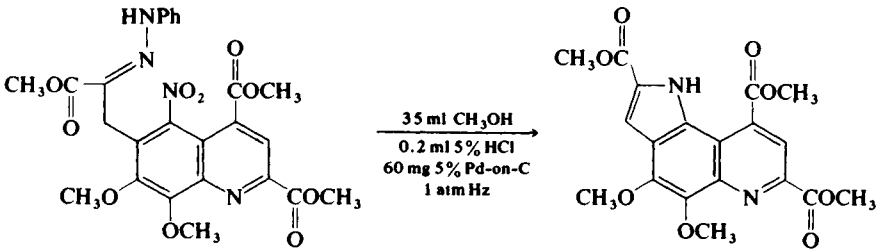


An unusual solvent system was chosen for the intramolecular reductive alkylation of the masked amino ketone (**15**). The purpose of the strongly acid system was to prevent cyclization of the deblocked amino ketone to **16**, further hydrogenation of which gives the unwanted isomer **17** by attack at the convex face. The desired opposite isomer can be obtained by reduction of **16** with $LiAlH_4$ (*52*).



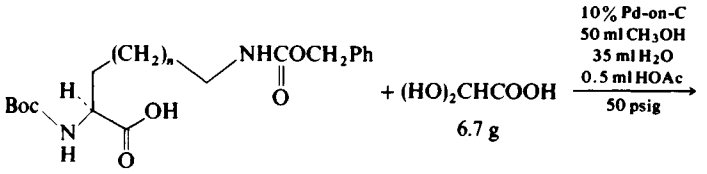
6.4. Amine and Carbonyl Precursors

Reductive alkylations have been carried out successfully with compounds that are not carbonyls or amines, but which are transformed during the hydrogenation to suitable functions. Azides, azo, hydrazo, nitro and nitroso compounds, oximes, pyridines, and hydroxylamines serve as amines; phenols, acetals, ketals, or hydrazones serve as carbonyls (*6,7,8,9,12,17,24,41,42,58*). Alkylations using masked functions have been successful at times when use of unmasked functions have failed (*2*). In a synthesis leading to methoxatin, a key



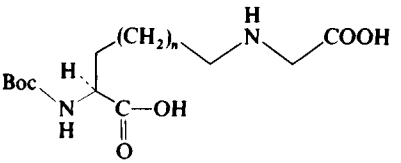
step involved a ring closure between a hydrazone and a nitro function (*23*).

Reductive alkylation has been used to prepare α-amino acids suitable for lactam formation and further elaboration. In a single step a carbobenzyloxy group was removed, and alkylation with glyoxylic acid hydrate was achieved (*18*).



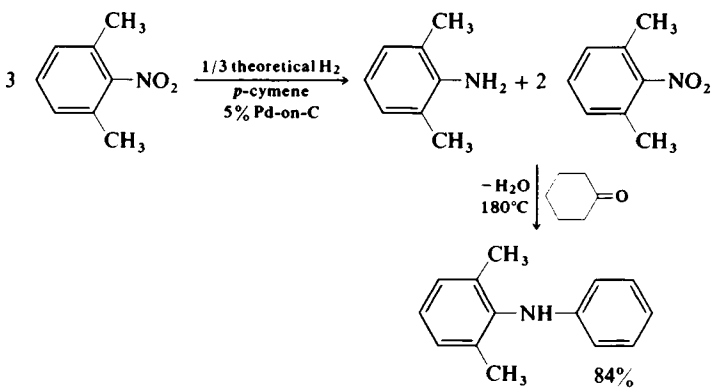
$n = 1,2$

11 g



54%

Cyclohexanones may serve as precursors to aromatic amines in a reductive alkylation, the source of hydrogen being aromatization of the cyclohexanone (*66*). In a variation, an aromatic nitro compound acts as both an amine precursor and a hydrogen acceptor (*64*).

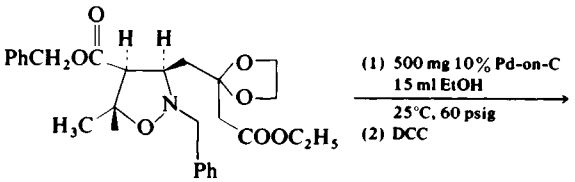


Alcohols also may serve as carbonyl precursors. The reaction with aliphatic alcohols is thought to go through a carbonyl intermediate, but since no hydrogen is actually consumed, the reaction appears to be an amination, as it

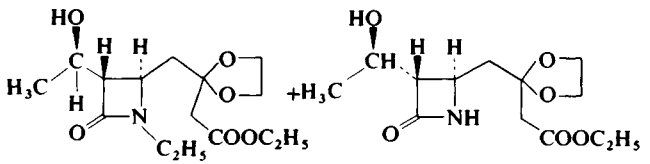
must be in the industrial production of aniline from phenol and ammonia. This type of reaction is illustrated by Baiker and Richarz (*4*).

$$Ph(CH_2)_nOH + HN(CH_3)_2 \xrightarrow[\substack{40\%\ Cu\text{-}on\text{-}\gamma\text{-}Al_2O_3\\ 3\times 4\ mm\ cylinders}]{240^\circ C} Ph(CH_2)_nN(CH_3)_2 + H_2O$$

Reductive alkylation by alcohol solvents may occur as an unwanted side reaction (*22,39*), and it is to avoid this reaction that Freifelder (*20*) recommends ruthenium instead of nickel in pyridine hydrogenation. Alkylation by alcohols may occur with surprising ease (*67*). Reduction of **18** in ethanol over 10% palladium-on-carbon to an amino acid, followed by cyclization with *N,N*-dicyclohexylcarbodiimide gave a mixture of **19** and **20** with the major product being the *N*-ethyl derivative (*49,50*). By carrying out the reduction in acetic acid, **20** was obtained as the sole cyclized product (*40*).



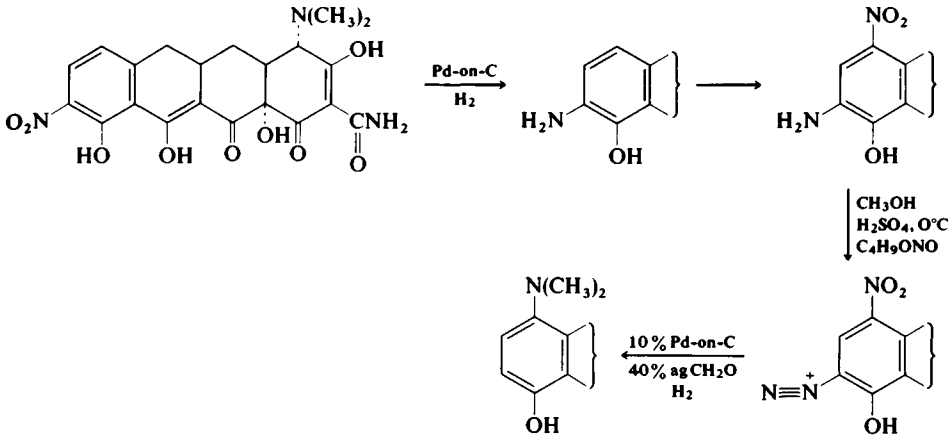
(18)



(19) **(20)**

Nitro functions are easily reductively alkylated; and a number of alkylated anilines are made industrially starting with the appropriate nitroaromatic in the ketone as solvent. The addition reaction can occur at the hydroxylamine intermediate as well as the aniline. A process step is saved by beginning with the nitro compound.

In a synthesis of minocycline, interesting use was made of a reductive alkylation of a nitro function, accompanied by loss of a diazonium group. The sequence provides a clever way of utilizing the unwanted 9-nitro isomer that arises from nitration of 6-demethyl-6-deoxytetracycline (*11*). When diazotization was complete, urea and 40% aqueous formaldehyde were added, and the entire solution was mixed with 10% palladium-on-carbon and reduced under hydrogen. No further use of this combined reaction seems to have been made.



6.5. Stereochemistry

Reductive alkylation with chiral substrates may afford new chiral centers. The reaction has been of interest for the preparation of optically active amino acids where the chirality of the amine function is induced in the prochiral carbonyl moiety (*34,35*). The degree of induced asymmetry is influenced by substrate, solvent, and temperature (*26,27,28,29,48,51,65*). Asymmetry also has been obtained by reduction of prochiral imines, using a chiral catalyst (*44*). Prediction of the major configurational isomer arising from a reductive alkylation can be made usually by the assumption that amine formation comes via an imine, not the hydroxyamino addition compound, and that the catalyst approaches the least hindered side (*57*).

References

1. A. G. Anderson, Jr., and M. T. Wills, *J. Org. Chem.* **33,** 2123 (1968).
2. M. Ando and S. Emoto, *Bull. Chem. Soc. Jpn.* **47,** 501 (1974).
3. S. Archer, T. R. Lewis, M. J. Unser, J. O. Hoppe, and H. Lape, *J. Am. Chem. Soc.* **79,** 5783 (1957).
4. A. Baiker and W. Richarz, *Synth. Commun.* **8,** 27 (1978).
5. P. C. Belanger and H. W. R. Williams, *Can. J. Chem.* **61,** 1383 (1983).
6. J. M. Bobbitt and T. E. Moore, *J. Org. Chem.* **33,** 2958 (1968).
7. J. M. Bobbitt and S. Shibuya, *J. Org. Chem.* **35,** 1181 (1970).

8. J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.* **30,** 2247 (1965).
9. R. E. Bowman, *J. Chem. Soc.*, 1346, 1349 (1950).
10. J. B. Campbell and E. P. Lavagnino, *in* "Catalysis in Organic Syntheses" (Jones, W. H., ed.), p. 43. Academic Press, New York, 1980.
11. R. F. R. Church, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.* **36,** 723 (1971).
12. R. M. Coomes, J. R. Falck, D. K. Williams, and F. R. Stermitz, *J. Org. Chem.* **38,** 3701 (1973).
13. A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.* **64,** 1503 (1942).
14. F. S. Dovell and H. Greenfield, *J. Am. Chem. Soc.* **87,** 2767 (1965).
15. F. S. Dovell and H. Greenfield, U.S. Patent No. 3,350,450 (1967).
16. W. S. Emerson, *Org. React. (N.Y.)* **4,** 174 (1948).
17. W. S. Emerson and C. A. Uraneck, *J. Am. Chem. Soc.* **63,** 749 (1941).
18. R. M. Freidinger, D. S. Perlow, and D. F. Veber, *J. Org. Chem.* **47,** 104 (1982).
19. M. Freifelder, *J. Med. Chem.* **6,** 813 (1963).
22. M. Freifelder and G. R. Stone, *J. Org. Chem.* **26,** 3805 (1961).
23. J. A. Gainor and S. M. Weinreb, *J. Org. Chem.* **47,** 2833 (1982).
24. W. J. Gensler, K. T. Shamasundar, and S. Marburg, *J. Org. Chem.* **33,** 2861 (1968).
25. H. Greenfield and R. E. Malz, Jr., *in* "Catalysis of Organic Reactions" (J. R. Kosak, ed.), p. 309. Dekker, New York, 1984.
26. K. Harada and K. Matsumoto, *J. Org. Chem.* **33,** 4467 (1968).
27. K. Harada and T. Yoshida, *Chem. Commun.*, 1071 (1970).
28. K. Harada and T. Yoshida, *J. Org. Chem.* **37,** 4366 (1973).
29. K. Harada, T. Iwasaki, and T. Okawara, *Bull. Chem. Soc. Jpn.* **46,** 1901 (1973).
30. J. Heeres, R. Hendrick, and J. Van Cutsen, *J. Med. Chem.* **26,** 611 (1983).
31. R. V. Heinzelman and B. D. Aspergren, *J. Am. Chem. Soc.* **75,** 3409 (1953).
32. R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.* **76,** 926 (1954).
33. D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.* **74,** 414 (1952).
34. R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.* **83,** 4798 (1961).
35. R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.* **87,** 1753 (1965).
36. W. Huckel and R. Kupka, *Chem. Ber.* **89,** 1694 (1956).
37. R. W. Iles and W. S. Worrall, *J. Org. Chem.* **26,** 5233 (1961).
38. K. A. Jacobson, D. Marr-Leisy, R. P. Rosenkranz, M. S. Verlander, K. L. Melmon, and M. Goodman, *J. Med. Chem.* **26,** 492 (1983).
39. J. I. Jones, *J. Chem. Soc.*, 1932 (1950).
40. T. Kametani, S.-P. Huang, and A. Nakayama, *J. Org. Chem.* **47,** 2328 (1982).
41. F. Kaplan and H. Conroy, *J. Org. Chem.* **28,** 1593 (1963).
42. H. W. Kilbroune, J. E. VanVerth, and G. R. Wilder, U.S. Patent No. 3,219,703 (1965).
43. S. Kiyooka and K. Suzuki, *Bull. Chem. Soc. Jpn.* **47,** 2081 (1974).
44. N. Langlois, T.-P. Dang, and H. B. Kagan, *Tetrahedron Lett.*, 4865 (1973).
45. R. W. Layer, *Chem. Rev.* **63,** 489 (1963).
46. R. E. Malz, Jr., and H. Greenfield, paper presented at Am. Chem. Soc. Metro Chem. 1982 Meeting, Rutgers University, New Brunswick, New Jersey, June, 1982.
47. R. H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.* **51,** 580 (1929).
48. K. Matsumoto and K. Harada, *J. Org. Chem.* **33,** 4526 (1968).
49. S.-I. Murahashi, T. Shimamura, and I. Moritani, *J.C.S. Chem. Commun.*, 931 (1974).
50. S.-I. Murahashi, K. Kondo, and T. Hakata, *Tetrahedron Lett.* **23,** 229 (1982).
51. D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, and R. D. Morin, *J. Med. Chem.* **16,** 480 (1973).
52. L. E. Overman, D. Lesuisse, and M. Hashimoto, *J. Am. Chem. Soc.* **105,** 5373 (1983).
53. I. J. Pachter and G. Suld, *J. Org. Chem.* **25,** 1680 (1960).
54. H. A. Patel and D. B. MacLean, *Can. J. Chem.* **61,** 7 (1983).

55. W. M. Pearlman, *Org. Synth. Coll. Vol.* **5,** 670 (1969).
56. C. D. Perchonock, I. Lantos, J. A. Finkelstein, and K. C. Holden, *J. Org. Chem.* **45,** 1950 (1980).
57. V. Prelog, *Bull. Soc. Chim. Fr.*, 987 (1956).
58. J. Sam, J. D. England, and D. W. Alwani, *J. Med. Chem.* **7,** 732 (1964).
59. M. C. Scaros, H. L. Dryden, Jr., J. P. Westrich, and O. J. Goodmonson, *in* "Catalysis of Organic Reactions" (J. R. Kosak, ed.), p. 279. Dekker, New York, 1984.
60. A. Skita and F. Keil, *Chem. Ber.* **61B,** 1452 (1928).
61. A. Skita and W. Stühmer, Ger. Offen 932,677 (1955).
62. A. Skita, F. Keil, and E. Baesler, *Chem. Ber.* **66B,** 858 (1933).
63. E. S. Stratford and R. W. Curley, Jr., *J. Med. Chem.* **26,** 1463 (1983).
64. J. E. VanVerth and G. R. Wilder, U.S. Patent No. 3,219,702 (1965).
65. F. Weinges and G. Graab, *Chem.-Ztg., Chem. Appar.* **94,** 728 (1970).
66. G. R. Wilder and J. E. VanVerth, U.S. Patent No. 3,219,704 (1965).
67. J. J. K. Wright, J. A. Albarella, and P. Lee, *J. Org. Chem.* **47,** 523 (1982).
68. M. J. Wyvratt, E. W. Tristram, T. J. Ikeler, N. C. Lohr, H. Joshua, J. P. Springer, B. H. Arison, and A. A. Patchett, *J. Org. Chem.* **49,** 2817 (1984).

- 7 -

Hydrogenation of Nitriles and Oximes

Nitriles and oximes are considered together because of common features. Both functions are reduced to primary amines, both undergo coupling reactions to secondary amines, and both are subject to reductive hydrolysis. These similarities arise from a common intermediate, an imine. The imine is

$$RCH{=}NOH \xrightarrow[-H_2O]{H_2} RCH{=}NH \xleftarrow{H_2} RC{\equiv}N$$

$$H_2 + RCH{=}NH \longrightarrow RCH_2NH_2$$

further reduced to an amine, and the amine and imine can give an addition product that undergoes either elimination of water to an imine, followed by saturation, or direct hydrogenolysis, resulting in a secondary amine. Tertiary amines are formed similarly by further reaction of secondary amines. The extent of coupling is sensitive to environment, increasing with increasing temperature and decreasing with increasing pressure.

$$RCH{=}NH + RCH_2NH_2 \longrightarrow \underset{\displaystyle NH_2}{\underset{|}{RCHNHCH_2R}} \longrightarrow (RCH_2)_2NH$$

$$\underset{\displaystyle NH_2}{\underset{|}{RCHNHCH_2R}} \xrightarrow{-NH_3} RCH{=}NCH_2R \xrightarrow{H_2} (RCH_2)_2NH$$

In aqueous media, the intermediate imine can undergo a reductive hydrolysis.

$$RCH{=}NH + H_2O \longrightarrow RCHO + NH_3 \xrightarrow{H_2} RCH_2OH$$

The aldehyde may be also a source of a secondary amine.

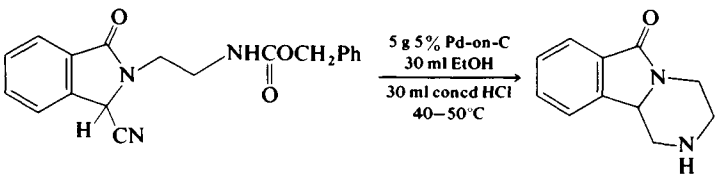
$$RCHO + RCH_2NH_2 \xrightarrow{H_2} (RCH_2)_2NH + H_2O$$

7.1. Nitriles

The above scheme to account for products of nitrile hydrogenation was proposed sixty years ago (*80*), and with minor variations (*28,45,86*) has withstood the test of time. It might be expected from the foregoing that, if a nitrile were reduced in the presence of an amine, unsymmetrical amines would result (*48*), and indeed the reaction provides an excellent way of preparing these amines (*49,74*).

$$RCN + R'NH_2 \xrightarrow{H_2} RCH_2NHR' + NH_3$$

The amine and nitrile can be in the same molecule, as illustrated by the reductive coupling and cyclization of **1** to give tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one (**2**) (*84*).

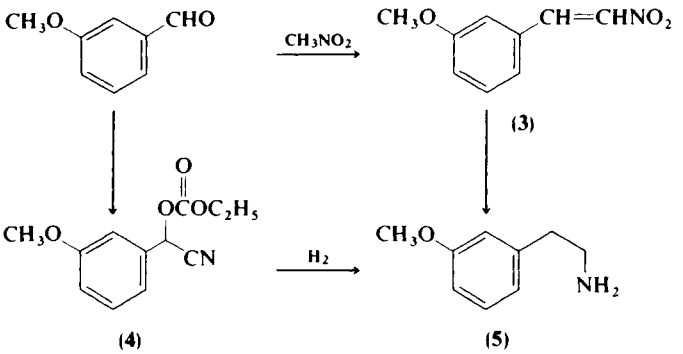


(**1**) (**2**)

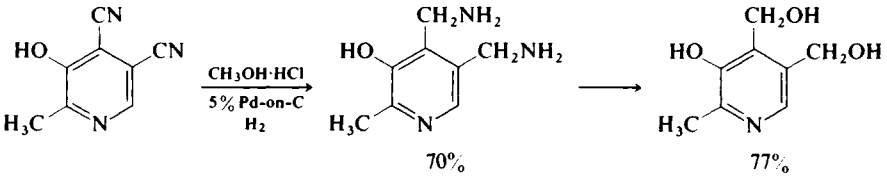
64%

7.1.1. Solvents

Both acidic and basic media are effective in suppressing coupling reactions. Strongly acidic solutions prevent further reaction of the initially formed primary amine by formation of an ammonium salt, and many workers have used such solutions for this purpose with success (*14,23,34,75,81*). For example, hydrogenation of mandelonitrile provides a good route to β-phenylethylamines. The procedure was resorted to when hydrogenation of the β-nitrostyrene **3** proved fickle, the products changing with scale. A solution of 23.5 g (0.1 mol) *O*-(ethoxycarbonyl)-3-methoxymandelonitrile (**4**) in 300 ml absolute ethanol was added dropwise (0.5 drop/sec) to a mechanically stirred solution of 300 ml absolute ethanol containing 1.5 g 10% Pd-on-C and 12.9 g (0.13 mol) concentrated sulfuric acid as hydrogen gas was bubbled through the solution. After addition was complete, stirring and bubbling continued for 8 h. After filtration and extraction, 2-(*m*-methoxyphenylethylamine) (**5**) was obtained in 92% yield (*47*) (procedure used with permission).

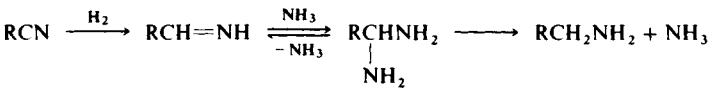


Inter- and intramolecular amine coupling was prevented by the use of hydrogen chloride in a synthesis of pyridoxine (*33*).



Another effective way of preventing coupling reactions is to acetylate the primary amine as formed by carrying out the reduction in an anhydride solvent. This technique is especially useful if the acetylated amine is the desired product (*17,30,59,77*).

A common technique for minimizing secondary amine formation is to carry out the hydrogenation in the presence of ammonia (*21,23,42*). Ammonia is thought to compete with the primary amine in attack on the intermediate imine. Anhydrous ammonia is preferred to prevent hydrolysis reactions.

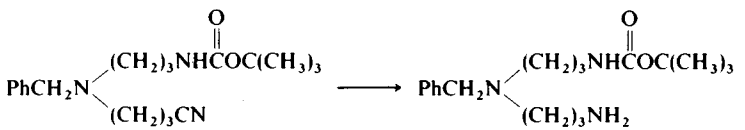


The above equation adequately accounts for the action of ammonia, but it may function in other ways as well, for a variety of bases, such as tertiary amines, carbonates (*46*), and hydroxides (*20,32*), also suppress formation of coupled products. Greenfield (*28*) suggested that bases may function by suppressing the hydrogenolysis reaction leading to secondary and tertiary amines.

The solvent for ammonia may have an important influence. In reduction of C_{10} unsaturated dinitriles to primary amines over ruthenium-on-alumina, ammonia–*t*-butanol proved the preferred system; normal alcohols gave poor rates and secondary alcohols produced N-alkylated products (*18*).

7.1.2. Catalysts

Nickel in the presence of ammonia is often used for reduction of nitriles to primary amines. The reaction is done at elevated temperatures and pressures ($\sim 100°C$, 1000 psig) unless massive amounts of nickel are used. Cobalt is used similarly but mainly under even more vigorous conditions. Nitriles containing a benzylamine can be reduced over Raney nickel to an amine without hydrogenolysis of the benzyl group (*7*). A solution of *N*-[*N*-(*t*-butoxycarbonyl)-3-aminopropyl]-*N*-(3-cyanopropyl)benzylamine (13.6 g) in 100 ml of ethanol containing 4 g. NaOH was reduced over 3.0 g Raney nickel at 40 psig for 28 h. The yield of N^4-benzyl-N^1-(*t*-butoxycarbonyl)spermidine was 95% (*7*).



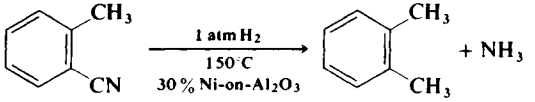
Platinum, palladium, and rhodium will function well under milder conditions and are especially useful when other reducible functions are present. Freifelder (*23*) considers rhodium–ammonia the system of choice when reducing β-amino nitriles and certain β-cyano ethers, compounds that undergo extensive hydrogenolysis under conditions necessary for base-metal catalysis.

Catalysts show remarkable product variation in hydrogenation of simple nitriles. Propionitrile, in neutral, nonreactive media, gives on hydrogenation over rhodium-on-carbon high yields of dipropylamine, whereas high yields of tripropylamine arise from palladium or platinum-catalyzed reductions (*71*). Parallel results were later found for butyronitrile (*28*) and valeronitrile (*74*) but not for long-chain nitriles. Good yields of primary aliphatic amines can be obtained by use of cobalt, nickel, nickel boride, rhodium, or ruthenium in the presence of ammonia (*4,11,67,68,69*).

The differences among palladium, platinum, and rhodium cited above for simple aliphatic nitriles do not apply to aromatic nitriles. Aromatic nitriles form only primary and secondary amines, and in this regard platinum and rhodium are alike, whereas palladium is much different. In hydrogenation of benzonitrile, palladium tends to form benzylamines; rhodium and platinum, dibenzylamine (*74*). Greenfield (*29*) used platinum-on-carbon effectively for hydrogenation of neat benzonitrile to dibenzylamine in a system containing one-half equivalent of water to prevent catalyst poisoning; more water encouraged hydrolysis products.

The cyano group in aromatic nitriles can be converted directly to a methyl group in vapor phase over 30% Ni-on-Al_2O_3 prereduced by hydrogen *in situ*

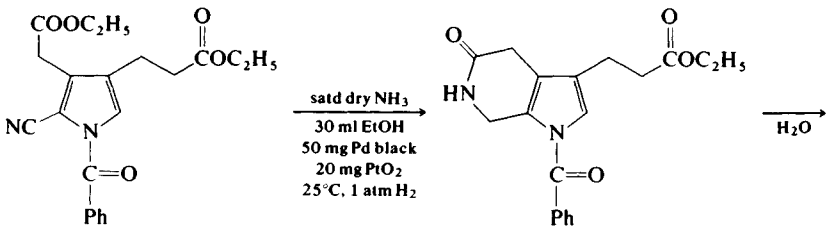
at 400°C (*3*). There is some evidence that benzylamine is not an intermediate in this synthesis (*31*).



The above technique is limited to compounds of sufficient volatility and thermal stability. The reaction can be made more general by the use of palladium (*44*), which will reduce an intermediate benzylamine.

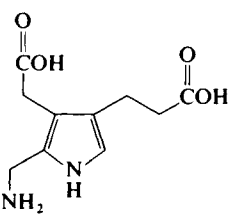
7.1.3. Cyclizations

A variety of ring systems have been prepared by reduction of nitriles containing a suitable second function. Cyclization may occur as a step subsequent to the hydrogenation proper, as in reduction of a nitrile to an amine, followed by ring closure through interaction of the amine with an acid, ester, or amide (*5,9,10,41,51,79,87*). These functions are all reduced with relative difficulty, making success in the cyclization dependent largely on prevention of secondary amine formation during nitrile reduction. Cyclization itself may be an important factor in preventing secondary amines and can serve as a trapping reaction for synthesis of the primary amine. The nitrile **6** was reduced to porphobilinogen (**8**) with difficulty. Reaction of **6** in acetic



304 mg

(**6**) (**7**)



(**8**)

anhydride over platinum oxide was foiled by accompanying ring reduction; over 10% Pd-on-C, only the double bonds were reduced. The primary amine could be trapped successfully as the lactam ester **7** by reduction in ethanol–ammonia over palladium black–platinum oxide; hydrolysis of **7** gave **8** (*17*).

The catalyst has more influence on nitrile cyclizations in which the second function is itself easily reducible. The sequence of functional group reduction can markedly alter the products. For instance, cyclization of cyano ketones presumably goes through a normal reductive alkylation after preferential reduction of the nitrile to an amine; if the ketone is reduced first, the product will be an amino or cyano alcohol, and cyclization will not occur. Reduction of 2-(β-cyanoethyl)cyclohexanone in methanol over palladium or rhodium gives high yields of decahydroquinoline, but over platinum the product is the amino alcohol. Raney nickel (*10,53,79*) and palladium (*55,56,64*) have each given excellent results in the hydrogenation of cyano ketones. The stereochemistry of cyclization has been altered by the presence of ammonia, which in essence changes the functions undergoing cyclization (*64*).

7.2. Oximes

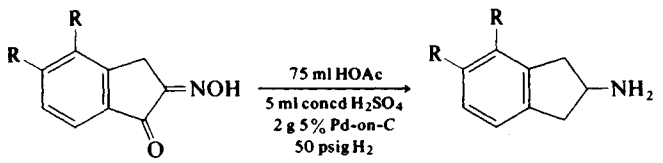
Hydrogenation of oximes to primary amines usually can be made to proceed smoothly despite the potential complications cited earlier. Many of the same considerations applicable to control of nitrile reductions hold for oxime reductions as well. Oximes, unlike nitriles, can be reduced to hydroxylamines.

7.2.1. Catalysts

Both base and noble-metal catalysts have been used with success in the hydrogenation of oximes. Base metals, such as nickel (*1,13,50,76*) or cobalt (*26,63*), are used at elevated temperatures and pressures (~80–100°C, 100 atm), and under these conditions runaway reactions have occurred with easily reduced compounds. Due caution must be exercised by limiting the catalyst or hydrogen or by sufficient dilution with solvent (*22*).

Noble-metal catalysts can be used under mild conditions. Rhodium (*16,24,61,73*) has given excellent results. Rhodium seems especially useful when other catalysts give excessive secondary amine. Ruthenium functions best in aqueous media, but under these conditions it is apt to promote extensive

hydrolysis reactions (*72,73*). Palladium has been used often (*52*), especially in acidic media (*19,25,34,65,78,82*). Smooth hydrogenolysis and hydrogenation of 4,5-dimethoxy-2-oximino-1-indanone (**9**) to 4,5-dimethoxy-2-aminoindan (**10**) (R = OCH_3) occurred over 5% Pd-on-C in H_2SO_4–HOAc (*12*).



5.0g

(**9**) (**10**)

This result stands in contrast to hydrogenation of 2-oximino-1-indanone (R = H), which stopped spontaneously at the 2-amino-1-indanol stage under similar conditions (*43*). This latter result accords with the general experience in reduction of aromatic β-oximino ketones (*35,37,38,39,40*). The amino function usually severely inhibits hydrogenolysis of the alcohol.

Oximes can form either an imine or a hydroxylamine, and these in turn can be reduced to an amine.

$$H_2O + RCH{=}NH \xleftarrow{H_2} RCH{=}NOH \xrightarrow[Pt,\,H^+]{H_2} RCHNHOH$$

Imines are easily reduced and rarely accumulate (*62,83*). Hydroxylamines are reduced relatively slowly and can be obtained in good yield; platinum in acidic media appears to be the preferred system (*6,27,54,58,65*). Best yields are obtained from oximes of aliphatic carbonyls; aromatic oximes give amines.

7.2.2. Solvents

Solvents influence the hydrogenation of oximes in much the same way as they do hydrogenation of nitriles. Acidic solvents prevent the formation of secondary amines through salt formation with the initially formed primary amine. A variety of acids have been used for this purpose (*66*), but acids cannot always be used interchangeably (*43*). Primary amines can be trapped also as amides by use of an anhydride solvent (*2,15,57*). Ammonia prevents secondary amine formation through competition of ammonia with the primary amine in reaction with the intermediate imine. Unless the ammonia is anhydrous hydrolysis reactions may also occur.

7.2.3. Oximino Ketones

Hydrogenation of α-oximino ketones provides a facile route to amino ketones and amino alcohols. Absorption of only 2 mol of hydrogen invariably leads to the amino ketone (*8,57,58a*). The reduction is carried out usually in acid to prevent formation of secondary amines and dihydropyrazines, although alkaline reductions are satisfactory also (*36*). Palladium is often used in these reductions. Equal weights of palladium and platinum together have been claimed to give superior results (*85*). Even small amounts (1%) of platinum or rhodium show beneficial effects (*60*). Hydrogenation of α-oximino ketones usually gives the amino alcohol as a single diastereoisomeric racemate.

References

1. H. Adkins, "Reactions of Hydrogen," p. 92. Univ. of Wisconsin Press, Madison, 1937.
2. N. F. Albertson, B. F. Tullar, J. A. King, B. B. Fishburn, and S. Archer, *J. Am. Chem. Soc.* **70,** 1150 (1948).
3. J. C. Andrade, W. F. Maier, L. Zapf, and P. v. R. Schleyer, *Synthesis*, 802 (1980).
4. C. Barnett, *Ind. Eng. Chem. Prod. Res. Dev.* **8,** 145 (1969).
5. W. Barr and J. W. Cook, *J. Chem. Soc.*, 438 (1945).
6. F. Benington, R. D. Morin, and I. C. Clark, Jr., *J. Med. Chem.* **8,** 100 (1965).
7. R. J. Bergeron, J. R. Garlich, and N. J. Shtolowich, *J. Org. Chem.* **49,** 2997 (1984).
8. S. Bien and D. Ginsburg, *J. Chem. Soc.*, 2065 (1963).
9. V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.* **75,** 3243 (1953).
10. R. F. Borch, C. V. Grudzinskas, D. A. Peterson, and L. D. Weber, *J. Org. Chem.* **37,** 1141 (1972).
11. W. A. Butte, W. J. Murtaugh, and R. E. Mitchell, Br. Patent Appl. 2,042,529A (1980).
12. J. G. Cannon, J. A. Perez, R. K. Bhatnager, J. P. Long, and F. M. Sharabi, *J. Med. Chem.* **25,** 1442 (1982).
13. M. Carmack, O. H. Bullitt, Jr., G. R. Handrick, L. W. Kissinger, and I. Von. *J. Am. Chem. Soc.* **68,** 1222 (1946).
14. W. H. Carothers and G. A. Jones, *J. Am. Chem. Soc.* **47,** 3051 (1925).
15. W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.* **21,** 999 (1956).
16. A. A. Deana, G. E. Stokker, E. M. Schultz, R. L. Smith, E. J. Cragoe, Jr., H. F. Russo, and L. S. Watson, *J. Med. Chem.* **26,** 580 (1983).
17. B. J. Demopoulos, H. J. Anderson, C. E. Loader, and K. Faber, *Can. J. Chem.* **61,** 2415 (1983).
18. C. A. Drake, R. W. Campbell, H. W. Will, J. W. Vanderveen, and S. J. Marwil, *Chem. Eng. Process. Dev.* 83 (1982).
19. R. Duschinsky and L. S. Dolan, *J. Am. Chem. Soc.* **67,** 2079 (1945).
20. M. L. A. Fluchaire and F. Chambert, *Bull. Soc. Chim. Fr.*, 22 (1944).
21. M. Freifelder, *J. Am. Chem. Soc.* **82,** 2386 (1960).
22. M. Freifelder, "Practical Catalytic Hydrogenation," p. 262. Wiley, New York, 1971.

23. M. Freifelder and Y. H. Ng, *J. Pharm. Sci.* **54,** 1204 (1965).
24. M. Freifelder, W. D. Smart, and G. R. Stone, *J. Org. Chem.* **27,** 2209 (1962).
25. O. Fuentes and W. W. Paudler, *J. Org. Chem.* **40,** 1210 (1975).
26. R. Fuhrmann, J. Pisanchyn, and F. Koff, *Ann. N.Y. Acad. Sci.* **214,** 243 (1973).
27. R. T. Gilsdorf and F. F. Nord, *J. Am. Chem. Soc.* **74,** 1837 (1952).
28. H. Greenfield, *Ind. Eng. Chem. Prod. Res. Dev.* **6,** 142 (1967).
29. H. Greenfield, *Ind. Eng. Chem. Prod. Res. Dev.* **15,** 156 (1976).
30. G. W. Griffin, J. E. Basinski, and L. I. Peterson, *J. Am. Chem. Soc.* **84,** 1012 (1962).
31. P. Grubmüller, W. F. Maier, P. v. R. Schleyer, M. A. McKervey, and J. J. Rooney, *Chem. Ber.* **113,** 1989 (1980).
32. V. Guth, J. Leitich, W. Specht, and F. Wessely, *Monatsh. Chem.* **94,** 1262 (1963).
33. E. E. Harris, R. A. Firestone, K. Pfister, 3rd, F. J. Cross, R. R. Carrie, M. Monaco, E. R. Peterson, and W. Reuter, *J. Org. Chem.* **27,** 2705 (1962).
34. W. H. Hartung, *J. Am. Chem. Soc.* **50,** 3370 (1928).
35. W. H. Hartung, *J. Am. Chem. Soc.* **53,** 2248 (1931).
36. W. H. Hartung and Y. T. Chang, *J. Am. Chem. Soc.* **74,** 5927 (1952).
37. W. H. Hartung and J. C. Munch, *J. Am. Chem. Soc.* **51,** 2262 (1929).
38. W. H. Hartung, J. C. Munch, W. A. Deckert, F. Crossley, *J. Am. Chem. Soc.* **52,** 3317 (1930).
39. W. H. Hartung, J. C. Munch, E. Miller, and F. Crossley, *J. Am. Chem. Soc.* **53,** 4149 (1931).
40. W. H. Hartung, J. C. Munch, and F. S. Crossley, *J. Am. Chem. Soc.* **87,** 1091 (1935).
41. H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.* **84,** 3139 (1962).
42. W. Huber, *J. Am. Chem. Soc.* **66,** 876 (1944).
43. C. F. Huebner, E. M. Donoghue, C. J. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.* **35,** 1149 (1970).
44. E. C. Jorgensen, W. J. Murray, and P. J. Block, Jr., *J. Med. Chem.* **17,** 434 (1974).
45. R. Juday and H. Adkins, *J. Am. Chem. Soc.* **77,** 4559 (1955).
46. M. Kalina and J. Pasek, *Kinet. Katal.* **10**(3), 574 (1969).
47. D. S. Kashdam, J. A. Schwartz, and H. Rapoport, *J. Org. Chem.* **47,** 2638 (1982).
48. K. Kindler and F. Hesse, *Arch. Pharm (Weinheim, Ger.)* **271,** 439 (1933).
49. K. Kindler, K. Shrader, and B. Middlehoff, *Arch. Pharm. (Weinheim, Ger.)* **283,** 184 (1950).
50. F. E. King, T. Henshall, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1373 (1948).
51. C. F. Koelsch, *J. Am. Chem. Soc.* **65,** 2093 (1943).
52. D. J. LeCount, *J.C.S. Perkin Trans. I*, 813 (1983).
53. E. Lette, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.* **37,** 4465 (1972).
54. R. T. Major and K. W. Ohly, *J. Med. Chem.* **4,** 51 (1961).
55. L. Mandell, J. U. Piper, and K. P. Singh, *J. Org. Chem.* **28,** 3440 (1963).
56. L. Mandell, K. P. Singh, J. T. Gresham, and W. J. Freeman, *J. Am. Chem. Soc.* **87,** 5234 (1965).
57. T. Matsumoto, M. Ohne, M. Koshi, S. Ohuchi, and H. Shirahama, *J. Org. Chem.* **27,** 79 (1962).
58. E. Müller, D. Fries, and H. Metzger, *Ber. Dtsch. Chem. Ges.* **88,** 1891 (1955).
58a. J. G. Murphy, *J. Org. Chem.* **26,** 3104 (1961).
59. C. G. Overberger and J. E. Mulvaney, *J. Am. Chem. Soc.* **81,** 4697 (1959).
60. L. Neelakantan and W. H. Hartung, *J. Org. Chem.* **23,** 964 (1958).
61. M. S. Newman and V. Lee, *J. Org. Chem.* **40,** 381 (1975).
62. R. L. Rapport and H. J. Kupferberg, *J. Med. Chem.* **16,** 599 (1973).
63. W. Reeve and J. Christian, *J. Am. Chem. Soc.* **78,** 860 (1956).
64. M. M. Robinson, B. F. Lambert, L. Dorfman, and W. G. Pierson, *J. Org. Chem.* **31,** 3220 (1966).
65. W. E. Rosen and M. J. Green, *J. Org. Chem.* **28,** 2797 (1963).
66. K. W. Rosenmund and E. Phannkuch, *Ber. Dtsch. Chem. Ges.* **75B,** 1859 (1942).
67. A. Rosenthal and D. A. Baker, *Tetrahedron Lett.*, 397 (1969).

68. A. Rosenthal and D. A. Baker, *J. Org. Chem.* **38,** 193, 198 (1973).
69. T. W. Russell, R. C. Hoy, and J. E. Cornelius, *J. Org. Chem.* **37,** 3552 (1972).
71. P. N. Rylander and J. Kaplan, *Am. Chem. Soc. Meet.* (1960).
72. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **4,** 20 (1963).
73. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **5,** 113 (1965).
74. P. N. Rylander, L. Hasbrouck, and I. Karpenko, *Ann. N.Y. Acad. Sci.* **214,** 100 (1973).
75. M. A. Schwartz, M. Zoda, B. Vishnuvajjala, and I. Mami, *J. Org. Chem.* **41,** 2502 (1976).
76. E. R. Shepard, J. F. Noth, H. D. Porter, and C. K. Simmans, *J. Am. Chem. Soc.* **74,** 4611 (1952).
77. E. S. Stratford and R. W. Curley, Jr., *J. Med. Chem.* **26,** 1463 (1983).
78. R. A. Turner, C. F. Huebner, and C. R. Scholz, *J. Am. Chem. Soc.* **71,** 2801 (1949).
79. H. Uchida and M. Ohta, *Bull. Chem. Soc. Jpn.* **46,** 3612 (1973).
80. J. Von Braun, G. Blessing, and F. Zobel, *Ber. Dtsch. Chem. Ges.* **56B,** 1888 (1923).
81. E. E. Van Tamelen and E. E. Smissman, *J. Am. Chem. Soc.* **75,** 2031 (1953).
82. G. N. Walker and D. Alkalay, *J. Org. Chem.* **32,** 2213 (1967).
83. G. N. Walker, D. Alkalay, A. R. Engle, and R. J. Kempton, *J. Org. Chem.* **36,** 466 (1971).
84. W. M. Welsh, *J. Org. Chem.* **47,** 886 (1982).
85. G. Wilbert and P. Sosis, U.S. Patent No. 3,028,429 (1962).
86. C. F. Winans and H. Adkins, *J. Am. Chem. Soc.* **54,** 306 (1932).
87. C. F. Winans and H. Adkins, *J. Am. Chem. Soc.* **55,** 4167 (1933).

- 8 -

Hydrogenation of Nitro Compounds

Aromatic nitro compounds are hydrogenated very easily; aliphatic nitro compounds considerably more slowly. Hydrogenations have been carried out successfully under a wide range of conditions including vapor phase (*89*). Usually the goal of reduction is the amine, but at times the reduction is arrested at the intermediate hydroxylamine or oxime stage; nitroso compounds never accumulate, although their transient presence may appreciably influence the course of reaction. In practice, nitro compounds often contain other reducible functions that are to be either maintained or reduced as well.

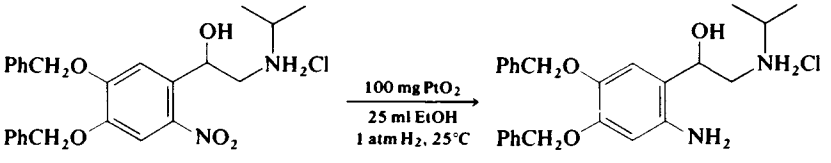
Reduction of aromatic nitro compounds may give products sensitive to air. Moder and Leonard (*65*) stressed the importance of rigid exclusion of air during reduction of a nitro compound to a complex air-sensitive diamine in order to maximize the yield. It is quite likely that in these cases the oxidation products will have an adverse influence on catalyst life.

8.1. Catalysts

Palladium, platinum, or nickel, supported or unsupported, are the metals usually used in nitro-group reductions. The choice of catalyst often depends on what other functions are present and on the products desired.

Platinum may be more useful than palladium in reduction of nitro compounds containing functions easily reduced by palladium. Hydrogenation of **1** over 5% Pd-on-C was nonselective with hydrogenolysis of the benzyl ethers competing with nitro hydrogenation, but over PtO_2 in ethanol **2** was obtained in 96% yield (*4*).

Hydrogenation of aromatic nitro compounds is very fast, and the rate is limited often by the rate of hydrogen transfer to the catalyst. It is accordingly easy to use inadvertently more catalyst than is actually necessary. Aliphatic nitro compounds are reduced much more slowly than are aromatic, and higher catalyst loadings (*6,11*) or relatively lengthy reduction times may be

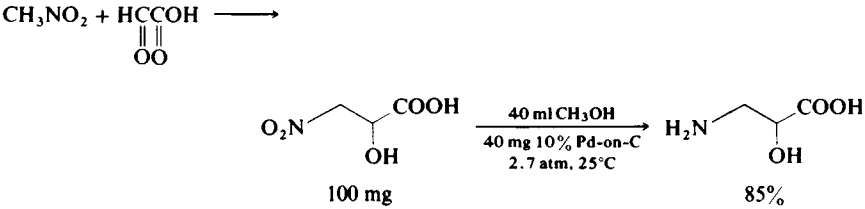


(1) (2)

0.80 g

required (*48,69*). Nonetheless, the reduction is very useful (*7,8,9,59,60, 63,72,90,91,99*), notably for synthesis of amino sugars.

Palladium proved especially useful in the hydrogenation of 2-hydroxy-3-nitropropanoic acid. Reduction over palladium-on-carbon gave pure, powdery isoserine, whereas platinum failed to reduce the nitro function under neutral or acidic conditions; reduction over Raney nickel gave a bright green powder (*96*).



100 mg 85%

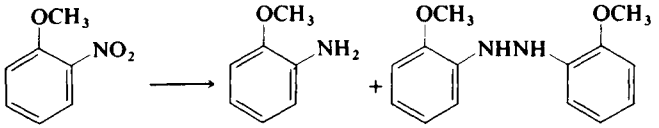
8.2. Solvents

A great variety of solvents has been used with success. Reactive solvents, such as acetic anhydride, will react with the amine as formed. Basic solvents cause the formation of azo, azoxy, and hydrazo compounds, paralleling chemical reductions (*39,73*).

8.3. Influence of Impurities

Various materials, present by accident or design, can alter the course of reduction by arresting the reaction at an intermediate product or by causing the formation of coupled products (*94,95*). These deviations can range from only a small yield loss to the formation of a major product. The work of Kosak (*56*) on *o*-nitroanisole is instructive in this regard, where small amounts of

impurities were shown to exert an appreciable influence on the rate and quality of reduction.



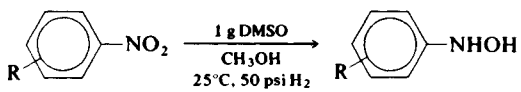
99.82% pure	94–97%	3–1%
98.87% pure	82–85%	14–12%

Catalyst: 0.03 g 4.5% Pd, 0.5% Pt, 5% Fe-on-carbon per mole of nitroanisole

Impurities identified as having an influence on promoting *o,o'*-hydrazoanisole formation are in declining effectiveness: *o,o'*-dichloroazobenzene > *o*-chloronitrobenzene ≫ *o*-nitrophenol ~ *o,o'*-azoxyanisole. Hydrogen chloride had a marked depressing effect on rate but not on product quality; with the Pd–Pt–Fe catalyst, complete poisoning occurs at a mole ratio of only 0.042. Palladium-on-carbon catalysts were shown to be more sensitive to the above modifiers than were platinum catalysts (*56*). Palladium gave a high quality *o*-anisidine when starting with high-purity *o*-nitroanisole, but platinum catalysts were clearly superior when the starting material was less pure. This conclusion illustrates one reason why different investigators, doing ostensibly the same thing, may come to opposite conclusions regarding the relative effectiveness of catalysts.

8.4. Aromatic Hydroxylamines

Hydroxylamines ordinarily do not accumulate in the reduction of aromatic nitro compounds for, with some exceptions, most systems in competition will reduce the hydroxylamine function preferentially. Nonetheless, systems have been found that afford the intermediate aromatic hydroxylamine in excellent yield. With hydrogen gas as a reductant and platinum-on-carbon or -on-alumina and about 1 wt % of DMSO based on nitro compound as a modifier, aromatic hydroxylamines can be formed in 90% yield under mild conditions. The reduction slows markedly after absorption of the second mole of hydrogen and should be stopped at this stage (*80*).

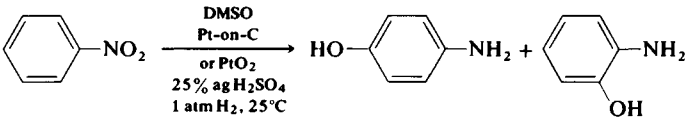


100 g

Two hydrogen-transfer systems have been developed that also give good yields of hydroxylamines. One uses 5% palladium-on-carbon in aqueous tetrahydrofuran with phosphinic acid or its sodium salt as hydrogen donor; the other uses 5% rhodium-on-carbon in aqueous tetrahydrofuran and hydrazine as donor. These systems are complementary and which is the better may depend on the substrate (*36*). The reductions cannot be followed by pressure drop, and both require analysis of the product to determine when the reduction should be terminated.

Sometimes hydroxylamines are formed in systems where the amino compound would have been expected. This occurs usually in compounds containing either sulfur or basic nitrogen; impurities may have had an influence also (*1,12,46,50,98*).

Phenylhydroxylamine rearranges in sulfuric acid to give mainly *p*-aminophenol. Industrial routes to this compound have been developed in which phenylhydroxylamine, formed by hydrogenation of nitrobenzene in sulfuric acid over platinum-on-carbon, is rearranged as it is formed. Conditions are adjusted so that the rate of rearrangement is high relative to the rate of hydrogenation of hydroxylamine to aniline (*15,17,86*). An easy way to obtain a favorable rate ratio is to carry out the reduction with about 1% DMSO present in the sulfuric acid (*79,81*).



85–90% combined yield

If the hydrogenation is carried out in hydrochloric instead of sulfuric acid, chloroaniline is formed (*20*), while in hydrofluoric acid, fluoroaniline is produced (*37*).

8.4.1. Cyclic Products

During hydrogenation, intermediate aromatic hydroxylamines may undergo various cyclization reactions in molecules containing a suitably disposed carbonyl group, or carbonyl derivative, such as an oxime (*13*). The cyclized product may or may not maintain the N—OH bond, depending on the solvent, the catalyst, and the electrophilicity of the carbonyl (*27,28,29,32,67,68*).

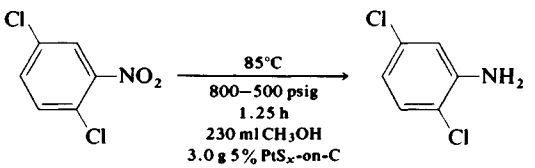
8.5. Bifunctional Molecules

A frequently occurring problem is the full or partial reduction of a nitro function in the presence of other reducible functions. Preferential hydrogenation of an aromatic nitro group can usually be achieved for it is very easily reduced.

8.5.1. Halonitro Aromatics

A problem of both academic and industrial interest is the hydrogenation of a halonitro aromatic to the haloaniline (*89*). At one time a difficult task, the reaction is now practiced industrially on a large scale. The extent of dehalogenation may depend on the halogen present, overall structure, catalyst support, catalytic metal, amount of catalyst, and reaction conditions. The influence of pressure, temperature, agitation, amount of catalyst, and catalyst activity have been related in part by the influence these variables exert on hydrogenation availability at the catalyst surface. Dehydrohalogenation relative to nitro group reduction is favored by hydrogen-poor catalysts and retarded by hydrogen-rich catalysts.

In general, platinum, with or without modifiers, makes the best catalyst for minimizing dehalogenation, combined with a fast rate of reduction of the nitro function. Excellent results have been obtained by use of supported noble-metal sulfides (*41*). These catalysts [manufactured by Engelhard Industries, Newark, New Jersey (*51*)] have a high intrinsic selectivity for this type of reduction and have given excellent results under a wide range of conditions. Elevated temperatures and pressures are necessary to achieve reasonable rates (*33,34*).



103.5 g

A variety of inorganic (*31,87*) and organic bases have been added to the catalyst to improve selectivity. The effectiveness of organic bases is very sensitive to structure. Morpholine is an effective inhibitor, more so than *N*-methylmorpholine > *N*-ethylmorpholine > 3,5-dimethylmorpholine (55). Piperazine is effective, but ethanolamine and ethylenediamine are poisons.

Many other systems have been disclosed (*85a*). Pressure has a marked effect on the course of this reduction, especially when excess morpholine is used. At low pressure (< 50 psi) complete displacement of halogen by morpholine occurs to give *p*-(*N*-morpholino)nitrobenzene; above 200 psi, the product is *p*-chloroaniline (*55*).

8.5.2. Acetylenic and Olefinic Nitro Compounds

Aliphatic, nonconjugated nitroolefins can be reduced to the saturated nitro compound without difficulty (*30,36a,40,76*). Both platinum and palladium have been used. The reverse selectivity seems not to have been reported.

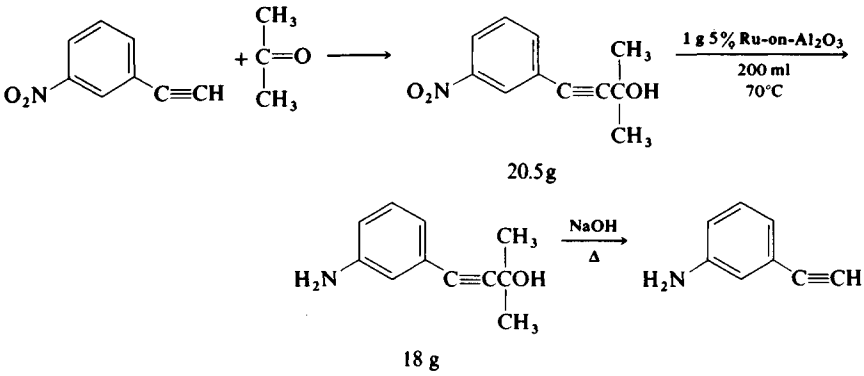
Unsaturated aromatic nitro compounds, on the other hand, are more likely to be hydrogenated preferentially at the nitro group (*10,16,19,21*). Conjugated nitroolefins may afford a variety of products through partial or complete reduction as well as products arising by reductive hydrolysis. Reduction of β-nitrostyrenes in neutral medium result in products derived through coupling of two molecules at the α carbons to give 2,3-diphenylbutane derivatives (*54,85*). Coupling is avoided in strong acid media, such as sulfuric–hydrochloric acid (*26*), or dilute aqueous hydrochloric acid (*22*). Wagner *et al.* (*92*) obtained a good yield of β-phenylethylamines from hydrogenation of nitrostyrenes over 5% Pd-on-C in dil aq HCl at 50–80°C and 500–1000 psig.

Excellent yields of the oximes of phenylacetaldehydes are obtained by reduction of β-nitrostyrenes over Pd-on-C in a pyridine solvent (*74,75*). The technique gives yields of only about 60% when applied to aliphatic α,β-unsaturated nitro compounds; better yields are obtained in acidic media (*83*). Over 5% Rh-on-Al_2O_3 in ethanol–acetic acid–ethyl acetate, 2-β-dinitrostyrenes are converted to 2-nitrophenylacetaldehyde oximes (*13*).

In molecules containing both an acetylenic and a nitro function, either or both may be reduced. Preferential reduction of the acetylenic function is best achieved with palladium (*42,44*). Ruthenium, on the other hand, favors selective reduction of an aromatic nitro function; high yields of (3-aminophenyl)acetylene were obtained from the corresponding nitro compound. Catalyst life is prolonged by protection of the acetylenic function (*70*). Cobalt polysulfide and ruthenium sulfide catalysts have been used similarly, but more vigorous conditions are required (100°C, 25–70 atm) (*71*).

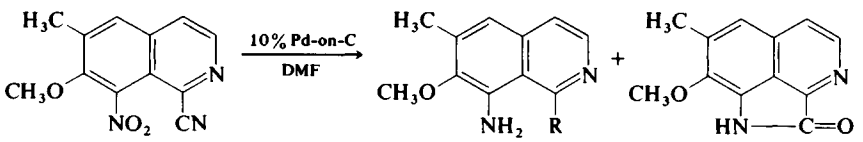
8.5.3. Nitronitriles

The nitro group is reduced easily in preference to a nitrile (*23,25,45,84*) especially if the nitro group is aromatic and the groups are unable to interact, but the reverse preference has been seen (*100*) in certain aliphatic molecules.



Reductions of nitronitriles situated to favor interaction are apt to involve both functions (*84,93*). Hydrogenation of *o*-nitrobenzonitrile over either palladium or platinum gave *o*-aminobenzamide (*78*), with the amide oxygen transferred from the nitro group (*66*). On the other hand, 1-amino-2-cyanonaphthalene gave the amino amide on reduction over PtO_2, but the amino nitrile over palladium (*82*).

Hydrogenation of **3** over 10% Pd-on-C led to the expected cyanoamine (**4**), the amide (**5**), the lactam (**7**), as well as **6**, in which the nitrile carbon is lost (*58*). The nitrile function is lost before formation of the amine, for **4** resists reduction. A somewhat different distribution is obtained over PtO_2, as expected, and accords with the tendency of platinum to produce more intermediate hydroxylamine (*82*).



(3)

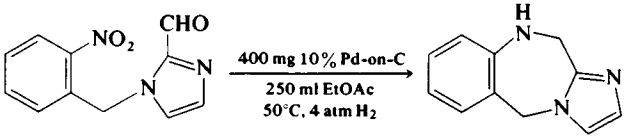
(4) R = CN 43%
(5) R = $CONH_2$ 13%
(6) R = H 17%

(7)

8.5.4. Nitroaldehydes and Nitroketones

There is little difficulty in reducing a nitro function in preference to a carbonyl (*38*) unless the functions are spatially proximate, in which case the tendency to ring closure provides an easy entry into a variety of systems. A

facile synthesis of the tricyclic compound **9** was achieved by reductive cyclization of the nitroaldehyde **8** (*88*).



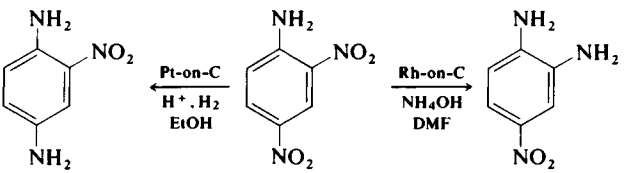
2.31 g (**8**) (**9**)

A similar synthesis starting with 1-(2-nitrobenzyl)pyrrol-2-aldehyde used ethanol–ethyl acetate as solvent (*62*). Indoles are prepared in excellent yield by hydrogenation of *o*-nitrobenzyl ketones over Pd-on-C (*3*). Azaindoles are correspondingly prepared from nitropyridines (*97*).

In the aliphatic series, hydrogenation of γ-nitroketones gives pyrrolidines in good yields (*52*) and α-nitroketones give a mixture of pyrazines and piperazines (*35*).

8.5.5. Dinitro Compounds

Formation of diamines from dinitro compounds, which are unable to interact intramolecularly, presents no problem. Very large volumes of diaminotoluene, a precursor to toluene diisocyanate, are produced by hydrogenation of dinitrotoluene over either nickel or palladium-on-carbon. Selective hydrogenation of one or the other of two nitro groups is much more of a challenge, but a number of outstanding successes have been recorded. A case in point is the hydrogenation of 2,4-dinitroaniline (**11**) to 4-nitro-1,2-benzenediamine (**12**) (*2*) or to 2-nitro-1,4-benzenediamine (**10**).



(**10**) (**11**) (**12**)

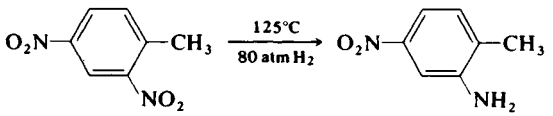
70% high yield

Most catalyst systems, if they show selectivity at all, favor preferential reduction of the less hindered 4-nitro group; hydrogenation of **11** over Pt-on-C in acidic alcohol affords **10** in 70% yield (*24*). Similarly, Lazer *et al.* (*61*), selectively prepared **10** from 27 mmol **11**, 10 ml of 50% H_2SO_4, 60 ml HOAc, and 350 mg 5% Pt-on-C at 85°C and 30 psig. The hydrogenation is stopped at

absorption of 3 mol. The same reduction is nonselective when applied to 2,4-dinitrophenol or 2,4-dinitroanisole.

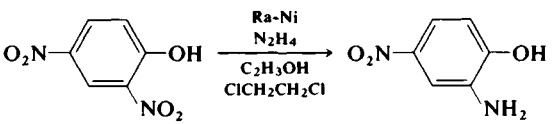
Selective reduction of **11** to **12** is achieved in high yield by the use of 5% Rh-on-C in DMF containing NH_4OH. Reduction essentially stops after absorption of 3 mol of hydrogen. Yields were lower in ethanol. Platinum oxide in ammonical DMF showed fair selectivity, but Pd-on-C none. In a typical experiment, 0.1 mol of **11** in 250 ml DMF containing 3 ml 28% NH_4OH solution and 0.7 g 5% Rh-on-Al_2O_3 was reduced at 40 psig until 0.3 mol of hydrogen were absorbed (*2*).

Reductions of 2,4-dinitroalkylbenzenes tend to favor selective reduction at the least hindered nitro group, but only Raney copper, of many catalysts tested, gave very high selectivity. Selectivity for reduction of the 4-nitro group increases, as expected, with steric hindrance of the alkyl substituent. Reduction of 2,4-dinitro-1-(*N*-piperidyl)benzene gave 4-amino-2-nitro-1-(*N*-piperidyl)benzene in 99% yield (*49*). These reductions were carried out at 150°C and 200 psig with xylene solvent and a catalyst loading of 50% based on substrate. This exceptionally high catalyst loading is of little economic consequence since the catalyst could be reused repeatedly. Selectivity in the reverse sense, i.e., reduction of the more hindered nitro group in dinitroalkylbenzenes can be achieved with the homogeneous catalyst, $RuCl_2(Ph_3P)_3$ (*53*).



conversion 42%
selectivity 96%

Dinitroarenes containing substituents such as hydroxyl or amino groups are reduced with 3 mol equiv of hydrazine hydrate in the presence of Raney nickel to afford selectively a compound in which only one nitro group is reduced. In general, the main product is derived by reduction of the more hindered nitro function. For example,

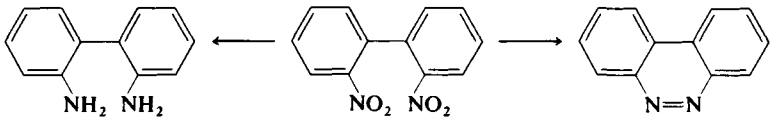


92%

Typically a mixture of dinitroarene (0.1 mol) and hydrazine hydrate (0.3 mol) is stirred for 10 min at 28–30°C in 1:1 (v/v) ethanol:1,2-dichloroethane (10 ml

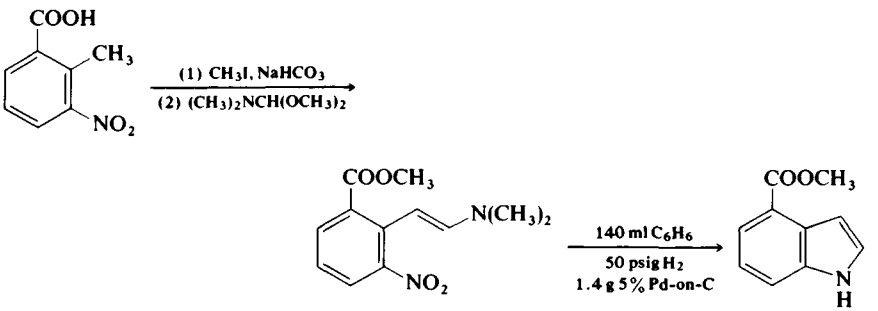
per g nitroarene). Over a period of 40 min 0.3 g Ra Ni is added in three portions. The temperature rises, but it is not allowed to go above 60°C. Stirring is continued for 3–8 hr at 50–60°C. The catalyst is filtered and the product recovered (*5*).

Nitro groups disposed toward cyclization may do so on reduction. Hydrogenations of 2-β-dinitrostyrenes over palladium provides a general way into the indole system (*14,43,47*). Reduction of 2,2′-dinitrobiphenyls gives a mixture of cinnolines and diaminobiphenyls in ratios that are influenced by the relative amounts of cis and trans configuration in the adsorbed substrate complex (*18,77*). Interestingly, high yields of 2,2′-diaminobiphenyl could be obtained over W-2 Raney Ni at 50 psig (1:3 ethanol–ethyl acetate), whereas at 600 and 2000 psig the results were erratic, and a number of products were formed.

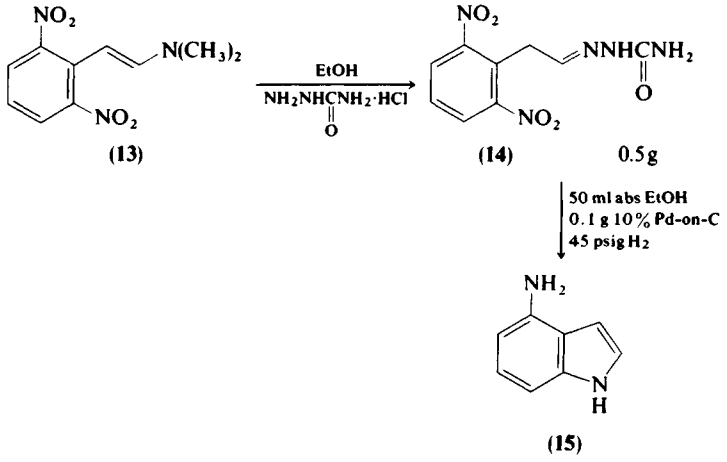


8.5.6. Nitroenamines

An excellent method for producing methyl indole-4-carboxylate from commercially available 3-nitro-2-methylbenzoic acid involves reduction of an intermediate nitroenamine (*57*).



In a similar system, Melhado and Leonard (*64*) obtained better results if the enamine (**13**) were first converted to a semicarbazone (**14**) before hydrogenation and cyclization to the indole (**15**).



References

1. P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **32,** 3211 (1967).
2. R. J. Alaimo and R. J. Storrin, *in* "Catalysis of Organic Reactions" (W. R. Moser, ed.), p. 461. Dekker, New York, 1981.
3. R. L. Augustine, A. J. Gustavsen, S. F. Wanat, I. C. Pattison, K. S. Houghton, and G. Koletar, *J. Org. Chem.* **38,** 3004 (1973).
4. M. A. Avery, M. S. Verlander, and M. Goodman, *J. Org. Chem.* **45,** 2750 (1980).
5. N. R. Ayyangar, U. R. Kalkote, A. G. Lugade, P. V. Nikrad, and V. K. Sharma, *Bull. Chem. Soc. Jpn.* **56,** 3159 (1983).
6. H. H. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.* **82,** 3709 (1960).
7. H. H. Baer and F. Kienzle, *J. Org. Chem.* **34,** 3848 (1969).
8. H. H. Baer and T. Neilson, *J. Org. Chem.* **34,** 560 (1969).
9. H. H. Baer and K. S. Ong, *J. Org. Chem.* **34,** 560 (1969).
10. B. R. Barker, and J. H. Jordaan, *J. Med. Chem.* **8,** 35 (1965).
11. R. Baker, *J. Org. Chem.* **29,** 869 (1964).
12. G. Barker and G. P. Ellis, *J. Chem. Soc. C*, 2230 (1970).
13. I. Baxter and G. A. Swan, *J. Chem. Soc. C*, 2446 (1967).
14. F. Benington, R. D. Morin, and L. C. Clark, Jr. *J. Org. Chem.* **25,** 1542 (1960).
15. R. G. Benner, U.S. Patent No. 3,383,416 (1965).
16. G. Benoit and D. Marinopoulos, *Bull. Soc. Chim. Fr.*, 829 (1950).
17. N. R. W. Benwell, Br. Patent 1,181,969 (1970).
18. A. E. Blood and C. R. Noller, *J. Org. Chem.* **22,** 711 (1957).
19. E. K. Blout and D. C. Silverman, *J. Am. Chem. Soc.* **66,** 1442 (1944).
20. W. C. Bradbury, U.S. Patent No. 3,265,735 (1966).
21. R. Braden, H. Knupfer, and S. Hartung, U.S. Patent No. 4,002,673 (1977).
22. A. Brossi, J. VanBurik, S. Teitel, *Helv. Chim. Acta* **51,** 1978 (1968).
23. W. F. Bruce and L. A. Perez-Medina, *J. Am. Chem. Soc.* **69,** 2571 (1947).

24. W. H. Brunner and A. Halasz, U.S. Patent No. 3,086,978 (1963).
25. R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.* **74,** 2226 (1952).
26. J. Daly, L. Horner, and B. Witkop, *J. Am. Chem. Soc.* **83,** 4787 (1961).
27. A. L. Davis, O. H. P. Choun, D. E. Cook, and T. J. McCord, *J. Med. Chem.* **7,** 632 (1964).
28. A. L. Davis, J. W. Hughes, R. L. Hance, V. L. Gault, J. Tommy, and T. J. McCord, *J. Med. Chem.* **13,** 549 (1970).
29. A. L. Davis, D. R. Smith, D. C. Foyt, J. L. Black, and T. J. McCord, *J. Med. Chem.* **15,** 325 (1972).
30. H. C. deMauny, *Bull. Soc. Chim. Fr.* **7,** 133 (1940).
31. A. J. Dietzler and T. R. Keil, U.S. Patent No. 3,051,753 (1962).
32. G. O. Doherty and K. H. Fuhr, *Ann. N.Y. Acad. Sci.* **214,** 221 (1973).
33. F. S. Dovell and H. Greenfield, *J. Am. Chem. Soc.* **87,** 2767 (1965).
34. F. S. Dovell and H. Greenfield, U.S. Patent No. 3,350,450 (1967).
35. A. F. Ellis, U.S. Patent No. 3,453,278 (1969).
36. I. D. Entwistle, T. Gilkerson, R. A. W. Johnstone, and R. P. Telford, *Tetrahedron* **34,** 213 (1978).
36a. H. Feuer and R. Harmetz, *J. Org. Chem.* **26,** 1061 (1961).
37. D. A. Fidler, J. S. Logan, and M. M. Boudakian, *J. Org. Chem.* **26,** 4014 (1961).
38. R. H. Fisher, and H. M. Weitz, *Syntheses*, 261 (1980).
39. W. V. Freed and F. K. Signaigo, U.S. Patent No. 2,344,244 (1944).
40. J. P. Freeman, *J. Am. Chem. Soc.* **82,** 3869 (1960).
41. H. Greenfield, *Ann. N.Y. Acad. Sci.* **145,** 108 (1967).
42. C. Grob and E. Jenny, U.S. Patent No. 3,118,946 (1964).
43. R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daley, and B. Witkop, *J. Am. Chem. Soc.* **85,** 1825 (1963).
44. G. F. Hennion, and S. O. Barrett, *J. Am. Chem. Soc.* **79,** 2146 (1967).
45. H. B. Hester, Jr., *J. Org. Chem.* **29,** 1158 (1964).
46. E. B. Hodge, *J. Org. Chem.* **37,** 320 (1972).
47. C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem. Soc.* **75,** 5887 (1953).
48. D. C. Iffland and F. A. Cassis, Jr., *J. Am. Chem. Soc.* **74,** 6284 (1952).
49. W. H. Jones, W. F. Benning, P. Davis, D. M. Mulvey, P. I. Pollak, J. C. Schaeffer, R. Tull, and L. M. Weinstock, *Ann. N.Y. Acad. Sci.* **158,** 471 (1969).
50. J. C. Kauer and W. A. Sheppard, *J. Org. Chem.* **32,** 3580 (1967).
51. C. D. Keith and D. Bair, U.S. Patent No. 3,275,567 (1966).
52. M. C. Kloetzel, *J. Am. Chem. Soc.* **69,** 2271 (1947).
53. J. R. Knifton, *J. Org. Chem.* **41,** 1200 (1976).
54. E. P. Kohler and N. L. Drake, *J. Am. Chem. Soc.* **45,** 1281 (1923).
55. J. R. Kosak, *Ann. N.Y. Acad. Sci.* **172,** 175 (1970).
56. R. J. Kosak, *in* "Catalysis of Organic Reactions" (W. R. Moser, ed.), p. 461. Dekker, New York, 1981.
57. A. P. Kozikowski, H. Ishida, Y.-Y. Chen, *J. Org. Chem.* **45,** 3350 (1980).
58. A. Kubo, N. Saito, S. Nakahara, and R. Iwata, *Angew. Chem. Int. Ed. Engl.* **21,** 857 (1982).
59. R. Kuhn and H. J. Haas, *Angew. Chem.* **67,** 785 (1955).
60. R. Kuhn and H. J. Haas, *Justus Liebigs Ann. Chem.* **611,** 57 (1958).
61. E. S. Lazer, J. S. Anderson, J. E. Kijek, and K. C. Brown, *Synth. Commun.* **12,** 691 (1982).
62. A. Marino, G. DeMartino, G. Filacchioni, and R. Giuliano, *Farmaco Ed. Sci.* **24,** 276 (1969).
63. F. H. Marquardt and S. Edwards, *J. Org. Chem.* **37,** 1861 (1972).
64. L. L. Melhado and N. J. Leonard, *J. Org. Chem.* **48,** 5130 (1983).
65. K. P. Moder and N. J. Leonard, *J. Am. Chem. Soc.* **104,** 2613 (1982).
66. H. Moll, H. Musso, and H. Schroeder, *Angew. Chem. Int. Ed. Engl.* **2,** 212 (1963).

67. C. W. Muth and R. N. Beers, *Proc. W. Va. Acad. Sci.* **41,** 235 (1969).
68. C. W. Muth, J. R. Elkins, M. L. DeMatte, and S. T. Chiang, *J. Org. Chem.* **32,** 1106 (1967).
69. A. T. Nielsen, *J. Org. Chem.* **27,** 1998 (1962).
70. A. Onopchenko, E. T. Sabourin, and C. M. Selwitz, *J. Org. Chem.* **44,** 1233 (1979).
71. A. Onopchenko, E. T. Sabourin, and C. M. Selwitz, *J. Org. Chem.* **44,** 3671 (1979).
72. C. G. Overberger, J. Reichenthal, and J. P. Anselme, *J. Org. Chem.* **35,** 138 (1970).
73. S. Pietra and M. Res, *Ann. Chim. (Rome)* **48,** 299 (1958).
74. B. Reichert and W. Koch, *Arch. Pharm. (Weinheim, Ger.)* **273,** 265 (1935).
75. B. Reichert and H. Marquardt, *Pharmazie* **5,** 10 (1950).
76. J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **76,** 4501 (1954).
77. S. D. Ross and I. Kuntz, *J. Am. Chem. Soc.* **74,** 1297 (1952).
78. H. Rupe and H. Vogler, *Helv. Chim. Acta* **8,** 832 (1925).
79. P. N. Rylander, I. M. Karpenko, and G. R. Pond, *Ann. N.Y. Acad. Sci.* **172,** 266 (1970).
80. P. N. Rylander, I. M. Karpenko and G. R. Pond, U.S. Patent No. 3,694,509 (1972).
81. P. N. Rylander, I. M. Karpenko and G. R. Pond, U.S. Patent No. 3,715,397 (1973).
82. H. Schroeder, U. Schwade, and H. Musso, *Chem. Ber.* **98**(8), 2556 (1965).
83. W. K. Seifert and P. C. Condit, *J. Org. Chem.* **28,** 265 (1963).
84. H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.* **80,** 4622 (1958).
85. A. Sonn and A. Schellenberg, *Chem. Ber.* **50,** 1513 (1917).
86. L. Spiegler, U.S. Patent No. 2,765,342 (1956).
87. L. Speigler, U.S. Patent No. 3,073,865 (1963).
88. G. Stefancich, M. Artico, S. Massa, and F. Carelli, *Synthesis,* 321 (1981).
89. A. M. Stratz, *in* "Catalysis of Organic Reactions" (J. R. Kosak, ed.), p. 335. Dekker, New York, 1984.
90. T. Takamoto, R. Sudoh, and T. Nakagawa, *Tetrahedron Lett.*, 2053 (1971).
91. T. Takamoto, Y. Yokota, R. Sudoh, and T. Nakagawa, *Bull. Chem. Soc. Jpn.* **46,** 1532 (1973).
92. D. P. Wagner, A. I. Rachlin, and S. Teitel, *Synth. Commun.* **1,** 47 (1971).
93. G. N. Walker, *J. Med. Chem.* **8,** 583 (1965).
94. A. Weizmann, *J. Am. Chem. Soc.* **71,** 4154 (1949).
95. R. E. Werner, N. Young, J. J. Prichett, and C. E. Brenner, U.S. Patent No. 3,156,724 (1964).
96. T. M. Williams, R. Crumbie, and H. S. Mosher, *J. Org. Chem.* **50,** 91 (1985).
97. L. N. Yakhontov, V. A. Azimov, and E. I. Lapan, *Tetrahedron Lett.*, 1909 (1969).
98. H. L. Yale, *J. Org. Chem.* **33,** 2382 (1968).
99. J. Yoshimura, K. Sato, K. Kobayashi, and C. Shin, *Bull. Chem. Soc. Jpn.* **46,** 1515 (1973).
100. V. V. Young, U.S. Patent No. 2,864,863 (1958).

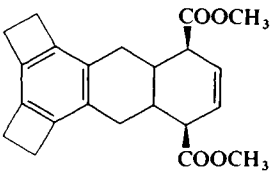
-9-

Hydrogenation of Carbocyclic Aromatic Compounds

Aromatic rings can be reduced without difficulty. Major problems connected with these reductions concern maintenence of other functions, control of regioselectivity in polycyclic aromatics, and control of stereochemistry.

9.1. Catalysts

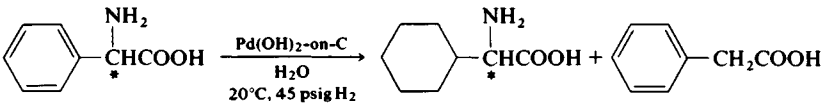
Greenfield (*14*), in agreement with others, established a declining rate of activity in hydrogenation of benzene and isobutylbenzene as Rh > Ru ≫ Pt ≫ Pd > Ni > Co; a different order applies in fused systems. The relatively slow rate of ring saturation over palladium often makes this the preferred catalyst for reduction of other functions without ring attack in mononuclear aromatics; nonetheless, palladium is used industrially in several important aromatic hydrogenations, such as conversion of benzoic acid to hexahydrobenzoic acid, a nylon-6 intermediate (*44*), and of rosin to perhydrorosin (*26*). Ring saturation may occur with exceptional ease over palladium if the ring is activated by strain. For instance, it was found impossible to reduce the double-bond in (**1**) over Pd-on-$CaCO_3$ without some reduction of the aromatic ring as well (*7*).



(**1**)

A surprising use of palladium hydroxide-on-carbon in the hydrogenation of (*R*)-α-phenylglycine to (*R*)-α-cyclohexylglycine was described by Tamura

and Harada (*43*). Surprising, for this type of catalyst is used frequently for hydrogenolysis of benzylamines without ring reduction. Hydrogenolysis increased with increasing temperature, as might be expected. The hydrogenation was very slow, and rhodium or ruthenium would likely have proved more effective and selective. In aqueous alkaline solution over $Pd(OH)_2$-on-C, the product is phenylacetic acid (*15*).



66%

Rhodium (*21*) and ruthenium are excellent catalysts for the reduction of aromatic rings. It is with these catalysts that the best chance resides for preservation of other reducible functions (*2,10,13,18,41,42,52*). Rhodium (*41*) and ruthenium (*45*) each reduced methylphenylcarbinol to methylcyclohexylcarbinol in high yield. Palladium, on the other hand, gives ethylbenzene quantitatively. Water has a powerful promoting effect, which is unique in ruthenium catalysis (*36*).

Platinum, especially as platinum oxide, has been used by many investigators. If this catalyst contains residual alkali, it is apt to be ineffective for aromatic ring reduction unless an acidic solvent is used (*1,3,19*) or unless the compound also contains a carbonyl group, as in acetophenone, where 1,4- and 1,6-addition are possible (*46*). Nickel, unless especially active, requires vigorous conditions—conditions that may promote side reactions.

9.2. Olefin Intermediates

Olefins have often been shown to be intermediates in the saturation of aromatics (*6,29,35,37,48,49*), but their formation, in varying amounts, lacks synthetic utility. In the presence of an acidic catalyst, the intermediate olefin can be trapped by alkylation. Phenylcyclohexane has been obtained in good yield from benzene by this technique (*40*).

Hydrogenation of aromatics under mild conditions gives mainly the all-cis isomer as if hydrogen addition takes place from only one side of the molecule (*23,24*). Reductions under more vigorous conditions may give other isomers by isomerization of the initially formed all-cis product. Under mild conditions, other isomers are accounted for by desorption and readsorption in a new orientation of intermediate olefins, as well as by double-bond migration in the

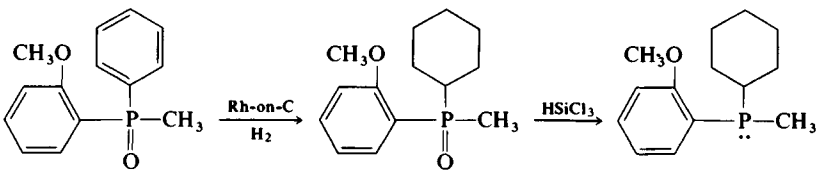
olefin (*16,38,39*). Catalysts may differ appreciably in their tendency to release adsorbed olefin and consequently give products of quite different stereochemical composition. Rhodium tends to produce the greatest amount of isolatable olefin (*30*).

9.3. Effect of Substrate Structure

The rate of aromatic hydrogenation is influenced by both steric and electronic factors (*20,25,53*). In general, rates decrease as substitution by alkyl groups increases (*47*), unless the substituents introduce exceptional strain. Strained aromatic systems will undergo facile saturation even over palladium under mild conditions (*31,32,33*).

Ethylbenzene and toluene are hydrogenated faster than benzene over Cu–ZnO, contrary to the general rule. Such behavior is evidence for a π-bonded intermediate, the surface concentration of which increases with the increasing electron-donating ability of the system (*50*).

A synthesis of CAMP depends on the selective hydrogenation of the least substituted of two aromatic rings in PAMPO (*51*).



PAMPO CAMPO CAMP

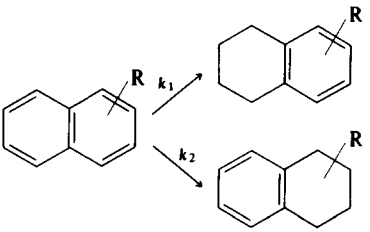
9.3.1. Polycyclic Systems

A frequently occurring problem is the saturation of only one aromatic ring in a molecule containing several. Success in this endeavor is dependent heavily on substrate structure and in some molecules is achieved easily, the reaction essentially stopping at absorption of 3 mol of hydrogen (*4,9,54*). In other cases, selectivity is influenced strongly by catalyst and reaction parameters. Selectivity in hydrogenation of biphenyl to phenylcyclohexane was found to be influenced by catalyst, support, temperature, and solvent. Palladium was much more selective than were platinum, rhodium, or ruthenium (*34*). (Palladium was also most selective in partial hydrogenation of diphenylmethane, naphthalene, and bipyridyl; the trend may be general). Selectivity

increased with increasing temperature in the range 25–125°C and was almost independent of pressure. Selectivity was highest on unsupported palladium, less on an alumina support, and less still on carbon. This trend might be expected to be general in reactions of the type A → B → C, with selectivity to B falling as pore structure develops. Over 5% Rh-on-C, maximal selectivity to phenylcyclohexane (50°C) varied appreciably with solvent; ethanol (49%), methanol (50%), *t*-butanol (57%), cyclohexane (59%), ethyl acetate (66%), tetrahydrofuran (78%).

9.3.2. Fused Rings

Either ring of an alkyl-substituted naphthalene may be reduced and the rate ratio (k_1/k_2) depends both on the position of R and its size (*28*). Naphthalenes

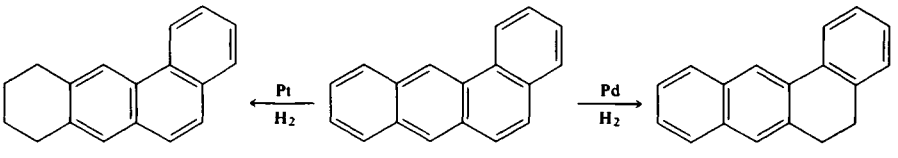


substituted in the 2-position are reduced preferentially at the unsubstituted ring, whereas the reverse is true for 1-alkyl substitution, and perhaps running contrary to expectations, the larger the 1-substituent, the greater the selectivity toward reduction of the substituted ring. For example, 1-*t*-butylnaphthalene (*28*) and 1,4-di-*t*-butylnaphthalene (*8*) are hydrogenated only at the substituted ring and at relatively high rates. These results have been explained in terms of release of peri strain, the steric interaction of the 1-alkyl group with the 8-hydrogen atom or 8-alkyl group. Naphthalenes carrying 1,8-substituents are hydrogenated preferentially at the ring carrying the larger substituent (*31*).

The above generalities apply particularly to palladium. Hydrogenation over platinum or rhodium are far less sensitive to the influence of steric crowding. Reduction of 1-*t*-butylnaphthalene over platinum, rhodium, and palladium resulted in values of k_1/k_2 of 0.42, 0.71, and 0.024, respectively. Also, unlike mononuclear aromatics, palladium reduces substituted naphthalenes at substantially higher rates than does either platinum or rhodium. For example, the rate constants, $k \times 10^6$ in mol sec^{-1} g $catalyst^{-1}$, in acetic acid at 50°C and 1 atm, were (for 1,8-diisopropylnaphthalene) Pd (142), Pt (18.4), and Rh (7.1) (*28*).

A great deal of control can nowadays be exerted over the products obtained on partial hydrogenation of fused aromatic systems. Selectivity depends on

the substrate structure and the catalyst (*5*). Fu and Harvey (*11*) and Fu *et al.* (*12*) found that hydrogenation of polynuclear systems over palladium afforded regiospecifically the corresponding *k*-region dihydroarenes, whereas over platinum reduction takes place regiospecifically on terminal rings to give tetrahydroarenes. For example, hydrogenation of benz[*a*]anthracene (**3**) in the presence of Pd-on-C at 20 psig and 25°C gave (**4**) in 97% yield, whereas reduction over platinum gave (**2**) in 95% yield.



(2) (3) (4)

Hydrogenation of 4,5-dihydropyrene (2 g) over 10% Pd-on-C (500 mg) in 20 ml of EtOAc at 50 psig afforded tetrahydropyrene quantitatively (*17*). These and many other highly regioselective results (*22*) contrast with the complex mixture reported earlier when more strenuous conditions were employed.

Mylroie and Stenberg (*27*) reported interesting differences between Ru-on-C and RuO_2. Hydrogenation of 9,10-hydroxymethyltriptycene over either Pd-on-C or Ru-on-C (4000 psig, 150°C, EtOH) gave high yields of the perhydro compound, but over RuO_2 extensive hydrogenolysis of the hydroxy groups occurred as well.

References

1. R. Adams and J. R. Marshall, *J. Am. Chem. Soc.* **50,** 1970 (1928).
2. H. W. Arnold, U.S. Patent No. 2,555,912 (1951).
3. R. H. Baker and R. D. Schuetz, *J. Am. Chem. Soc.* **69,** 1250 (1947).
4. R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.* **26,** 3669 (1961).
5. K. D. Cowen and E. J. Eisenbraun, Unpublished Ph.D. Thesis of K. D. Cowen, Oklahoma State Univ., Stillwater, 1977.
6. J. R. Cozort, J. F. Outlaw, Jr., A. Hawkins, and S. Siegel, *J. Org. Chem.* **48,** 4190 (1983).
7. C. W. Doecke, P. J. Garratt, H. Shahriari-Zavareh, and R. J. Zahler, *J. Org. Chem.* **49,** 1412 (1984).
8. R. W. Franck and K. Yanagi, *J. Org. Chem.* **33,** 811 (1968).
9. M. Freifelder, *J. Org. Chem.* **29,** 979 (1964).
10. M. Freifelder and G. R. Stone, *J. Am. Chem. Soc.* **80,** 5270 (1958).
11. P. P. Fu and R. G. Harvey, *Tetrahedron Lett.*, 415 (1977).

12. P. P. Fu and H. M. Lee, and R. G. Harvey, *J. Org. Chem.* **45,** 2797 (1980).
13. E. Galantay, *Tetrahedron* **19,** 319 (1963).
14. H. Greenfield, *Ann. N.Y. Acad. Sci.* **214,** 233 (1973).
15. K. Harada, *J. Org. Chem.* **32,** 1790 (1967).
16. F. Hartog and P. Zwietering, *J. Catal.* **2,** 79 (1963).
17. R. G. Harvey, M. Konieczny, and J. Pataki, *J. Org. Chem.* **48,** 2930 (1983).
18. J. A. Hirsch and G. Schwartzkopf, *J. Org. Chem.* **39,** 2044 (1974).
19. C. W. Keenan, B. W. Gieseman, A. A. Smith, *J. Am. Chem. Soc.* **76,** 229 (1954).
20. A. P. G. Kieboom, *Bull. Chem. Soc. Jpn.* **49,** 331 (1976).
21. G. Leclere, N. Decker, and J. Schwartz, *J. Med. Chem.* **25,** 709 (1982).
22. H. Lee and R. G. Harvey, *J. Org. Chem.* **47,** 4364 (1982).
23. R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.* **64,** 1985 (1942).
24. R. P. Linstead, R. R. Whetstone, and P. Levine, *J. Am. Chem. Soc.* **64,** 2014 (1942).
25. I. Mochida and Y. Yoneda, *J. Catal.* **11,** 183 (1968).
26. J. B. Montgomery, A. N. Hoffmann, A. L. Glasebrook, and J. I. Thigpen, *Ind. Eng. Chem.* **50,** 313 (1958).
27. V. L. Mylroie and J. F. Stenberg, *Ann. N.Y. Acad. Sci.* **214,** 255 (1973).
28. J. T. Nieuwstad, P. Klapwijk, and H. van Bekkum, *J. Catal.* **29,** 404 (1973).
29. J. R. Outlaw, Jr., J. R. Cozort, N. Gasti, and S. Siegel, *J. Org. Chem.* **48,** 4186 (1983).
30. G. R. Pettit and E. G. Thomas, *Can. J. Chem.* **60,** 629 (1982).
31. N. Pourahmody, E. H. Vickery, and E. J. Eisenbraun, *J. Org. Chem.* **47,** 2590 (1982).
32. H. Rapoport and J. Z. Pasky, *J. Am. Chem. Soc.* **78,** 3788 (1956).
33. H. Rapoport and G. Smolinsky, *J. Am. Chem. Soc.* **82,** 1171 (1960).
34. P. N. Rylander and D. R. Steele, U.S. Patent No. 3,387,048 (1968).
35. P. N. Rylander and X. Vaflor, *Am. Chem. Soc., Northeast Reg. Meet. 6th* (1974).
36. P. N. Rylander, N. Rakoncza, D. Steele, and M. Bollinger, *Engelhard Ind. Tech. Bull.* **4,** 95 (1963).
37. S. Siegel, *Adv. Catal.* **16,** 123 (1966).
38. S. Siegel, G. V. Smith, B. Dmuchovsky, D. Dubbell, and W. Halpren, *J. Am. Chem. Soc.* **84,** 3136 (1962).
39. S. Siegel, V. Ku, and W. Halpren, *J. Catal.* **2,** 348 (1963).
40. L. H. Slaugh and J. A. Leonard, *J. Catal.* **13,** 385 (1969).
41. J. H. Stocker, *J. Org. Chem.* **27,** 2288 (1962).
42. J. H. Stocker, *J. Org. Chem.* **29,** 3593 (1964).
43. M. Tamura and K. Harada, *Synth. Commun.* **8,** 345 (1978).
44. M. Taverna and M. Chita, *Hydrocarbon Process.* (Nov.), 137 (1970).
45. K. Taya, M. Hiramoto, and K. Hirota, *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.)* **62**(4), 145 (1968).
46. W. Theilacker and H. G. Drössler, *Chem. Ber.* **87,** 1676 (1954).
47. W. S. Trahanovsky and D. H. Bohlen, *J. Org. Chem.* **37,** 2192 (1972).
48. H. van Bekkum, *Proc. Int. Congr. Catal., 3rd, 1964,* **2,** 1208 (1965).
49. H. van Bekkum, H. M. A. Buurmans, G. van Minnen-Pathuis, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas* **88,** 779 (1969).
50. G. Vedage and K. Klier, *J. Catal.* **77,** 558 (1982).
51. B. O. Vineyard, W. S. Knowles, and M. J. Sabacky, *J. Mol. Catal.* **19,** 159 (1983).
52. Y. H. Wu, W. A. Gould, W. G. Lobeck, Jr., H. R. Roth, and R. F. Feldkamp, *J. Med. Chem.* **5,** 752 (1962).
53. T. Yoshida, *Bull. Chem. Soc. Jpn.* **47,** 2061 (1974).
54. H. E. Zaugg, R. J. Michaels, H. J. Gleen, L. R. Swett, M. Freifelder, G. R. Stone, and A. W. Weston, *J. Am. Chem. Soc.* **80,** 2763 (1958).

-10-

Hydrogenation of Anilines, Phenols, and Derivatives

Many of the considerations discussed in the previous chapter apply to anilines and phenols, but the presence of amino and hydroxy groups introduce new problems and opportunities.

10.1. Anilines

Anilines are saturated easily. The reduction may be accompanied by several side reactions, including loss of the nitrogen atom by hydrogenolysis (*2*) and by reductive hydrolysis, coupling to secondary amines, and, in certain compounds, reductive cyclization. The major features of aniline hydrogenations are accounted for by formation of partially saturated rings to afford vinylic and allylic amino derivatives, susceptible to hydrogenolysis, and, through isomerization to imines, susceptible to hydrolysis and to reductive coupling (*22*).

10.1.1. Catalysts

Anilines have been reduced successfully over a variety of supported and unsupported metals, including palladium, platinum, rhodium, ruthenium, iridium, (*54*), cobalt, and nickel. Base metals require high temperatures and pressures (*76*), whereas noble metals can be used under much milder conditions. Currently, preferred catalysts in both laboratory or industrial practice are rhodium at lower pressures and ruthenium at higher pressures, for both display high activity and relatively little tendency toward either coupling or hydrogenolysis.

A variety of mixed metal catalysts, either as fused oxides (*42,57,58*) or coprecipitated on supports (*25,50*) or as physical mixtures of separate catalysts (*59*), have been tested in aniline reductions. In the hydrogenation of ethyl *p*-aminobenzoate, a coprecipitated 3% Pd, 2% Rh-on-C proved superior to 5% Rh-on-C, inasmuch as hydrogenolysis to ethyl cyclohexanecarboxylate was less (*61*) (Table 1).

TABLE 1

Hydrogenation of Ethyl *p*-Aminobenzoate[a]

Catalyst and loading	Reduction time (h)[b]	Temperature (°C)	Hydrogenolysis	Conversion (%)
10% of 5% Rh-on-C	3.0	60	13.4	100
10% of 5% Rh-on-C	2.2	80	16.0	100
5% of 5% Rh-on-C	6.0	80	19.4	100
10% of 3% Pd, 2% Rh-on-C	3.2	60	11.4	10
10% of 3% Pd, 2% Rh-on-C	2.0	80	11.7	100
5% of 3% Pd, 2% Rh-on-C	2.0	80	10.9	100

[a] Reduction done in 3A Ethanol (a denatured ethanol) with 85% H_3PO_4 at 60 psig.
[b] Time to 90% completion.

These data show hydrogenolysis to increase with temperature, a general observation supported by many experiments. Here the influence of temperature is less with the mixed-metal catalysts.

10.1.2. Catalyst Reactivation

A general problem in the economical use of catalysts is to maximize the pounds of product obtained per pound of catalyst, commensurate with acceptable space–time yields. Lower catalyst loadings are less costly than are higher loadings on a once-through basis, but on reuse the lower loading may decline in activity more rapidly than higher loadings. An example of this is hydrogenation of ethyl *p*-aminobenzoate (benzocaine) over 5% Rh-on-C in ethanol containing phosphoric acid. At 20% catalyst loadings at least 10 batches of benzocaine could be reduced without loss in activity with intermediate catalyst regeneration, but at 5% and 10% loadings the rate of hydrogenation fell rapidly with reuse, even with repeated regeneration.

Regeneration was based on removing ammonium dihydrogen phosphate, formed in hydrogenolysis of benzocaine, from the catalyst. The catalyst was

first washed with water, then with 6 *N* phosphoric acid, and finally with ethanol while being kept free from air (*61*).

A rhodium-on-alumina catalyst deactivated in bis-(4-aminophenyl)-methane saturation (115°C, 100 psig) was regenerated by two washings with aqueous ammonia at 65°C, followed by drying at 90°C (*16*) or by washing with acetic acid.

10.1.3. Control of Coupling

Hydrogenation of anilines normally gives cyclohexylamines and varying amounts of the coupled products, dicyclohexylamines. The ratio of these products is influenced by temperature, catalytic metal, support, additives, and solvent. It is possible to exert substantial control over the product composition. Coupled products increase with increasing temperature (*23*).

In a study on the influence of supports on rhodium, the amount of dicyclohexylamine was found to decrease in the order carbon > barium carbonate > alumina > barium sulfate > calcium carbonate. Plain carbon added to rhodium-on-alumina-catalyzed reactions was found to cause an increase in the amount of dicyclohexylamine, suggesting that carbon catalyzes the formation of the intermediate addition product (*59*).

The amount of coupled product was found to depend importantly on the catalytic metal; a sequence for increased coupling to dicyclohexylamine was found to be Ru < Rh ≪ Pd ~ Pt (*59*), a sequence that reflects one reason for the industrial preference for rhodium and ruthenium in hydrogenation of anilines.

Basic additives such as alkali-metal and alkaline-earth hydroxides and carbonates, amines, and ammonia are useful in suppressing formation of coupled products (*4,29*). Lithium hydroxide specifically seems especially effective in promoting reductions over ruthenium oxide catalysts (*46*). Amines suppress coupled products but at the expense of rate. Aqueous ammonia is less inhibiting than anhydrous ammonia, but in aqueous solution, oxygenated products form (*22,37*). The inhibiting effects of ammonia and amines, formed in hydrogenolysis of aniline and *N*-alkylanilines, can be alleviated by venting and repressuring the reactor (*5*).

The extent of coupling is also influenced by the solvent. In the hydrogenation of aniline over ruthenium oxide, coupling decreased with solvent in the order methanol > ethanol > isopropanol > *t*-butanol. The rate was also lower in the lower alcohols, probably owing to the inhibiting effect of greater concentrations of ammonia (*44*). Carboxylic acid solvents increase the amount of coupling (*42*).

10.1.4. Reductive Hydrolysis

Reductive hydrolysis of anilines, which may occur as an unwanted side reaction when anilines are reduced in aqueous media, can be turned to synthetic advantage. Reductive cleavage is facilitated by substitution on the nitrogen and by acidic media. Palladium is the preferred catalyst (*33*). Reductive hydrolysis of substituted anilines carrying chiral N-substituents gives chiral cyclohexanones (*34*).

10.1.5. Synthetic Applications

An excellent route to cyclohexylamines is by hydrogenation of the corresponding aniline over rhodium or ruthenium (*17,18,19,32,36,63,64*). Rhodium has proved especially useful in saturation of alkoxyanilines with minimal hydrogenolysis of the alkoxy function (*45*). The extent of hydrogenol ysis occurring in saturation of alkoxyanilines depends also on the solvent. Hydrogenolysis of *p*-methoxyaniline over $Ru(OH)_2$ fell with alcohol solvent in the order methanol (35%) > ethanol (30%) > propanol (26%) > butanol (22%) > isopropanol (16%) > *t*-butanol (8%) (*43*).

Reduction of anilines containing acid, ester, or carbonyl functions provides a convenient entry to bi- and tricyclic systems, cyclization occurring once the rigidity of the aromatic ring has been lost through saturation (*1,2,61,77*).

10.2. Phenols and Derivatives

Phenols are reduced easily to either the corresponding cyclic ketone or to the alcohol, depending in large measure on the catalyst. Hydrogenolysis of the oxygen atom may be a major side reaction. Hydrogenolysis occurs more readily than hydrogenolysis of the nitrogen atom in anilines, and in molecules containing both functions, the oxygen is lost preferentially. In lower-alcohol solvents, the major product of a phenol hydrogenation might be an alkyl cyclohexyl ether, the extent of this reaction again depending mainly on the catalyst.

10.2.1. Partial Hydrogenation of Phenols to Cyclohexanones

An important industrial synthesis of cyclohexanone is by partial hydrogenation of phenol over palladium, carried out in either liquid or vapor phase.

Because of the industrial magnitude of these processes, many catalysts have been examined with variations in metal distribution, pore size, and alkalinity. In most synthetic work where catalyst life and small variations in yield are not of great importance, most palladium-on-carbon or -on-alumina powder catalysts will be found satisfactory for conversion of phenols to cyclohexanones. Palladium has a relatively low tendency to reduce aliphatic ketones, and a sharp decrease in the rate of absorption occurs at about 2 mol of consumed hydrogen. Nickel may also be used but overhydrogenation is more apt to occur.

Examples of palladium-catalyzed reduction are 4-chloro-2,6-di-*t*-butylphenol to 2,6-di-*t*-butylcyclohexanone (750 psig, 25°C) with loss of halogen (*24*), 1,8-dihydroxynaphthalene to 8-hydroxy-1-tetralone (*30*), and 2,4-dimethylphenol to 2,4-dimethylcyclohexanone (*27*).

Palladium may not be preferred for dihydric aromatics. Dihydroresorcinol was obtained in 87% yield by alkaline hydrogenation of resorcinol over 5% Rh-on-C (*65*) and in only 50–60% yield over Pd-on-C (*15*). A 77% yield of the dione was obtained by alkaline hydrogenation of 3,5-dihydroxyphenylacetic acid over a 10% loading of 5% Rh-on-Al_2O_3 at 55°C and 55 psig (*39a*).

10.2.2. Deoxygenation with Ring Saturation

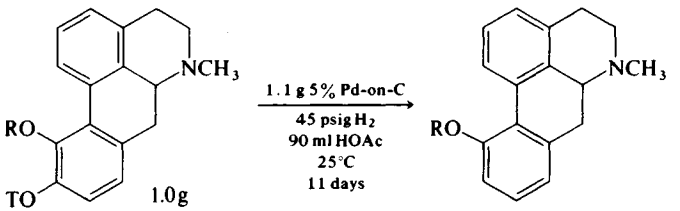
Hydrogenolysis on saturation of aromatic phenols or phenyl ethers may range from a trivial to a major side reaction. The extent of hydrogenolysis depends very much on structure. It is influenced also strongly by reaction parameters. Hydrogenolysis is enhanced by the presence of acids, by elevated temperatures, and by polar solvents; it is diminished by nonpolar solvents and increased pressure (*35*). The extent of hydrogenolysis is influenced strongly also by the catalyst; platinum and iridium tend to favor deoxygenation and are suggested if this reaction is desired; ruthenium, rhodium, and palladium at higher pressures are suggested when hydrogenolysis is to be avoided. Rhodium and ruthenium are especially useful if the phenol as phenyl ether also contains a benzyl substituent that is to be preserved.

10.2.3. Deoxygenation without Ring Reduction

Hydrogenolysis, without ring reduction, of the carbon–oxygen bond in phenols cannot be depended on, but by conversion of the phenol to a better leaving group, such as is formed by interaction of the phenol with 2-chlorobenzoxazole, 1-phenyl-5-chlorotetrazole, phenylisocyanate,

or 2,4,6-trichloro-*s*-triazines, the reaction acquires synthetic utility (*3,11,40,60,62,70,71,73*). The usual catalyst is palladium-on-carbon.

An unusual sensitivity of this reaction to structure was reported by Ram and Neumeyer (*51*). When R = H (**1**), hydrogenolysis could not be effected either directly or by catalytic hydrogen transfer (*13*), but etherification to give **2** (R = CH_3) permitted slow formation of **3**. The mild conditions of hydrogenation were required to avoid racemization at the 6a-position. Hydrogenolysis is usually much more facile than is indicated by this example.

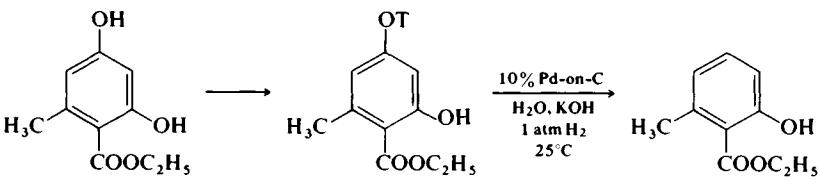


(**1**) R = H
(**2**) R = CH_3

T = 1-phenyltetrazolyl

(**3**) R = CH_3

Hydrogenolysis of 1-phenyltetrazolyl ether has been applied to deoxygenation of several heavily substituted phenols, for example, ethyl orsellinate (*4a*).



Hydrogenolysis of 2-phenyltetrazolyl ethers has been accomplished cleanly, using Pd-on-C and hydrazine or sodium phosphinate (*13*).

10.2.4. Ring Saturation without Hydrogenolysis

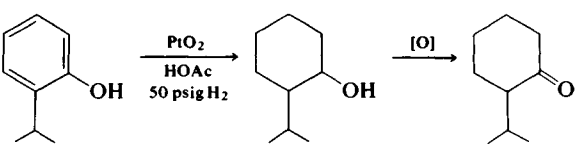
Hydrogenation of phenols to the corresponding saturated alcohols usually can be accomplished cleanly if appropriate conditions and catalysts are chosen. At one time, palladium was the preferred catalyst for achieving this reaction, both elevated pressures (1000–2000 psig) and temperatures (80–175°C) usually being used (*9,35,49,67*).

In saturation of ethyl *p*-tolyl ether in ethanol solvent, hydrogenolysis rose with metal in the order Pd < Ru ≪ Rh < Ir < Pt (*47*). The various complex factors contributing to this ordering are discussed at length in this reference.

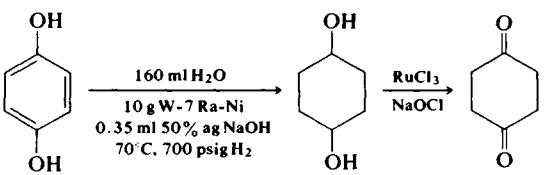
Palladium may also show exceptional selectivities, as in the conversion of *o*,*o*′-biphenol to *o*-(2-hydroxycyclohexyl)phenol (*55*), or *p*-phenylphenol to *p*-cyclohexylphenol (90%). If this latter reduction is continued in methanol solvent, the main product is not 4-cyclohexylcyclohexanol, but rather 4-cyclohexylcyclohexyl methyl ether (84%) (*56*).

Nowadays, rhodium or ruthenium are often the preferred catalysts. Rhodium can be used under mild conditions, whereas ruthenium needs elevated pressures. If pressure is available, it might as well be used even with rhodium, for increased pressure makes more efficient use of the catalyst, as well as decreases whatever hydrogenolysis might occur at lower pressure. Rhodium (*7,8,12,20,21,38,39,45,65,66,68,69,75*) and ruthenium (*18,26,28,52,68,69,72,74*) are especially advantageous in reductions of sensitive phenols and phenyl ethers that undergo extensive hydrogenolysis over catalysts such as platinum oxide.

An alternative to cyclohexanones from phenols involves ring saturation to the alcohol, followed by oxidation (*14*).



The sequence has been applied to the synthesis of 1,4-cyclohexanedione from hydroquinone (*10*), using W-7 Raney nickel as prepared by Billica and Adkins (*6*), except that the catalyst was stored under water. The use of water as solvent permitted, after filtration of the catalyst, direct oxidation of the reaction mixture with ruthenium trichloride and sodium hypochlorite via ruthenium tetroxide (*78*). Hydroquinone can be reduced to the diol over 5% Rh-on-C at ambient conditions quantitatively (*20*).



140 g

Hydrogenation of 2-naphthol can proceed at either ring with the general tendency to reduce the unsubstituted ring preferentially. The ratio *R* of

unsubstituted ring saturation to phenolic ring saturation varies with the metal (*48*).

Catalyst	*R*
Ru	7.0
Rh	8.5
Pd-on-C	3.2
Os	9.3
Ir	9.8
Pt	13.3

Nishimura (*41*) developed a binary catalyst (30% Pt, 70% Rh oxide) prepared by fusion of platinum and rhodium salts with sodium nitrate in the manner of the well-known preparation of Adams' PtO_2 catalyst (*31*). This particular composition has been recommended when hydrogenolysis is to be avoided. For example, hydrogenation of diphenyl ether over 30% Pt–70% Rh oxide at lower pressure gave dicyclohexyl ether in 50% yield, whereas over rhodium oxide the yield was only 20%, and over platinum oxide none of this product formed (*53*). Much higher yields of dicyclohexyl ether are formed over the binary catalyst at elevated pressures (*42*), again illustrating the efficiency of elevated pressures in decreasing hydrogenolysis. Dicyclohexyl ether can be obtained in 90% yield from diphenyl ether by saturation over 5% Pd-on-C in an ethanol solvent at 68 atm (*43*).

References

1. R. L. Augustine and W. G. Pierson, *J. Org. Chem.* **34,** 1070, 2235 (1969).
2. R. L. Augustine and L. A. Vag, *J. Org. Chem.* **40,** 1074 (1975).
3. C. E. Barfnecht, R. V. Smith, and V. V. Reif, *Can. J. Chem.* **48,** 2138 (1970).
4. A. E. Barkdoll, D. C. England, H. W. Gray, W. Kirk, Jr., and G. M. Whitman, *J. Am. Chem. Soc.* **75,** 1156 (1953).

4a. A. J. Bartlett, J. S. E. Holker, E. O'Brien, and T. J. Simpson, *J.C.S. Perkin Trans. 1,* 667 (1983).

5. C. R. Bauer, U.S. Patent No. 3,376,341 (1968).
6. H. R. Billica and H. Adkins, *Org. Synth. Coll. Vol* **3** 176 (1955).
7. A. W. Burgstahler and Z. J. Bithos, *J. Am. Chem. Soc.* **82,** 5466 (1960).
8. S. E. Cantor and D. S. Tarbell, *J. Am. Chem. Soc.* **86,** 2902 (1964).
9. W. R. Christian, C. J. Gogek, and C. B. Purves, *Can. J. Chem.* **29,** 911 (1951).
10. R. J. Crawford, *J. Org. Chem.* **48,** 1366 (1983).
11. E. J. Eisenbraun, J. W. Burnham, J. D. Weaver, and T. E. Webb, *Ann. N.Y. Acad. Sci.* **214,** 204 (1973).
12. E. L. Eliel and T. J. Brett, *J. Org. Chem.* **28,** 1923 (1963).
13. I. D. Entwistle, B. J. Hussey, R. A. W. Johnston, *Tetrahedron Lett.* **21,** 4747 (1980).
14. W. W. Epstein, J. R. Grua, and D. Gregonis, *J. Org. Chem.* **47,** 1128 (1982).

15. B. Esch and H. J. Schaeffer, *J. Am. Pharm. Assoc. Sci. Ed.* **49,** 786 (1960).
16. W. J. Farrissey, Jr., and F. F. Frulla, Ger. Offen 1,948,566 (1970); *CA* **72,** 132163 (1970).
17. M. Freifelder and G. R. Stone, *J. Org. Chem.* **27,** 3568 (1962).
18. M. Freifelder, V. H. Ng, and P. F. Helgren, *J. Org. Chem.* **30,** 2485 (1965).
19. T. M. Frunze, V. V. Korshak, and Z. V. Romanova, *Vysokomol. Soedin.* **1,** 518 (1959).
20. G. Gilman and G. Cohn, *Adv. Catal.* **9,** 733 (1957).
21. T. A. Giudici and T. C. Bruice, *J. Org. Chem.* **35,** 2386 (1970).
22. H. Greenfield, *J. Org. Chem.* **29,** 3082 (1964).
23. H. Greenfield, *Ann. N.Y. Acad. Sci.* **214,** 233 (1973).
24. H. Hart and F. A. Cassis, Jr., *J. Am. Chem. Soc.* **73,** 3179 (1951).
25. K. Ikedate and S. Suzuki, *Bull. Chem. Soc. Jpn.* **44,** 325 (1971).
26. R. E. Ireland and P. W. Schiess, *J. Org. Chem.* **28,** 6 (1963).
27. F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Am. Chem. Soc.* **86,** 118 (1964).
28. W. S. Johnson, E. R. Rogier, and J. Ackerman, *J. Am. Chem. Soc.* **78,** 6322 (1956).
29. M. Kalina and J. Pasek, *Kinet. Katal.* **10** (3), 574 (1969); *CA* **71,** 54119 (1969).
30. I. A. Kaye and R. S. Matthew, *J. Org. Chem.* **28,** 325 (1963).
31. C. W. Keenan, B. W. Gieseman, and H. A. Smith, *J. Am. Chem. Soc.* **76,** 229 (1954).
32. J. E. Kirby, U.S. Patent No. 2,606,926 (1952).
33. R. Kuhn and H. J. Haas, *Justus Liebigs Ann. Chem.* **611,** 57 (1958).
34. R. Kuhn, H. E. Driesen, and H. J. Haas, *Justus Liebigs Ann. Chem.* **718,** 78 (1968).
35. R. H. Levin and J. H. Pendergrass, *J. Am. Chem. Soc.* **69,** 2436 (1947).
36. E. F. Litvin, L. K. Freidlin, G. K. Oparina, V. I. Kheifets, V. V. Yakubenok, L. P. Pivonenkova, and M. K. Bychkova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 854 (1973); *CA* **79,** 31603 (1973).
37. E. B. Maxted, *Adv. Catal.* **3,** 129 (1951).
38. A. I. Meyers and K. Baburao, *J. Heterocycl. Chem.* **1,** 203 (1964).
39. A. I. Meyers, W. Beverung, and G. Garcia-Munoz, *J. Org. Chem.* **29,** 3427 (1964).
39a. M. Mokotoff and R. C. Cavestri, *J. Org. Chem.* **39,** 409 (1974).
40. W. J. Musliner and J. W. Gates, Jr., *J. Am. Chem. Soc.* **88,** 4271 (1966).
41. S. Nishimura, *Bull. Chem. Soc. Jpn.* **33,** 566 (1960).
42. S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Jpn.* **36,** 873 (1963).
43. S. Nishimura and H. Yoshino, *Bull. Chem. Soc. Jpn.* **42,** 499 (1969).
44. S. Nishimura, T. Shu, T. Hara, and Y. Takagi, *Bull. Chem. Soc. Jpn.* **39,** 329 (1966).
45. S. Nishimura, H. Uchino, and H. Yoshino, *Bull. Chem. Soc. Jpn.* **41,** 2194 (1968).
46. S. Nishimura, Y. Kono, Y. Otsuki, and Y. Fukaya, *Bull. Chem. Soc. Jpn.* **44,** 240 (1971).
47. S. Nishimura, M. Uramoto, and T. Watanabe, *Bull. Chem. Soc. Jpn.* **45,** 216 (1972).
48. S. Nishimura, S. Ohbuchi, K. Ikeno, and Y. Okada, *Bull. Chem. Soc. Jpn.* **57,** 2557 (1984).
49. F. C. Novello and M. E. Christy, *J. Am. Chem. Soc.* **73,** 1267 (1951).
50. W. M. Pearlman, *Org. Synth. Coll. Vol.* **5,** 670 (1969).
51. V. J. Ram and J. L. Neumeyer, *J. Org. Chem.* **47,** 4372 (1982).
52. O. R. Rodig and L. C. Ellis, *J. Org. Chem.* **26,** 2197 (1961).
53. P. N. Rylander and M. Kilroy, *Engelhard Ind. Tech. Bull.* **9,** 14 (1968).
54. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **3,** 19 (1962).
55. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **7,** 153 (1967).
56. P. N. Rylander and X. Vaflor, *Am. Chem. Soc., Northeast Reg. Meet. 6th* (1974).
57. P. N. Rylander, L. Hasbrouck, S. G. Hindin, I. Karpenko, G. Pond, and S. Starrick, *Engelhard Ind. Tech. Bull.* **8,** 25 (1967).
58. P. N. Rylander, L. Hasbrouck, S. G. Hindin, R. Iverson, I. Kaspenko, and G. Pond, *Engelhard Ind. Tech. Bull.* **8,** 93 (1967).
59. P. N. Rylander, L. Hasbrouck and I. Karpenko, *Ann. N.Y. Acad. Sci.* **214,** 100 (1973).

60. S. Sakai, A. Kabo, T. Hamamoto, M. Wakabayashi, K. Takahashi, Y. Ohtani, and J. Haginiva, *Tetrahedron Lett.*, 1489 (1969).
61. M. G. Scaros, H. L. Dryden, Jr., J. P. Westrich, and O. J. Goodmonson *in* "Catalysis of Organic Reactions" (J. R. Kosak, ed.), p. 279, Dekker, New York, 1984.
62. H. J. Shine, J. Habdas, H. Kwart, M. Brechbiel, A. G. Horgan, and J. S. Filppo, Jr., *J. Am. Chem. Soc.* **105,** 2823 (1983).
63. E. C. Shokal and H. A. Newey, U.S. Patent No. 2,817,644 (1957).
64. A. I. Smith, U.S. Patent No. 3,167,586 (1965).
65. H. A. Smith and B. L. Stump, *J. Am. Chem. Soc.* **83,** 2739 (1961).
66. H. A. Smith and R. G. Thompson, *Adv. Catal.* **9,** 727 (1957).
67. W. T. Sommerville, and E. T. Theimer, U.S. Patent No. 2,927,127 (1960).
68. Y. Takagi, *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.)* **64,** 39 (1970).
69. Y. Takagi, T. Naito, and S. Nishimura, *Bull. Chem. Soc. Jpn.* **38,** 2119 (1965).
70. A. W. Van Muijlwijk, A. P. G. Kieboom, and H. Van Bekkum, *Rec. Trav. Chim. Pays-Bas* **93,** 204 (1974).
71. V. Viswanatha and V. J. Hruby, *J. Org. Chem.* **45,** 2010 (1980).
72. E. Walton, A. N. Wilson, A. C. Haven, Jr., C. H. Hoffman, E. L. Johnston, W. F. Newhall, F. M. Robinson, and F. W. Holly, *J. Am. Chem. Soc.* **78,** 4760 (1956).
73. J. D. Weaver, E. J. Eisenbraun, and L. E. Harris, *Chem. Ind. (London)*, 187 (1973).
74. P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.* **37,** 34 (1972).
75. C. W. Whitehead, J. J. Traverso, F. J. Marshall, and D. E. Morrison, *J. Org. Chem.* **26,** 2809 (1961).
76. C. F. Winans, *Ind. Eng. Chem.* **32,** 1215 (1940).
77. J. Witte and V. Boekelheide, *J. Org. Chem.* **37,** 2849 (1972).
78. S. Wolfe, S. K. Hasan, and J. R. Campbell, *Chem. Commun.*, 1420 (1970).

-11-

Hydrogenation and Hydrogenolysis of Heterocycles

Two types of heterocyclic compounds are discussed in this chapter: those that undergo saturation and those that undergo fission of the heterocyclic ring. Both types of reduction have wide synthetic application.

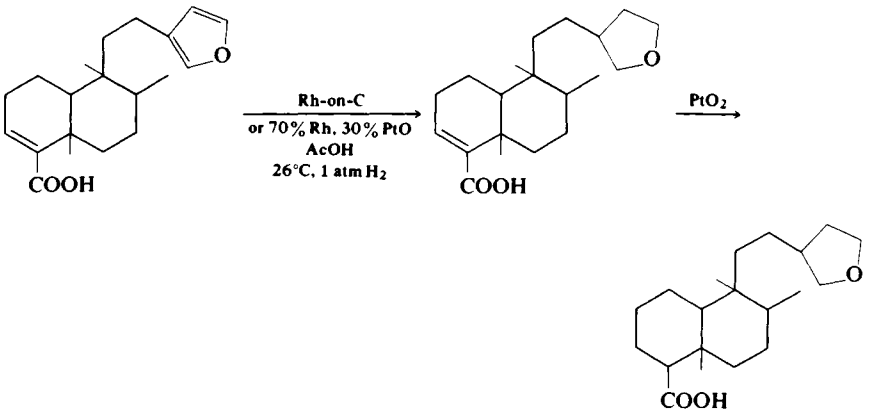
11.1. Ring Saturation

A variety of compounds fall into this category, among which are pyrroles, pyridines, pyrimidines, quinolines, and furans. In general, oxygen-containing rings are reduced more easily than are nitrogen rings owing in part to self poisoning of the latter by loss of aromaticity with consequent increased base strength and increased tendency to adsorb preferentially on catalyst sites. Oxygen-containing rings are also more likely to undergo hydrogenolysis.

11.1.1. Furans

Furans undergo both saturation and hydrogenolysis with the tendency toward hydrogenolysis increasing with increasing temperature, becoming at 250–300°C very extensive (*17,18*). Hydrogenolysis is favored also by the presence of acid (*54,96*).

The catalyst may have a marked influence on the course of reduction. Palladium (*13,39,45,76,99*), ruthenium (*77,86,115*), and rhodium (*11,18,73,123*) tend to favor hydrogenation. The Nishimura catalyst (70% Rh–30% Pt oxide) tends also to favor hydrogenation rather than hydrogenolysis, as is general for this catalyst (*69,70*). Rhodium-on-carbon or 70% Rh–30% Pt oxide selectively reduced the furan ring of methyl hardwickiate, leaving the trisubstituted conjugated olefin intact. Further hydrogenation over prereduced platinum oxide saturated the olefin as well to methyl hexahydrohardwickiate (*64*).



A variety of solvents have been used successfully. Extensive hydrolysis or alcoholysis may accompany reduction in aqueous or alcoholic solvent, attack presumably occurring on the intermediate vinyl ether (*58*).

11.1.2. Pyrroles

Pyrroles are hydrogenated with more difficulty than are carbocyclic aromatics. In compounds containing both rings, hydrogenation will proceed nonselectively or with preference for the carbocyclic ring (*19*), unless reduction of the carbocyclic ring is impeded by substituents. Acidic solvents are frequently used but are not necessary.

Platinum oxide has been used with success (*6,15,23,52,80*), but nowadays supported rhodium is apt to be the catalyst of choice, (*2,24,35,63,72,75,88,116*). Excellent results have been reported by Freifelder (*32*) using RuO_2 without solvent at 100–200°C and 1500 psig.

Kaiser and Muchowski (*41*) reduced *N*-(*t*-butoxycarbonyl) pyrroles to the corresponding pyrrolidines over 5% Pt-on-C at room temperature and atmospheric pressure. Under these conditions *O*-benzyl groups are retained and 2,5-disubstituted pyrroles are reduced mainly or exclusively to the *cis*-2,5-disubstituted pyrrolidines. In some cases Pt-on-C proved superior to either Rh-on-C or PtO_2.

11.1.3. Indoles

Indoles are reduced with relative difficulty (*12,81,82*), and, depending on structure, either ring may be reduced. *N*-Acetylindoles are reduced at the

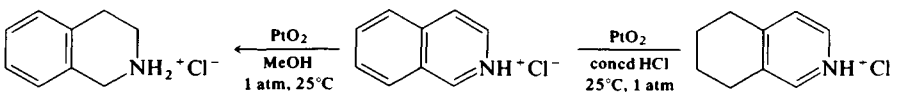
nitrogen ring more selectively than are unsubstituted indoles, but *N*-alkyl compounds are reduced with more difficulty (*110*). Acidic media favor selective reduction of the nitrogen ring (*14,40,42,97,124*).

11.1.4. Pyridines and Derivatives

Many pyridines have been hydrogenated with diverse catalysts. The relative effectiveness of catalysts depends on the reaction conditions and solvent (*84*). Rhodium is the most active under mild conditions, but as severity of the conditions is increased, differences among catalysts diminish. Nickel requires high temperatures and pressures, and if lower alcohols are used as solvents, N-alkylation may become a troublesome side reaction. This difficulty can be circumvented completely by use of ruthenium (*29,33*). Industrial producers of reduced pyridines tend toward palladium or ruthenium, combining a satisfactory rate with economical use. Palladium makes the most selective metal for hydrogenation of only one ring in bipyridyls (*85*). Platinum is often used, a choice stemming from a long history of success.

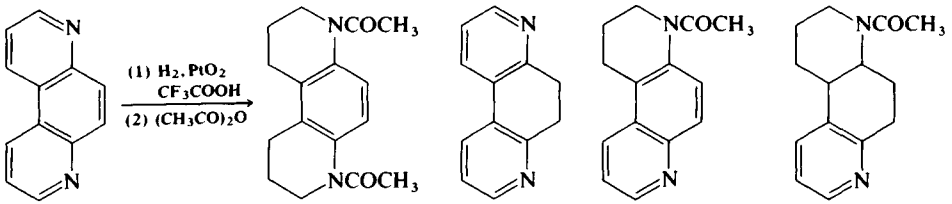
Acidic solvents are commonly used to prevent catalyst inhibition by the basic nitrogen atom of the substrate (*62*), and especially the more basic piperidine (*30*). Formation of pyridinium ions, besides diminishing inhibition, is thought to change the nature of adsorption from edgewise to flat (*95*). An interesting system requiring specifically hydrobromic acid has been reported (*10*). Quaternary pyridinium salts are reduced more readily than are hydrohalide salts, which in turn are more easily reduced than the free bases. This sequence of activities offers a possibility for controlling selectivity in complex compounds.

Normally, catalytic hydrogenation of pyridines containing a carbocyclic aromatic ring, whether fused or detached, occurs preferentially in the nitrogen ring. For example, reduction of 4-benzylpyridine (5% Rh-on-C, EtOH, 50 psig, 60°C) gave quantitative yields of 4-benzylpiperidine (*34*), and reduction of quinoline or isoquinoline (*120*) gave high yields of the 1,2,3,4-tetrahydro derivative (PtO_2, HOAc, 25°C, 1 atm). This usual selectivity can be reversed if reduction is carried out in concentrated, strong acid (*112,113*), as illustrated by hydrogenation of isoquinoline hydrochloride (*36*).



Selectivity may be a function of pressure as well as solvent, as suggested by the data of Cardellini *et al.* (*16*) on the hydrogenation of 4,7-phenanthroline in

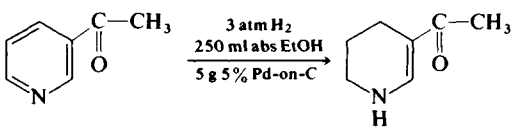
trifluoroacetic acid; here lower pressure favors reduction of the carbocyclic ring.



50 psig	44%	4%	5%	39%
15 psig	18%	2%	22%	45%

11.1.4.1. Partial Hydrogenation

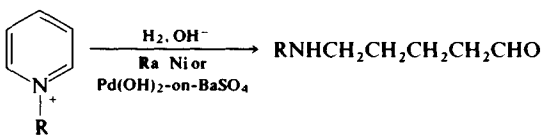
Most pyridines are reduced to the corresponding piperidines, but certain substituents, notably 2-amino and 2-hydroxy, tend to arrest the hydrogenation at the tetrahydro stage (*55,56,57*). Wenkert *et al.* (*118*) noted that in hydrogenation of any aromatic system capable of unmasking a stable, vinylogous amide unit, absorption may cease at this stage. An example is reduction of 3-acetylpyridine (**1**) to **2**, a compound that resisted further attempts at reduction (*31*).



(**1**) 45 g (**2**) 70%

Other examples are cited by Wenkert and Wickberg (*117*), Wenkert *et al.* (*118*), Eisner (*27*), and VanBergen and Kellogg (*111*).

Partial hydrogenation of *N*-alkylpyridinium salts in hydrolytic media provides a convenient route to ω-alkylaminovaleraldehydes (*87*).



11.1.4.2. Decarboxylation

Hydrogenation of 3-pyridinecarboxylic acids is apt to be accompanied by extensive decarboxylation (*28*), but this unwanted reaction can be prevented by carrying out the reaction in the presence of one equivalent of base (*33,79*). Ruthenium (*33*), rhodium (*29*), platinum oxide (*28,59*), and palladium (*30*) have all proved effective catalysts for reduction of pyridinecarboxylic acids to the saturated acid.

11.2. Ring Hydrogenolysis

Heterocyclic rings do not undergo hydrogenolysis readily unless they are strained, are activated by unsaturation, or contain a weak bond, e.g., N—O, (*38,61,114*), but these exceptions constitute a wide variety of compounds, whose reductions have proved very useful in syntheses.

11.2.1 Oxiranes

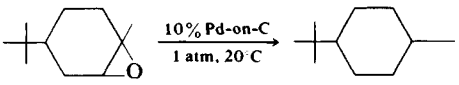
Hydrogenation of epoxides lends itself well to both synthetic applications and mechanistic studies. The reaction is complex, for either carbon–oxygen bond may break with or without inversion of configuration, and the product may contain deoxygenated products (*92,93*) as well as ketones derived by isomerization (*26*). The reaction is especially sensitive to both catalyst and environment (*74*).

It is not easy to deduce, without a close analogy, which carbon–oxygen bond will be broken, nor in what direction. Various investigators have concluded that ring opening will occur at the carbon atom with the least steric hindrance (*83*), or fewest substituents (*100*), or at the weakest bond (*3,37,68,119,121*), or in acidic solution so as to give the most stable carbocation (*60*). It is difficult to form any rule that does not include catalyst, environment, and structure of the substrate as a whole.

11.2.1.1. Deoxygenation

Deoxygenation may occur to an unacceptable extent. Its occurrence may be eliminated or greatly curtailed by the addition of small amounts of alkali (*67,98*) and/or by use of elevated pressures (*66*).

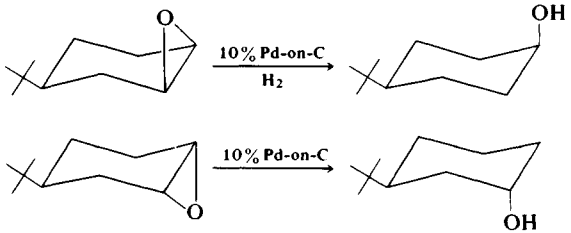
Deoxygenation is sensitive to solvent and structure. Alcohols tend to favor loss of oxygen, as illustrated in selected data of Accrombessi *et al.* (*1*). Additionally, methanol and ethanol may give substantial amounts of solvolysis products, in this case methoxy- and ethoxycyclohexanols.



	% Hydrocarbon	
Solvent	From cis isomer	From trans isomer
2-Propanol	20%	72%
Ether	8%	54%
Cyclohexane	trace	8%

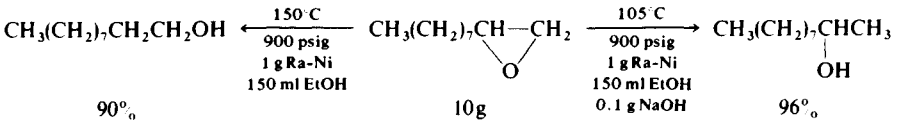
11.2.1.2. Direction of Ring Opening

In conformationally fixed *trans*- and *cis*-4-*t*-butylcyclohexene epoxides, the direction of ring opening is such as to give the axial alcohol, regardless of solvent (*1*).



Both regio- and stereospecificity may be influenced by the catalyst and by alkali. Raney nickel opens *cis*-2,3-diphenylbut-2-ene epoxide with retention of configuration to give *erythro*-2,3-diphenylbutan-2-ol, whereas palladium-on-carbon gives the inverted threo isomer. If a small amount of alkali is added to nickel-catalyzed reductions, nickel too gives the threo isomer (*65*).

A marked influence of alkali on regiospecificity is found in the hydrogenation of 1,2-epoxydecane (*68*).



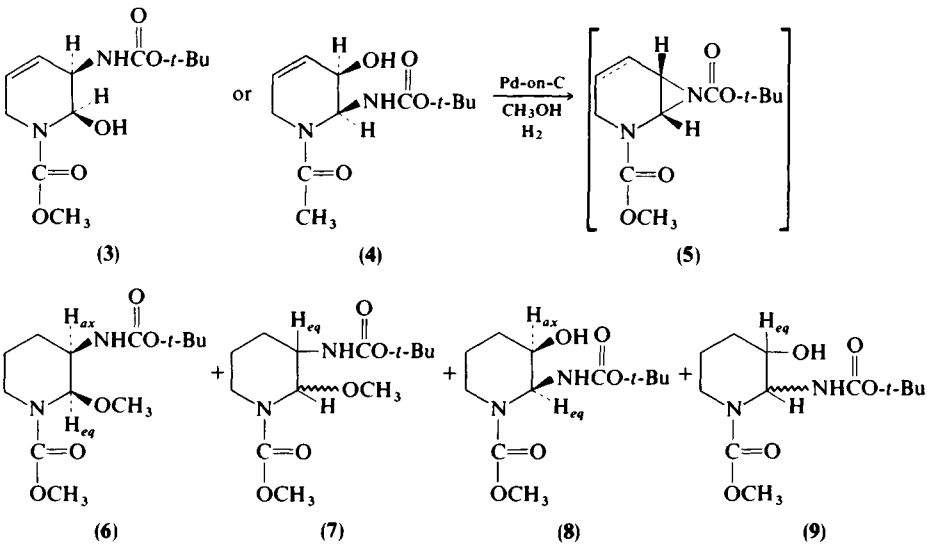
Hydrogenation of styrene oxide over palladium in methanol (*66*) gives exclusively 2-phenylethanol, but in buffered alkaline methanol the product is 1-phenylethanol. If alcoholysis of the epoxide by the product is troublesome, the problem can be eliminated by portion-wise addition of the epoxide to the reaction, so as always to maintain a high catalyst-to-substrate ratio. The technique is general for reactions in which the product can attack the starting material in competition with the hydrogenation.

11.2.2. Aziridines

Aziridines, like oxiranes, undergo hydrogenolysis easily with or without inversion of configuration, depending on the catalyst, reaction parameters, and various additives (*65a,108*). For example, hydrogenolysis of 2-methyl-2-phenylaziridine in ethanol occurs mainly with inversion over palladium but with retention over platinum, Raney nickel, or Raney cobalt. Benzene solvent or alkali favor retention over palladium as well.

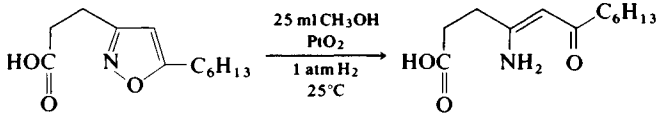
Ring opening occurs mainly at the least hindered carbon–nitrogen bond, unless the more hindered is activated by unsaturation or aromatic substituents (*53,101,102,108*).

The intermediacy of an aziridine (**5**) was invoked to account for the unexpected array of products [(**6**), (**7**), (**8**), and (**9**)] arising from saturation of the 4,5-olefinic bond in the 1,2,3,6-tetrahydropyridines **3** and **4** (*25*).

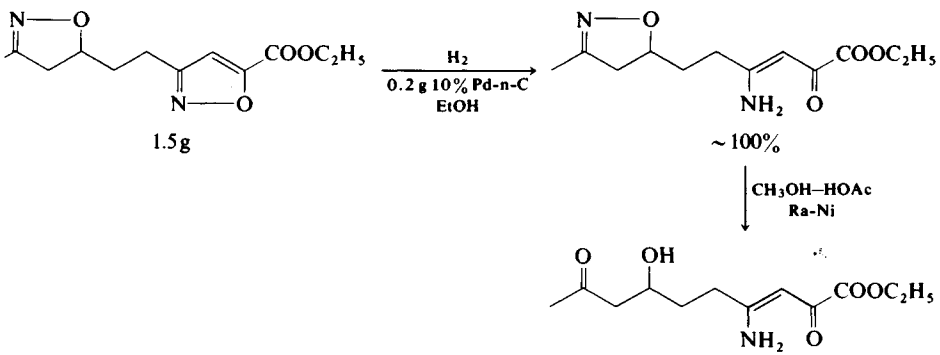


11.2.3. Isoxazoles

Isoxazoles are stable toward many reagents yet undergo alkylation and hydrogenolysis readily. These features make isoxazoles, which may be considered masked diketones, a useful grouping in synthesis (*22*). Alkylation of 3,5-dimethylisoxazole, followed by hydrogenolysis and hydrolysis, have been used to prepare a number of diketones (*44*) and tetraones (*43*). Isoxazoles can be opened readily to the amino ketone, a vinylogous amide (*9*).



Isoxazoles are reduced more easily than are isoxazolines and may be opened selectively (*8*).



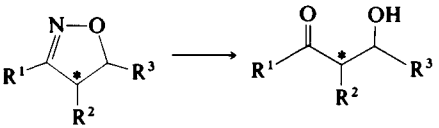
Hydrogenolysis of methylenediisoxazoles have been useful in preparing substituted resorcinols and aminophenols (*7*). The isoxazole annelation reaction (*71,89,90,91,103*) is well suited to the synthesis of steroids and other complex molecules.

Palladium is usually used in the hydrogenolysis of isoxazoles, but platinum and nickel have been used successfully. The rate of hydrogenolysis may be affected markedly by the pH (*104*). Neutral or alkaline media are frequently used.

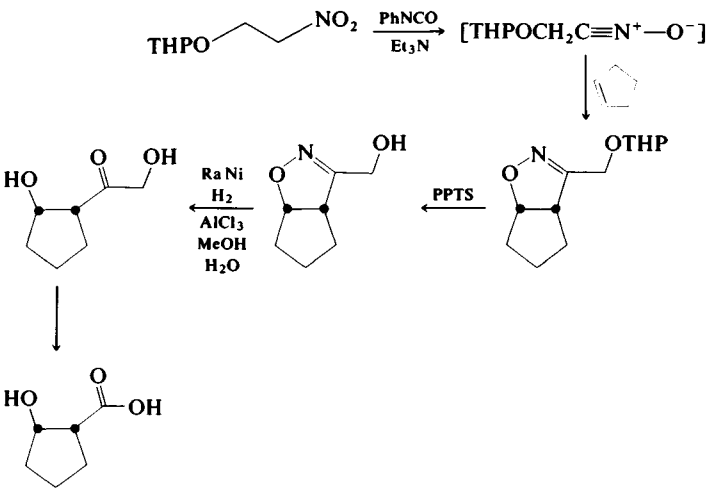
11.2.4. Isoxazolines

Kozikowski and Adamczyk (*46*) developed an excellent procedure for conversion of isoxazolines to β-hydroxy ketones without any epimerization at

the α-asymmetric center. Their procedure was based on the observation that extensive epimerization occurred when W-2 Ra Ni, and acetic acid (*122*) or Pd-on-C and acetic acid (*5*) was used for the hydrogenolysis, even though the hydroxy ketone did not undergo epimerization in acetic acid. These facts suggested that epimerization must occur at the β-hydroxyimine stage via a tautomeric enamine. To prevent this, the reduction was carried out over W-2 Ra-Ni with 4 equiv of concentrated HCl in 5:1 methanol–water. No trans isomer formed, and the yield of hydroxy ketone was nearly quantitative. The same results were achieved with W-2 Ra Ni and 4 equiv of $AlCl_3$ in 5:1 methanol–water. Raney nickel and boric acid appear equally as effective (*21,50*).

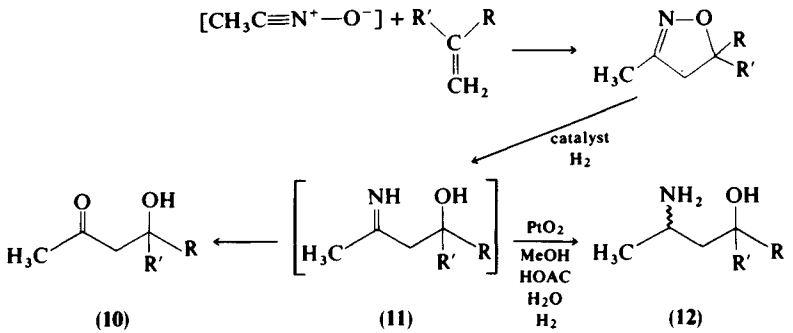


Hydrogenolytic cleavage of isoxazolines has also proved useful in preparation of β-dihydroxy ketones and β-hydroxy carboxylic acids (*47*). The isoxazolines were prepared by a [3 + 2] cycloaddition.



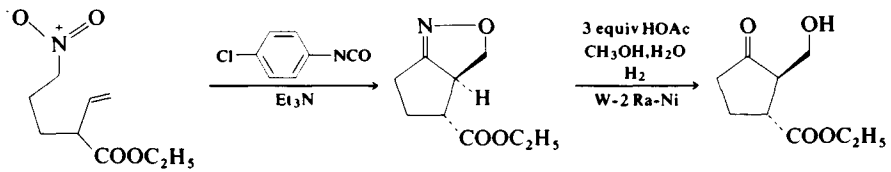
THPO = tetrahydropyranyl
PPTS = pyridinium *p*-toluenesulfonate

A two-step sequence of nitrile oxide–olefin cycloaddition and reduction of the resulting Δ^2-isoxazolines offers a unique and attractive alternative to the classical aldol reaction and its many variants (*21*). The procedure bypasses traditional problems, including enolate equilibrium and cross condensation (*20*).



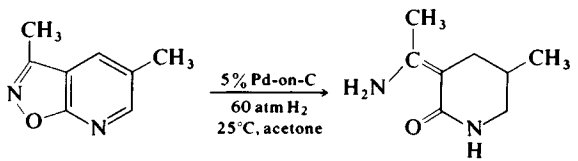
(10) (11) (12)

By selection of conditions and catalyst, the intermediate hydroxyimine (**11**) can be directed to either the hydroxy ketone (**10**) or amino alcohol (**12**). Over platinum oxide in methanol–acetic acid–water the amino alcohol forms, whereas over alkali-free Ra-Ni in methanol–water or over 10% Pd-on-C in methanol–water containing boric acid, the hydroxy ketones form in excellent yield. Nitrile oxide cycloadditions have been applied to five-membered ring syntheses (*50*).



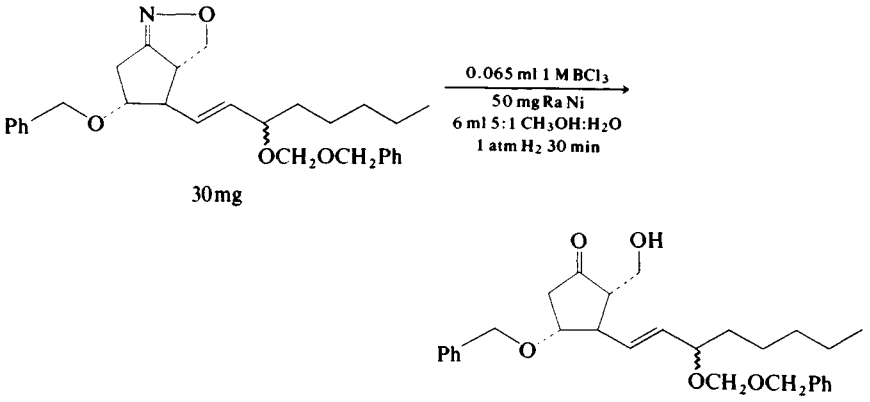
Hydrogenation was accomplished over freshly prepared W-2 Ra-Ni in a 5:1 methanol–water mixture containing 3 equiv of acetic or boric acid. The hydrogenolysis has been applied smoothly to the synthesis of *C*-nucleosides (*49*).

Reduction of 3,5-dimethylisoxazolo[5,4-*b*]pyridine over 5% Pd-on-C proceeded with loss of the aromatic system to give 3-(1-aminoethyliden)-5-methyl-2-oxopiperidine (*94*). The product is a vinylogous amide, a type of structure resistant to further hydrogenation (*118*).



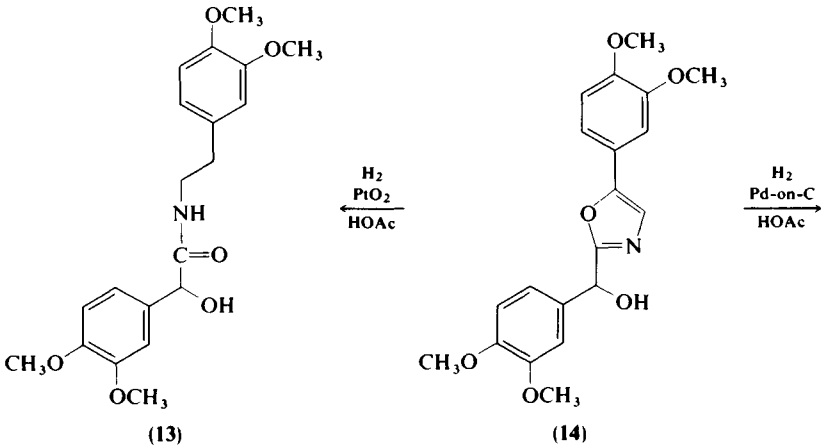
A formal total synthesis of the prostaglandin $F_{2\alpha}$ involved unmasking of an isoxazoline ring by hydrogenation over W-2 Raney Ni/BCl_3/MeOH, H_2O to reveal a β-hydroxyketone. It was necessary in this case to deactivate the Raney

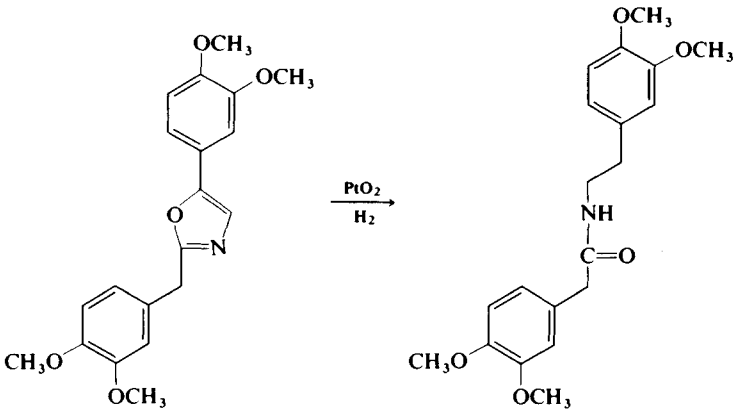
Ni prior to use by refluxing it for 3 h with acetone, in order to suppress hydrogenolysis of the benzylic protecting groups (*51*).



11.2.5. Oxazoles and Oxazolines

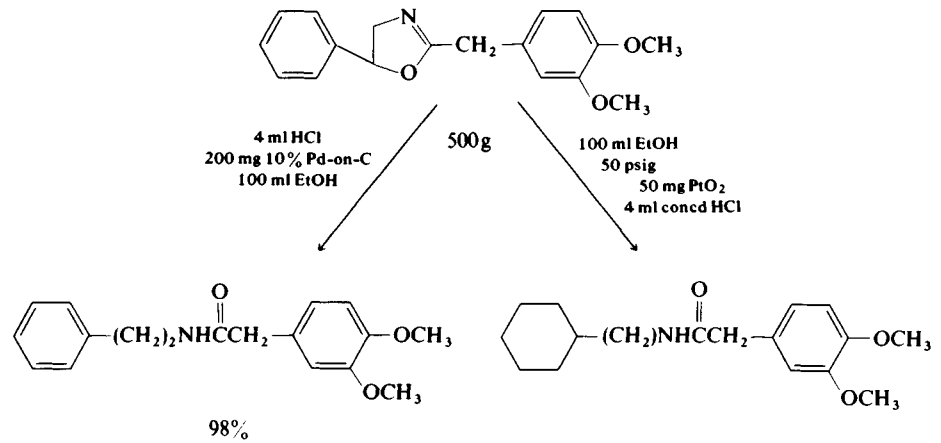
Extreme differences between 5% palladium-on-carbon and platinum oxide were found on reduction of the 5-aryl substituted oxazole **14**. Over palladium, **15** was formed in quantitative yield by hydrogenolysis of the benzyl hydroxyl, whereas over Pt, scission of the oxazole occurred to give **13** quantitatively (*48*). Hydrogenation of **15** over platinum oxide gave the phenethylamide **16**.





(15) (16)

A more expected difference between platinum oxide and palladium-on-carbon was found in the hydrogenolysis of 5-phenyl-2-(3,4-dimethoxybenzyl)-2-oxazoline. Cleavage occurred at the benzyl–oxygen bond over both catalysts, but over platinum, the less substituted phenyl group was saturated as well (*78*).



References

1. G. C. Accrombessi, P. Geneste, J. L. Olive, and A. A. Pavia, *J. Org. Chem.* **45,** 4139, (1980).
2. R. Adams, S. Miyano, and D. Fles, *J. Am. Chem. Soc.* **82,** 1466 (1960).
3. E. A. Adegoke, P. Ojechi, and D. A. H. Taylor, *J. Chem. Soc.*, 415 (1965).

5. M. Asaoka, T. Mukuta, and H. Takei, *Tetrahedron Lett.* **22,** 735 (1981).
6. J. H. Atkinson, R. Grigg, and A. W. Johnson, *J. Chem. Soc.*, 893 (1964).
7. S. Auriccho, S. Morrocchi, and A. Ricca, *Tetrahedron Lett.*, 2793 (1974).
8. P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollini, and D. Simoni, *J. Org. Chem.* **48,** 1297 (1983).
9. A. Barco, S. Benetti, G. P. Pollini, B. Veronesi, P. G. Baraldi, M. Guarneri, and C. B. Vicentini, *Synth. Commun.* **8,** 219 (1978).
10. D. F. Barringer, Jr., G. Berkelhammer, S. D. Carter, L. Goldman, and A. E. Lanzilotti, *J. Org. Chem.* **38,** 1933 (1973).
11. E. R. Bissell and M. Finger, *J. Org. Chem.* **24,** 1259 (1959).
12. V. Boekelheide and C.-T. Liu, *J. Am. Chem. Soc.* **74,** 4920 (1952).
13. D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and D. L. Colebrook, *J. Org. Chem.* **31,** 2192 (1966).
14. I. Butula and R. Kuhn, *Angew. Chem. Int. Ed. Engl.* **7,** 208 (1968).
15. P. A. Cantor and C. A. VanderWerf, *J. Am. Chem. Soc.* **80,** 970 (1958).
16. M. Cardellini, G. M. Cingolani, F. Claudi, G. Cristalli, U. Gulini, and S. Martelli, *J. Org. Chem.* **47,** 688 (1982).
17. N. I. Chouikine and I. F. Belsky, *Dokl. Akad. Nauk SSSR* **115,** 330 (1957).
18. N. I. Chouikine and I. F. Belsky, *Actes Congr. Int. Catal., 2nd, 1960,* **2,** 2625 (1961).
19. L. C. Craig and R. M. Hixon, *J. Am. Chem. Soc.* **52,** 804 (1930).
20. D. P. Curran, *J. Am. Chem. Soc.* **104,** 4024 (1982).
21. D. P. Curran, S. A. Scanga, and C. J. Fenk, *J. Org. Chem.* **49,** 3474 (1984).
22. S. D'Alcontres, *Gazz. Chim. Ital.* **80,** 441 (1950).
23. O. Dann and W. Dimmling, *Ber. Dtsch. Chem. Ges.* **86,** 1383 (1953).
24. L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.* **37,** 3691 (1972).
25. S. K. Dubey and E. E. Knaus, *Can. J. Chem.* **61,** 565 (1983).
26. J. C. Duchet and D. Cornet, *Bull. Soc. Chim. Fr.*, 1135, 1141 (1975).
27. U. Eisner, *Chem. Commun.*, 1348 (1969).
28. M. Freifelder, *J. Org. Chem.* **27,** 4046 (1962).
29. M. Freifelder, *J. Org. Chem.* **28,** 1135 (1963).
30. M. Freifelder, *Adv. Catal.* **14,** 203 (1963).
31. M. Freifelder, *J. Org. Chem.* **29,** 2895 (1964).
32. M. Freifelder, "Practical Catalytic Hydrogenation," p. 577. Wiley (Interscience), New York, 1971.
33. M. Freifelder, and G. R. Stone, *J. Org. Chem.* **26,** 3805 (1961).
34. M. Freifelder, R. M. Robinson, and G. R Stone, *J. Org. Chem.* **27,** 284 (1962).
35. D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.* **80,** 6249 (1958).
36. J. Z. Ginos, *J. Org. Chem.* **40,** 1191 (1975).
37. W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.* **35,** 3338 (1970).
38. L. Horner and E. Jürgens, *Ber. Dtsch. Chem. Ges. B* **90,** 2184 (1957).
39. J. W. Huffman and L. E. Browder, *J. Org. Chem.* **29,** 2598 (1964).
40. M. Janot, J. Keufer, and J. LeMen, *Bull. Soc. Chim. Fr.*, 230 (1952).
41. H. P. Kaiser, and J. M. Muchowski, *J. Org. Chem.* **49,** 4203 (1984).
42. P. Karrer and P. Waser, *Helv. Chim. Acta* **32,** 409 (1949).
43. C. Kashima, *J. Org. Chem.* **40,** 526 (1975).
44. C. Kashima, S. Tobe, N. Sugiyama, and M. Yamamoto, *Bull. Chem. Soc. Jpn.* **46,** 310 (1973).
45. D. D. Kaufman, L. R. Worden, E. T. Lode, M. K. Strong, and N. C. Reitz, *J. Org. Chem.* **35,** 157 (1970).
46. A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.* **23,** 3123 (1982).

47. A. P. Kozikowski and M. Adamczyk, *J. Org. Chem.* **48,** 366 (1983).
48. A. P. Kozikowski and A. Ames, *J. Org. Chem.* **45,** 2550 (1980).
49. A. P. Kozikowski and S. Goldstein, *J. Org. Chem.* **48,** 1141 (1983).
50. A. P. Kozikowski and P. D. Stein, *J. Am. Chem. Soc.* **104,** 4023 (1982).
51. A. P. Kozikowski and P. D. Stein, *J. Org. Chem.* **49,** 2301 (1984).
52. L. R. Kray and M. G. Reinecke, *J. Org. Chem.* **32,** 225 (1967).
53. N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.* **28,** 1499 (1963).
54. T. E. Londergan, N. L. Hause, and W. R. Schmitz, *J. Am. Chem. Soc.* **75,** 4456 (1953).
55. R. E. Lyle and G. G. Lyle, *J. Am. Chem. Soc.* **76,** 3536 (1954).
56. R. E. Lyle and S. E. Mallett, *Ann. N.Y. Acad. Sci.* **145,** 83 (1967).
57. R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.* **20,** 1761 (1955).
58. G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron* **20,** 1789 (1964).
59. S. M. McElvain and R. Adams, *J. Am. Chem. Soc.* **45,** 2738 (1923).
60. F. J. McQuillin and W. O. Ord, *J. Chem. Soc.*, 3169 (1959).
61. F. B. Mallory and S. P. Varimbi, *J. Org. Chem.* **28,** 1656 (1963).
62. E. B. Maxted and A. G. Walker, *J. Chem. Soc.*, 1093 (1948).
63. J. Meinwald and H. C. J. Ottenheym, *Tetrahedron* **27,** 3307 (1971).
64. R. Mistra, R. C. Pandey, and S. Dev, *Tetrahedron* **35,** 2301 (1979).
65. S. Mitsui and Y. Nagahisa, *Chem. Ind. (London)*, 1975 (1965).
65a. S. Mitsui and Y. Sugi, *Tetrahedron Lett.*, 1287, 1291 (1969).
66. S. Mitsui, S. Imaizumi, M. Hisashige, and Y. Sugi, *Tetrahedron* **29,** 4093 (1973).
67. S. Mitsui, Y. Sugi, M. Fujimoto, and K. Yokoo, *Tetrahedron* **30,** 31 (1974).
68. M. S. Newman, G. Underwood, and M. Renoll, *J. Am. Chem. Soc.* **71,** 3362 (1949).
69. S. Nishimura, *Bull. Chem. Soc. Jpn.* **33,** 566 (1960).
70. S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Jpn.* **36,** 873 (1963).
71. M. Ohashi, H. Kamachi, H. Kakisawa, and K. G. Stork, *J. Am. Chem. Soc.* **89,** 5460 (1967).
72. C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.* **77,** 4100 (1955).
73. L. A. Paguette, A. A. Youssef, and M. L. Wise, *J. Am. Chem. Soc.* **89,** 5246 (1967).
74. G. J. Park and R. Fuchs, *J. Org. Chem.* **22,** 93 (1957).
75. J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.* **27,** 1652 (1962).
76. C. W. Perry, M. V. Kalnins, and K. H. Deitcher, *J. Org. Chem.* **37,** 4371 (1972).
77. A. A. Ponomarev and A. S. Chegolya, *Dokl. Akad. Nauk SSSR* **145,** 812 (1962).
78. L. N. Pridgen, L. B. Killmer, and R. L. Webb, *J. Org. Chem.* **47,** 1985 (1982).
79. M. S. Raasch, *J. Org. Chem.* **27,** 1406 (1962).
80. H. Rapoport, C. B. Christian, and G. Spencer, *J. Org. Chem.* **18,** 840 (1954).
81. B. Robinson, *Chem. Rev.* **69,** 785 (1969).
82. M. M. Robison, F. P. Butler, and B. L. Robison, *J. Am. Chem. Soc.* **79,** 2573 (1957).
83. J. M. Ross, D. S. Tarbell, W. E. Lovett, and A. D. Cross, *J. Am. Chem. Soc.* **78,** 4675 (1956).
84. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **3,** 19 (1962).
85. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **5,** 113 (1965).
86. P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.* **7,** 153 (1967).
87. C. Schöpf, G. Herbert, R. Rausch, and G. Schroder, *Angew. Chem.* **69,** 391 (1957).
88. E. E. Schweizer and K. K. Light, *J. Org. Chem.* **31,** 870 (1966).
89. J. W. Scott and G. Saucy, *J. Org. Chem.* **37,** 1652 (1972).
90. J. W. Scott, B. L. Banner, and G. Saucy, *J. Org. Chem.* **37,** 1664 (1972).
91. J. W. Scott, R. Borer, and G. Saucy, *J. Org. Chem.* **37,** 1659 (1972).
92. G. Senechal and D. Cornet, *Bull. Soc. Chim. Fr.*, 773 (1971).
93. G. Senechal, J. C. Duchef, and D. Cornet, *Bull. Soc. Chim. Fr.*, 783 (1971).
94. C. Skötsch, I. Kohlmeyer, and E. Breitmaier, *Synthesis*, 449 (1979).

95. R. M. Skomoroski and A. Schriesheim, *J. Phys. Chem.* **65,** 1340 (1961).
96. H. A. Smith and J. F. Fuzek, *J. Am. Chem. Soc.* **71,** 415 (1949).
97. A. Smith and J. H. P. Utley, *Chem. Commun.*, 427 (1965).
98. A. Sohma and S. Mitsui, *Bull. Chem. Soc. Jpn.* **43,** 448 (1970).
99. D. Starr and R. M. Hixon, *J. Am. Chem. Soc.* **56,** 1595 (1934).
100. H. E. Stavely, *J. Am. Chem. Soc.* **64,** 2723 (1942).
101. C. L. Stevens and P. M. Pillai, *J. Org. Chem.* **37** 173 (1972).
102. C. L. Stevens, J. M. Cahoon, T. R. Potts, and P. M. Pillai, *J. Org. Chem.* **37,** 3130 (1972).
103. G. Stork and J. E. McMurry, *J. Am. Chem. Soc.* **89,** 5463, 5464 (1967).
104. G. Stork, S. Danishefsky, and M. Ohashi, *J. Am. Chem. Soc.* **89,** 5459 (1967).
105. Y. Sugi and S. Mitsui, *Bull. Chem. Soc. Jpn.* **42,** 2984 (1969).
107. Y. Sugi and S. Mitsui, *Bull. Chem. Soc. Jpn.* **43,** 1489 (1970).
108. Y. Sugi, M. Nagata, and S. Mitsui, *Bull. Chem. Soc. Jpn.* **48,** 1663 (1975).
110. T. Toth and A. Gerecs, *Acta. Chim. Acad. Sci. Hung.* **67**(2), 229 (1971); *CA* **74,** 125322 (1971).
111. T. J. VanBergen and R. M. Kellogg, *J. Org. Chem.* **36,** 2256 (1971).
112. F. W. Vierhapper and E. L. Eliel, *J. Am. Chem. Soc.* **96,** 2256 (1974).
113. F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.* **40,** 2729 (1975).
114. G. N. Walker, *J. Org. Chem.* **27,** 1929 (1962).
115. I. D. Webb and G. T. Borcherdt, *J. Am. Chem. Soc.* **73,** 752 (1951).
116. B. Weinstein and A. R. Craig, *J. Org. Chem.* **41,** 875 (1976).
117. E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.* **87,** 1580 (1965).
118. E. Wenkert, K. G. Dave, E. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.* **33,** 747 (1968).
119. W. F. Whitmore and A. L. Gebhart, *J. Am. Chem. Soc.* **64,** 912 (1942).
120. G. Witkop, *J. Am. Chem. Soc.* **70,** 2617 (1948).
121. B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.* **79,** 197 (1957).
122. R. H. Wollenberg and J. E. Goldstein, *Synthesis*, 757 (1980).
123. K. Yamakawa and M. Moroe, *Tetrahedron* **24,** 3615 (1968).
124. D. V. Young and H. R. Snyder, *J. Am. Chem. Soc.* **83,** 3161 (1961).

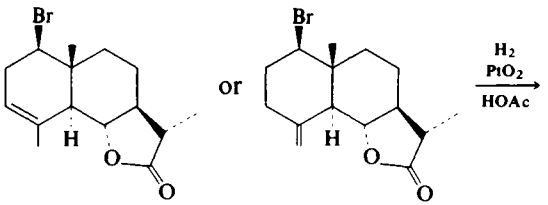
-12-

Catalytic Dehydrohalogenation

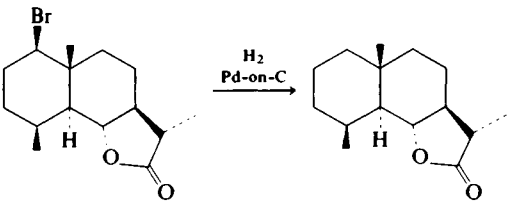
Most halogen–carbon bonds are cleaved easily by catalytic dehydrohalogenation. The hydrogenolysis can often be done selectively in the presence of other easily reducible groups (*14,25,64*). In molecules containing several halogens, one can often be removed preferentially. A useful way of making an aldehyde is by cleavage of a halogen–acyl bond, a procedure known as the Rosenmund reduction.

12.1. Catalysts

Catalysts differ widely in their ability to effect dehydrohalogenation. Palladium is usually the catalyst of choice. Platinum and rhodium are relatively ineffective and are often used in hydrogenations when halogen is to be preserved. A sequential use of platinum and palladium is illustrated in



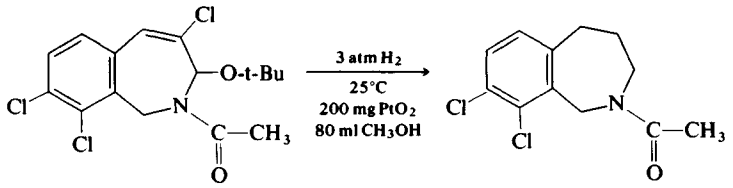
(1)



(2) (3)

hydrogenation of the lactones **1**. The initial reduction over platinum oxide gave 1-β-bromosantanolide "c" (**2**); further reduction over palladium-on-carbon gave **3** (*33*).

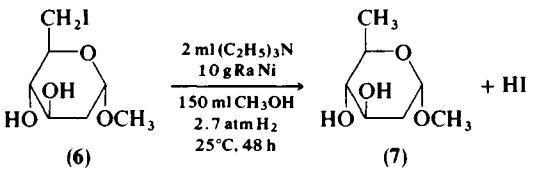
In some molecules, the loss of halogen is unexpectedly facile and may occur extensively even over platinum, as illustrated by reduction of the dihydro-2-benzazepine **4** to **5**. The authors (*53*) raised the possibility that such facile loss of halogen may involve neighboring-group assistance from the amide moiety.



(4) 1 g

(5) 80%

Nickel catalysts have been used for many dehydrohalogenations (*30*), but these catalysts are much more suspectible to poisoning by halide ion than are noble metals. As a result, the catalyst-to-substrate ratio must be much higher when using nickel, and reduction times are apt to be lengthy (*56*). Reductive deiodination of **6** to **7** was achieved over Raney nickel in methanol containing triethylamine. Despite massive loadings, the reduction was slow (*20*).



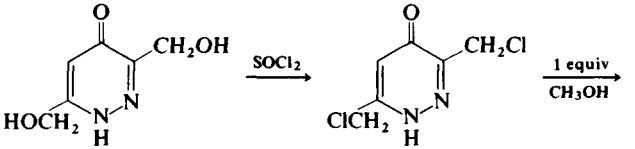
(6) 6.45 g

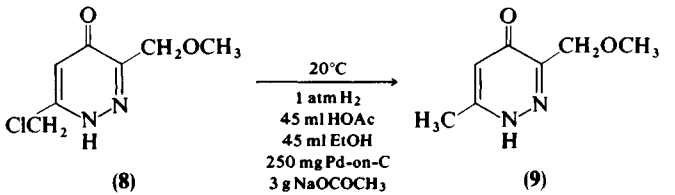
(7)

12.2. Basic and Acidic Media

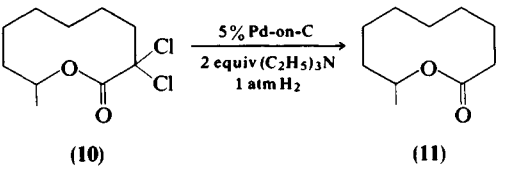
It is a common practice to add 1 mol or more of a base to dehydrohalogenations to minimize inhibition by the liberated hydrogen halide (*3,18*). The powerful inhibiting effect of halogen halide is illustrated by Mylroie and Stenberg (*50*), who reduced 9-chloromethyltriptycene to actadecahydro-9-chloromethyltriptycene over palladium-on-carbon in 1 *N* ethanolic hydrochloric acid; without added hydrogen chloride the halogen was lost during ring saturation.

A number of halogen acceptors, such as alkali and alkaline-earth hydroxides, acetates, ethoxides, amines, and ammonia, have been used successfully. The pyridazine **9** was prepared via dehydrohalogenation of **8** using sodium acetate as acceptor (*37*).

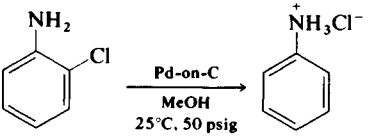




Triethylamine was used as acceptor in dehydrochlorination of **10** to give the macrolide phoracantholide I (**11**) (*44*).



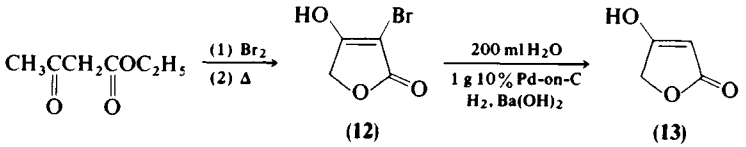
Compounds containing a basic nitrogen, such as 2-chloroaniline, may function as their own hydrogen-halide acceptor (*4*). The rate of reduction is greatly retarded by added hydrogen chloride.



Bases function in a more complex way than simply by acting as a halogen acceptor, for they cannot always be used interchangeably, and the product may depend on the base used (*58,68,69*). Diamines, such as ethylene-, propylene-, or hexamethylene diamines may function differently than monoamines. Diamines were thought to function through chelate formation (*32*). Loven and Speckamp (*40*) concluded that selectivity in reduction of a

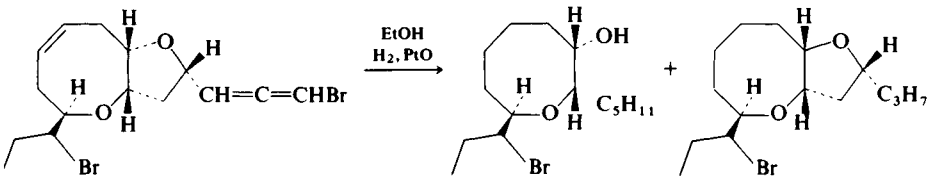
trichloromethyl function in piperidine sulfonamides was influenced strongly by the catalyst as well as by both the type and quantity of base.

Dehydrobromination of **12** to β-tetronic acid (**13**) in high yield could be achieved only under narrowly circumscribed conditions (*62*). The molar ratio of barium hydroxide to **12** needed to solubilize **12** and to neutralize the liberated hydrobromic acid must be at least two to one. Deionized water was the preferred solvent because of ease of workup. The yields were found to be concentration dependent. Concentrations of **12** in water of about 16% gave good yields of **13**, whereas at 33% concentration the yield was much lower. One gram of 10% Pd-on-C per 33 g of **12** was required; less catalyst gave incomplete reductions.



12.3. Polyhalo Compounds

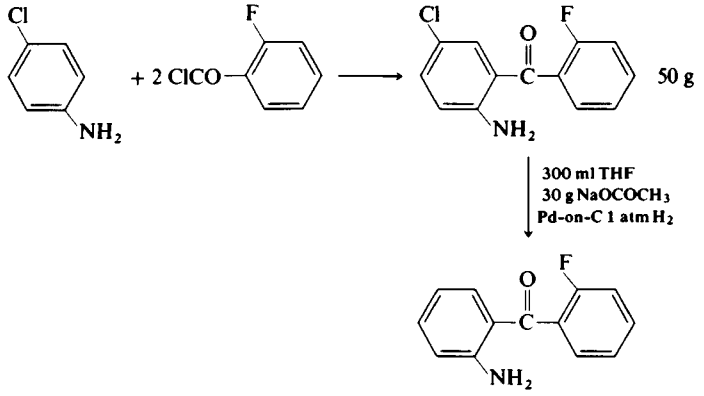
Selective dehydrohalogenation in compounds containing more than one halogen usually can be achieved readily and in a predictable fashion. Halogens activated by carbonyl (*3,5,6,9,17,21,31,42,47,61*), vinyl (*70,71*), allyl (*43*), aryl, or benzyl groups (*52*) are reduced more readily than are nonactivated halogens (*18*). Hydrogenation of epilaurallene (**14**) over platinum oxide in ethanol gave a mixture of **15** and **16**, which differ by the occurrence of hydrogenolysis of the allylic oxygen. The vinyl bromide is lost, while the nonactivated bromide is retained (*63*).



(**14**) (**15**) (**16**)

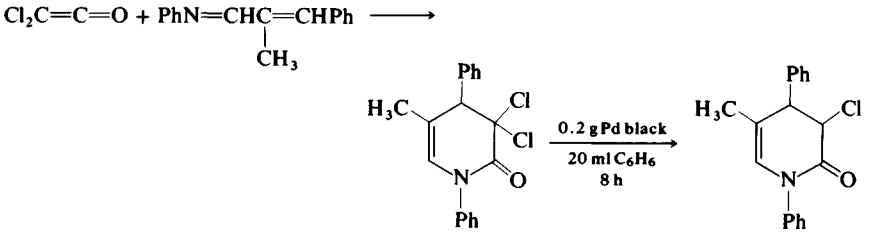
The ease of removal of halogen decreases with increasing electronegativity, I > Br > Cl > F (*39,66*); fluorine is usually quite difficult to remove unless highly activated (*19,22,41,43,45*). A synthesis of 2-amino-2′-fluorobenzophenone provides an example of a facile selective removal of

chloride in the presence of fluoride (*57*), as well as illustrating the use of halogen as a blocking group (*12,31*).

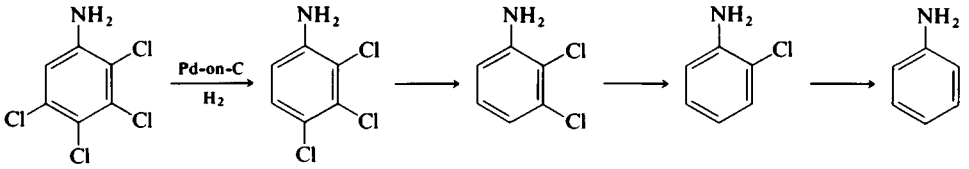


The above general sequence for ease of removal of halogen can be used at times to advantage in improving selectivity in molecules containing other reducible functions by first displacing the halogen with one of lower electronegativity before the hydrogenation (*1*).

The more halogens on a single carbon, the greater the ease of hydrogenolysis, a fact that makes stepwise dehydrohalogenation an easy process, since each loss increases the resistance to further loss (*4,13,21,24,29,71*). Reduction of the dichloro compound **17** over palladium black gave **18** in 98% yield (*8*).

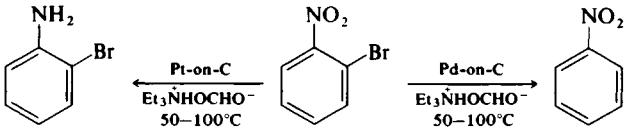


In polychloroanilines, the least hindered chlorine is the most reactive, producing the following sequence for the major products (*15*).



12.4. Halonitro Compounds

Selective hydrogenation of an aromatic halonitro compound to the corresponding haloaniline is a common industrial reaction, but the reverse selectivity, dehydrohalogenation to give the corresponding dehalonitro compound, is seldom seen. This latter reaction has been achieved in good yield by the method of Cortese and Heck (*16*), who used triethylammonium formate at 50–100°C as a reducing agent in the presence of either heterogeneous or homogeneous palladium catalyst. Platinum, on the other hand, favors preferential hydrogenation of the nitro group.



In contrast to aromatic halonitro compounds, selective removal of halogen in aliphatic halonitro compounds presents little problem. The reaction can be done by hydrogenation over palladium-on-carbon in the presence of a hydrohalide acceptor (*46,73*).

12.5. Coupling Reactions

Dehydrohalogenation at times follows an unusual course; halogen is eliminated and a new carbon–carbon bond forms. The reaction has been used to make biphenyls (*48*), bibenzyls (*11*), and bicyclopentadienes (*60*). Hydrogen, hydrazine, and methanol (as both reducing agent and solvent) have been used in these couplings. Long-chain hydrocarbons can be made in good yield by the reductive coupling of 1-iodoalkanes with hydrazine in the presence of palladium chloride or palladium metal as catalyst. Tetracontane was formed in 74% yield from 1-iodoeicosane (*51*); yields decrease with decreasing chain length.

$$2\,RI \xrightarrow[\substack{Pd\\CH_3OH}]{NH_2NH_2\cdot H_2O} R{-}R + 2\,HI + N_2 + H_2$$

12.6. Rosenmund Reduction

The selective hydrogenation of acid chlorides to aldehydes is known as the Rosenmund reduction (*49*).

$$RCOCl + H_2 \longrightarrow RCHO + HCl$$

The main difficulties connected with this hydrogenation arise from over-reduction to the alcohol, which is a yield loss per se

$$RCHO + H_2 \longrightarrow RCH_2OH$$

as well as loss because of reaction with the acid chloride.

$$RCH_2OH + RCOCl \longrightarrow RCH_2OCOR + HCl$$

If the resulting alcohol is susceptible to hydrogenolysis, still further yield loss occurs through formation of water.

$$RCH_2OH + H_2 \longrightarrow RCH_3 + H_2O$$

$$RCOCl + H_2O \longrightarrow RCOOH + HCl$$

In certain sensitive compounds, such as triphenylacetyl chloride, decarbonylation may be the major reaction (*59*). Palladium, the preferred catalyst for the Rosenmund reduction, is also an excellent catalyst for decarbonylation of aldehydes (*27,28,65*), and decarbonylation may occur after aldehyde formation.

12.6.1. Regulated Catalysts

Rosenmund reductions are known to be sensitive to trace modifiers, and various inhibitors are added commonly to control the extent of overhydrogenation. Hershberg and Cason (*26*) suggested that inhibitors always be used because of the possibility of inadvertent and uncontrolled poisoning, but other workers (*23*) have found nonpoisoned palladium-on-carbon catalysts to be sometimes more effective than conventional poisoned catalysts (*49*). Barnes (*5*) in *Organic Syntheses* has given detailed examples of the use of regulated and nonregulated catalysts. The use of quinoline–sulfur, a common regulator, has been examined in detail by Jethani *et al.* (*34*).

12.6.2. Procedure

Rosenmund reductions are carried out usually by bubbling hydrogen through a heated solution of the acid chloride in a solvent in the presence of a palladium catalyst and running the reaction until hydrogen chloride evolution ceases (*35*). Some workers have suggested that the temperature be kept as low as possible (*2,7*) and still evolve hydrogen chloride; low boiling solvents, such

as acetone, can be used to advantage (*54*). An excellent technique for successful reduction to sensitive aldehydes is to achieve reflux at low temperatures by maintaining a vacuum on the system (*23,36*).

Successful Rosenmund reductions have been carried out in the presence of halogen acceptors, such as anhydrous sodium acetate (*67*), dimethylaniline (*23*), ethyldiisopropylamine (*55*), or 2,6-dimethylpyridine (*10*).

References

1. E. L. Albano and D. Horton, *J. Org. Chem.* **34,** 3519 (1969).
2. T. Amakasu and K. Sato, *Bull. Chem. Soc. Jpn.* **40,** 1428 (1967).
3. V. Arkley, G. I. Gregory, and T. Walker, *J. Chem. Soc.* 1603 (1963).
4. R. Baltzly and A. P. Phillips, *J. Am. Chem. Soc.* **68,** 261 (1946).
5. R. P. Barnes, *Org. Synth. Coll. Vol.* **3,** 551 (1955).
6. R. A. Barnes and N. N. Gerber, *J. Org. Chem.* **26,** 4540 (1961).
7. T. Boehm and G. Schumann, *Arch. Pharm. (Weinheim Ger.)* **271,** 490 (1933).
8. W. T. Brady and C. H. Shieh, *J. Org. Chem.* **48,** 2499 (1983).
9. H. Bredereck, G. Simchen, A. Santos, and H. Wagner, *Agnew. Chem. Int. Ed.* **5,** 671 (1966).
10. A. W. Burgstahler, L. O. Weigel, and C. G. Schaefer, *Synthesis*, 767 (1976).
11. M. Busch and W. Schmidt, *Ber. Dtsch. Chem. Ges.* **62B,** 2612 (1929).
12. D. E. Butler and S. M. Alexander, *J. Org. Chem.* **37,** 215 (1972).
13. S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.* **27,** 3545 (1962).
14. H. Conroy, *J. Am. Chem. Soc.* **77,** 5960 (1955).
15. G. Cordier and Y. Colleuille, *in* "Catalysis of Organic Reactions" (J. R. Kosak, ed.), p. 197. Dekker, New York, 1984.
16. N. A. Cortese and R. F. Heck, *J. Org. Chem.* **42,** 3491 (1977).
17. N. H. Cromwell and D. J. Cram, *J. Am. Chem. Soc.* **65,** 301 (1945).
18. D. A. Denton, F. J. McQuillin, and P. L. Simpson, *J. Chem. Soc.*, 5535 (1964).
19. R. Duchinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.* **79,** 4559 (1957).
20. P. L. Durette, *Synthesis*, 1037 (1980).
21. C. Equchi and A. Kakuta, *Bull. Chem. Soc. Jpn.* **47,** 1704 (1974).
22. R. E. Florin, W. J. Pummer, and L. A. Wall, *J. Res. Natl. Bur. Stand.* **62,** 119 (Research pap. 2938) (1959).
23. W. O. Foye and W. E. Lange, *J. Am. Pharm. Assoc. Sci. Ed.* **45,** 742 (1956).
24. S. A. Fugua, R. M. Parkhurst, and R. M. Silverstein, *Tetrahedron* **20,** 1625 (1964).
25. G. E. Ham and W. P. Coker, *J. Org. Chem.* **29,** 194 (1964).
26. E. B. Hershberg and J. Cason, *Org. Synth. Coll. Vol.* **3,** 627 (1955).
27. N. E. Hoffman and T. Puthenpurackel, *J. Org. Chem.* **30,** 420 (1965).
28. N. E. Hoffman, A. T. Kanakkunatt, and R. F. Schneider, *J. Org. Chem.* **27,** 2687 (1962).
29. K. Hofmann, S. F. Orochena, S. M. Sax, and G. A. Jeffrey, *J. Am. Chem. Soc.* **81,** 992 (1959).
31. J. W. Huffman, *J. Org. Chem.* **24,** 1759 (1959).
32. K. Isogai, S. Kondo, K. Katsura, S. Sata, N. Yoshihara, Y. Kawamura, and T. Kazama, *Nippon Kagaku Zasshi* **91,** 561 (1970); *CA* **74,** 3186 (1971).
33. T. Jain, C. M. Banks, and J. E. McCloskey, *Tetrahedron* **35,** 885 (1979).
34. K. P. Jethani, P. H. Mehta, and S. B. Chandalia, *Indian J. Technol.* **19**(9), 349 (1981).
35. R. L. Johnson, *J. Med. Chem.* **25,** 605 (1982).

36. W. S. Johnson, D. G. Martin, D. Pappo, S. D. Darling, and R. A. Clement, *Proc. Chem. Soc. London*, 58 (1957).
37. D. E. Klinge, H. C. vanderPlas, and A. Koudijs, *Recl. Trav. Chim. Pay-Bas* **93,** 201 (1974).
39. M. Kraus and V. Bazant, *in* "Catalysis" (J. W. Hightower, ed.), Vol. 2, p. 1073. Elsevier, New York, 1973.
40. R. P. Loven and W. N. Speckamp, *Tetrahedron* **34,** 1027 (1978).
41. H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry* **3,** 1844 (1964).
42. R. E. Lyle, and H. J. Troscianiec, *J. Org. Chem.* **24,** 333 (1959).
43. F. T. McBee and D. K. Smith, *J. Am. Chem. Soc.* **77,** 387 (1955).
44. R. Malherbe, G. Rist, and D. Bellus, *J. Org. Chem.* **48,** 860 (1983).
45. S. L. Manatt, M. Vogel, D. Knutson, and J. O. Roberts, *J. Am. Chem. Soc.* **86,** 2645 (1964).
46. F. H. Marquardt and S. Edwards, *J. Org. Chem.* **37,** 1861 (1972).
47. E. L. May and E. Mosettig, *J. Org. Chem.* **11,** 429 (1946).
48. F. R. Mayo and M. D. Hurwitz, *J. Am. Chem. Soc.* **71,** 776 (1949).
49. E. Mosettig and R. Mozingo, *Org. React. (N.Y.)* **4,** 362 (1948).
50. V. L. Mylroie and J. F. Stenberg, *Ann. N.Y. Acad. Sci.* **214,** 255 (1973).
51. R. Nakajima, K. Morita, and T. Hara, *Bull. Chem. Soc. Jpn.* **54,** 3599 (1981).
52. C. G. Overberger and J. J. Monagle, *J. Am. Chem. Soc.* **78,** 4470 (1956).
53. C. D. Perchonock, I. Lantos, J. A. Finkelstein, and K. G. Holden, *J. Org. Chem.* **45,** 1950 (1980).
54. J. A. Peters and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas* **90,** 1323 (1971).
55. J. A. Peters and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas* **100,** 21 (1981).
56. A. R. Pinder, *Synthesis*, 425 (1980).
57. E. Reeder and H. Sternback, U.S. Patent No. 3,136,815 (1964) *CA* **64,** 9515 (1964).
58. M. G. Reinecke, *J. Org. Chem.* **29,** 299 (1964).
59. K. W. Rosenmund and F. Zetzsche, *Ber. Dtsch. Chem. Ges.* **54B,** 425 (1921).
60. S. T. Rucker, U.S. Patent No. 2,908,723 (1959).
61. L. J. Sargent, and J. H. Ager, *J. Org. Chem.* **23,** 1938 (1958).
62. D. G. Schmidt and H. Zimmer, *Synth. Commun.* **11,** 385 (1981).
63. M. Suzuki, K. Koizumi, H. Kikuchi, and T. Suzuki, *Bull. Chem. Soc. Jpn.* **56,** 715 (1983).
64. P. C. Traas, H. J. Takken, and H. Boelens, *Tetrahedron Lett.*, 2027 (1977).
65. J. Tsuji and K. Ohno, *Tetrahedron Lett.*, 2173 (1967).
66. G. Vanon and R. Mathieu, *C.R. Acad. Sci.* **206,** 1387 (1938).
67. D. P. Wagner, H. Gurien, A. I. Rachlin, *Ann. N.Y. Acad. Sci.* **172,** 186 (1970).
68. N. Whittaker, *J. Chem. Soc.*, 1565 (1950).
69. N. Whittaker, *J. Chem. Soc.*, 1646 (1953).
70. K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.* **31,** 2250 (1966).
71. J. W. Wilt and E. Vasiliauskas, *J. Org. Chem.* **37,** 1467 (1972).
72. R. L. Wineman, E.-P.T. Hsu, and C. E. Anagnostopoulos, *J. Am. Chem. Soc.* **80,** 6233 (1958).
73. B. L. Zenitz, E. B. Macks, and M. L. Moore, *J. Am. Chem. Soc.* **70,** 955 (1948).

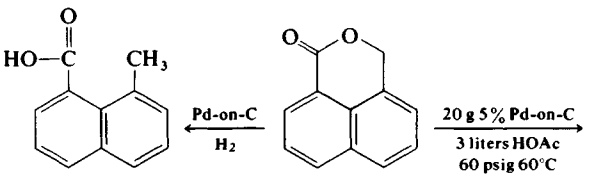
-13-

Miscellaneous Hydrogenolyses

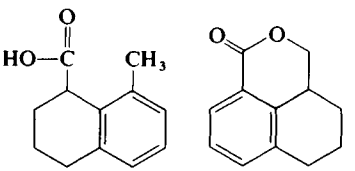
Catalytic hydrogenolysis is the cleavage of a molecule into fragments by hydrogen in the presence of a catalyst. It is a useful and frequent synthetic reaction. This chapter is organized around the type of bond being cleaved.

13.1. Benzyl Groups Attached to Oxygen

Hydrogenolysis of benzyl–oxygen bonds occurs readily. Many catalysts have been used, but palladium is by far the most often used, combining high activity for hydrogenolysis with a low tendency to promote ring reduction. Rhodium may prove useful if dehydrohalogenation is to be avoided (*50,106*), but ring saturation is a likely competing reaction. Sometimes ring saturation occurs with unexpected ease, even over palladium. Hydrogenolysis of the benzyl ester **2** was expected to proceed over palladium to give 8-methyl-1-naphthoic acid (**1**), but it did not. Instead, a mixture of 8-methyl-1,2,3,4-tetrahydro-1-naphthoic acid (**3**) and **4** was formed. Ring reduction was unusually facile here because it relieved peri strain (*138*).



(1) (2)

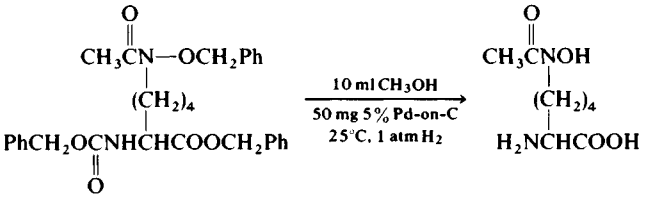


(3) 72% (4) 28%

13.1.1. Effect of Substrate Structure

Benzyl alcohols, acetals, ethers, esters, and phosphates all undergo hydrogenolysis readily. The rate of leaving parallels the ability of the leaving groups to bear a negative charge (*89,90*), and in $PhCH_2OR$, the rate increased in the order OH < O-alkyl < O-aryl < OH^+-alkyl < OH_2^+ < OAc < $OCOCF_3$.

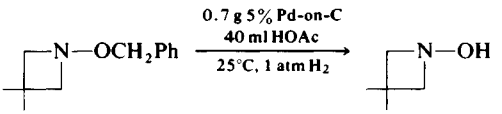
Benzyl–oxygen bonds may be cleaved under conditions mild enough to leave an allylic hydroxy group (*159*) or an easily reduced N—OH bond intact (*65,80*). *N*-Hydroxyamino acids can be prepared in good yield by hydrogenolysis of benzyl hydroxamates as shown in the synthesis of N^6-hydroxylysine (**6**) from **5** (*111*).



(**5**) 0.24 g

(**6**) 89%

Solvents may have an important influence on the reduction. No reaction occurred on attempted hydrogenolysis of the azetidine (**7**) over 5% Pd-on-C in ethanol, but in acetic acid reduction proceeded smoothly to give the 1-hydroxyazetidine (**8**) (*137*).



20 mmol

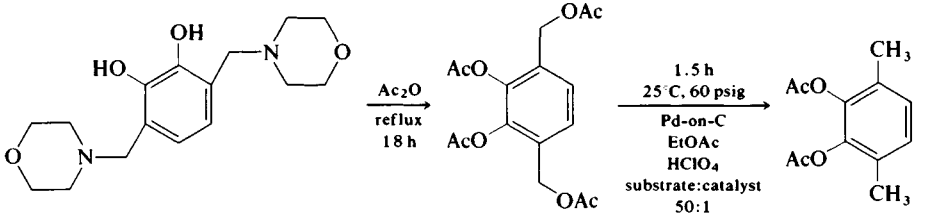
(**7**) (**8**)

Compounds containing both benzylic and homobenzylic oxygenated substituents may lose either or both functions on hydrogenolysis, in proportions that depend on the catalyst, stereochemistry of the starting material, and substituents (*38,54,64,119,183*).

13.1.2. Promoters

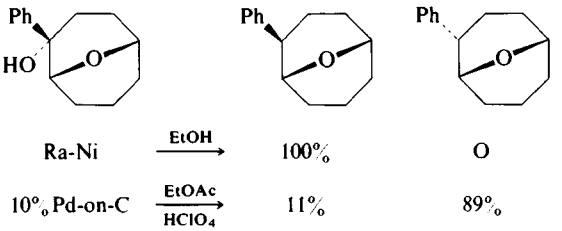
Strong acids such as hydrochloric, sulfuric, and especially perchloric are often added in small amounts to promote hydrogenolysis of benzyl–oxygen

functions (*72*). Hydrogenolysis of 3,6-bis(morpholinomethyl)catechol (**9**) proved very difficult, a general phenomenon with phenolic Mannich bases. Conversion to the tetraacetate **10** permitted ready hydrogenolysis to **11** if a trace of 70% perchloric acid were present; without acid, or with acetic or hydrochloric acids, hydrogenolysis was extremely slow (*161*).

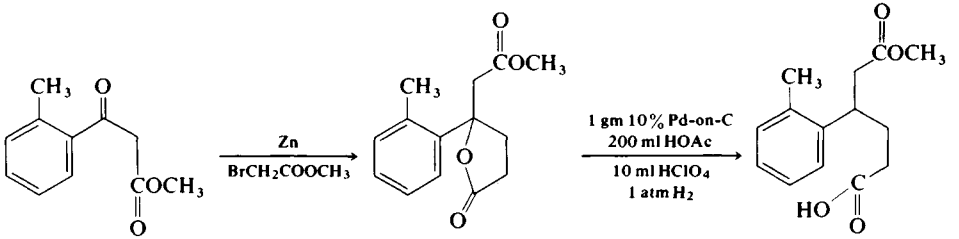


(**9**) (**10**) (**11**)

Hydrogenolysis of *exo*-2-phenyl-9-oxabicyclo[3.3.1]nonan-2-ol proceeds exclusively with retention over Raney nickel and with inversion over palladium. No reduction with palladium occurred at all until a drop of perchloric acid was added (*36*).



Another example of the use of an acid promoter is the conversion of **12** to **14** by way of lactone **13** (*143*).

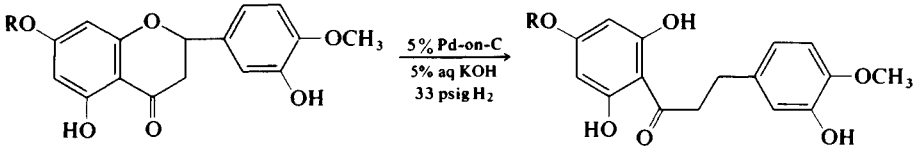


(**12**) (**13**) (**14**)

50 g

Tertiary amines are effective promoters in hydrogenolysis of hindered benzyl esters that otherwise may undergo cleavage only with difficulty (*187*).

Bases frequently impede hydrogenolysis, but hydrogenation of the flavanone **15** in aqueous potassium hydroxide over palladium gave **16** in high yield without reduction of an easily reduced aromatic ketone (*48*).



(15) (16)

13.1.3. Stereochemistry of Hydrogenolysis

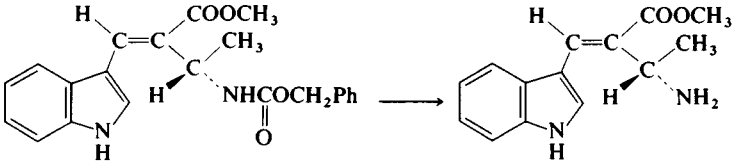
Many workers have examined the stereochemistry of hydrogenolysis of benzyl–oxygen compounds (*18,19,54,54a,55,116–119,157,184*). In general, hydrogenolysis usually proceeds with retention of configuration over nickel and with inversion over palladium or platinum (*36,144*). With nickel, the stereochemistry of hydrogenolysis may be inverted by addition of alkali and influenced by catalyst age and pretreatment (*116,168*). The effects of metals on stereospecificity of hydrogenolysis have been related to the affinity of the metal for oxygen (*119*). Because different metals may attack the benzyl function from opposite sides on the molecule, steric considerations may dictate the choice of catalyst (*21,57*).

13.1.4. Carbobenzyloxy Compounds

The carbobenzyloxy radical (*98*) and its derivatives, such as the *p*-bromo (*30*) or the *p*-nitro (*4,11,22*) are widely used as protecting groups in organic synthesis (*61,174*). An advantage is that they can usually be removed easily in the presence of other sensitive functions, including nitro (*6*) and benzyl (*101*) if steric requirements are not severe (*68*). Palladium makes the best catalyst for this hydrogenolysis and is used by most investigators. An unusual type of catalyst, a palladium–poly(ethylenimine) "ghost" catalyst is said to be very effective in peptide synthesis by hydrogenolysis of carbobenzyloxy groups. The matrix is prepared by adsorbing the polymer on inorganic beads, cross-linking the polymer, and leaching out the inorganic material to leave a macroporous spheroid with high surface area and high functional-group density (*34*).

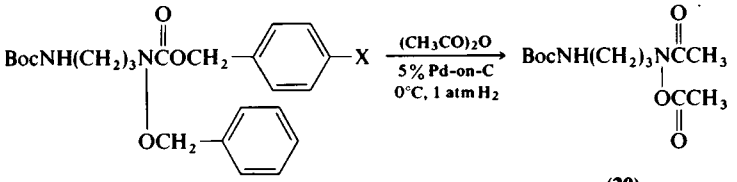
Hydrogenolysis of the carbobenzyloxy (cbz) function in **17** proceeded smoothly to give **18** in 95% yield. Hydrogen gas was bubbled through a

solution of 3.0 g of **17** in 40 ml of CH_3OH containing 1.0 ml of conc HCl and 0.5 g of 10% Pd-on-C at 20°C for 1.5 h with vigorous stirring. Hydrogenolysis without double-bond saturation was attributed to strong resonance interaction between the electron-releasing indole ring and the double bond (*121*).



(17) **(18)**

By careful hydrogenolysis of **19**, the cbz function can be removed selectively in the presence of another benzyl function; under the same conditions both functions are removed with longer reaction times (*101*). Surprisingly, the same sequence with the more liable *p*-nitrobenzyl carbamate **21** was less selective.

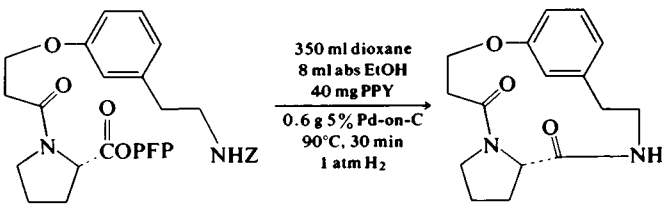


(19) X = H
(21) X = NO_2

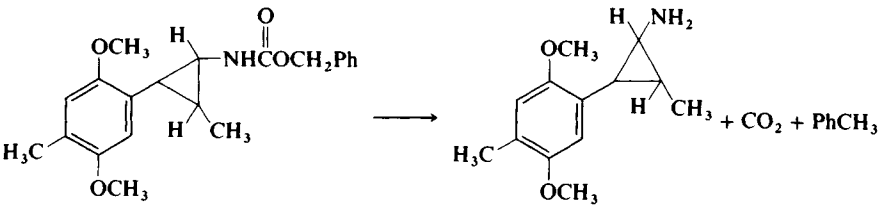
Boc = *t*-butoxycarbonyl

(20)

A key step in the synthesis of 13-membered meta ansa and 14-membered para ansa peptide alkaloids involves catalytic hydrogenolysis of carbobenzyloxypeptide pentafluorophenyl esters. The most suitable solvent is dioxane with addition of a catalytic amount of pyrrolidinopyridine and 2% ethanol. Temperature should not exceed 90°C. The authors believe that after deblocking, the amino function remains on the surface until ring formation with the activated carboxylic function is accomplished (*151*).



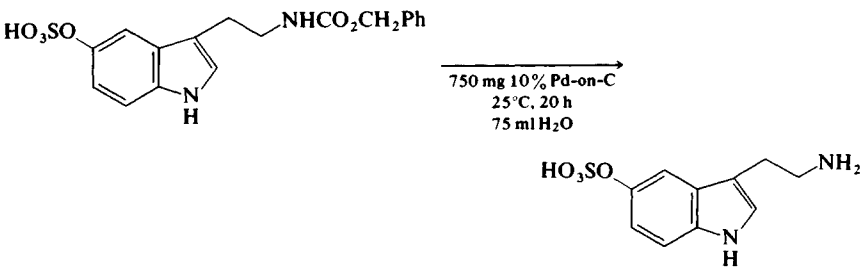
Selectivity is influenced by temperature. Hydrogenolysis of **22** to **23** was carried out at 5°C to prevent opening of the cyclopropane ring (*82*).



(22) (23)

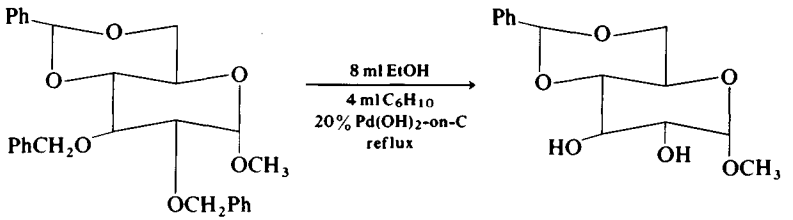
Catalytic hydrogenolysis of carbobenzyloxy compounds has been widely used in the synthesis of peptides (*10*), including those held on solid phase supports (*34,114*). In the latter case, the palladium catalyst is incorporated in the resin (*83,148*). Hydrogenolysis in peptides containing sulfur, as those with cysteine or methionine, is apt to proceed very slowly because of the poisoning action of the sulfur. This general difficulty has been circumvented by using palladium black catalysts and dry, refluxing liquid ammonia as a solvent (*96,112*). Another technique utilizes palladium catalysts in dry methanol containing boron trifluoride. Acidity per se is not the reason for success here; reduction in methanol containing *p*-toluenesulfonic acid or trifluoroacetic acid failed entirely (*180*).

Oxidized sulfur is not a catalyst poison (*20*).



Anwer and Spatola (*7b*) developed a convenient hydrogen-transfer method for removal of hydrogenolyzable protecting groups under ambient conditions, using ammonium formate as a source of hydrogen. A variety of benzyl protecting groups are easily removed. A solution of the protected peptide in methanol or dimethylformamide is mixed with 10% Pd-on-carbon (10–50% of the weight of peptide) and 2–4 equiv of ammonium formate at ambient conditions. The product is obtained rapidly in excellent yield. The technique is applicable also to deprotection of peptides on solid resins (*7,7c*) and provides

an alternative to hydrogen gas (*148*). Other hydrogen-transfer agents that have been used for deprotection are cyclohexene (*81a,127*) hydrazine (*7d*), cyclohexadiene (*49c*), and formic acid (*37,49a,161a,171a*). Isopropanol as a hydrogen donor has been found to be more selective than formic acid in an *O*-benzyl hydrogenolysis. Palladium-on-alumina was more effective than palladium-on-carbon in stepwise debenzylation (*142*). Selective reductions have been achieved with cyclohexene donor where normal hydrogenation procedures or formic acid donor were nonselective (*69*).



13.2. Benzyl Groups Attached to Nitrogen

The benzyl–nitrogen bond undergoes hydrogenolysis with more difficulty than does the benzyl–oxygen bond. Nonetheless, benzyl–nitrogen bond hydrogenolysis is a useful reaction, and a wide variety of benzylamines have been reduced under mild conditions without major side reaction (*72*). The facile cleavage of benzyl–nitrogen bonds has been used for preparation of optically active amino acids through induced asymmetry (*70,71,73*). Alcohols or acetic acid, at times with added mineral acid, are common solvents for debenzylation (*78*). Hydrogenolysis of *N*-benzyl compounds can be accomplished also by hydrogen transfer, a method that has succeeded where normal hydrogenation failed (*115*).

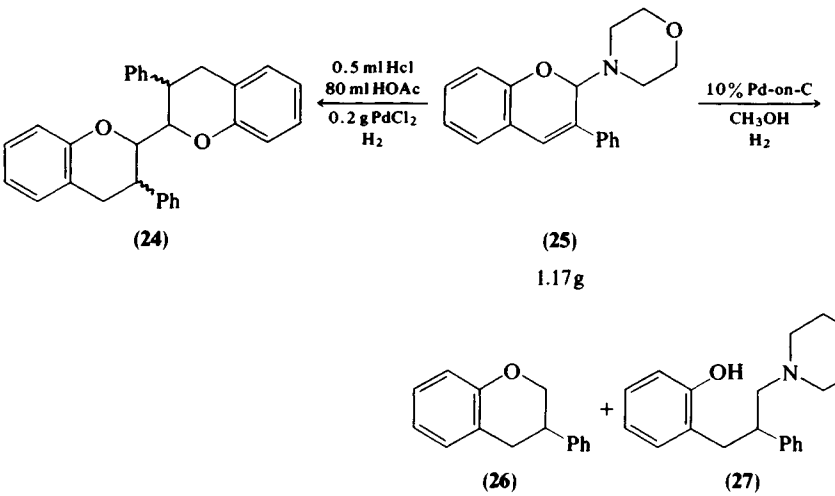
13.2.1. Catalysts

As with benzyl–oxygen compounds, benzyl–nitrogen compounds have been reduced by a number of catalysts, but palladium is by far preferred. Platinum might be the catalyst of choice in hydrogenolysis of benzyl compounds where dehydrohalogenation is to be avoided (*1a,124*). With platinum, the danger of ring reduction is present (*95*). Good results have been

obtained with the Pearlman (*136*) catalyst, 20% palladium hydroxide-on-carbon (manufactured by Engelhard Ind., Newark, New Jersey) (*61b*), even where other palladium catalysts have failed (*5,40,75*).

13.2.2. Effect of Structure

In general, the ease of hydrogenolysis of benzylamines under ambient conditions increases in the series primary < secondary < tertiary < quaternary ammonium salts (*43a*); under vigorous conditions, the order may change (*118*), suggesting a change in mechanism as conditions change (*121a*). Dibenzylamines are usually reduced over palladium stepwise, removal of the first being more rapid than removal of the second (*49b*). In competition, benzyl–oxygen bonds are usually broken in preference to benzyl–nitrogen bonds (*77b*) but this order can be reversed by quaternization. Hydrogenation of 2-morpholinoisoflav-3-ene (**25**) over 10% palladium-on-carbon gave only hydrogenolysis products, mainly isoflavan (**26**) accompanied by **27**. Hydrogenation of **25** in acetic acid containing hydrogen chloride over unsupported palladium followed an unusual course to give mostly a mixture of stereoisomers of structure **24** (*47*).



(24) (25) 1.17g (26) (27)

13.2.3. Stereochemistry

Benzylamines tend to undergo hydrogenolysis with inversion over both Raney nickel and palladium, unlike benzyl–oxygen compounds (*121a,167a*).

The anion associated with quarternary ammonium compounds can influence markedly the stereochemical outcome of hydrogenolysis (*43b,167a*).

13.2.4. Reverse Selectivity

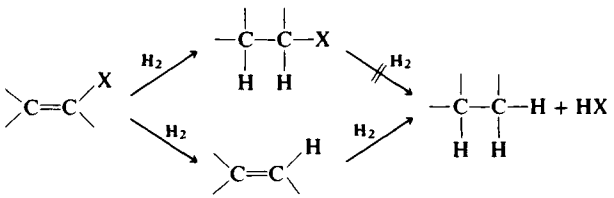
It is true generally that O-debenzylation take place with greater ease than does removal of *N*-benzyl, but this order can be reversed if both functions are present (*43*).

$$PhCH_2O(CH_2)_8\underset{\displaystyle CH_2Ph}{\overset{\displaystyle |}{N}}C_2H_5 \xrightarrow[95\%\ EtOH,\ 45\ psig,\ 25^\circ C]{Pd\text{-}on\text{-}C} PhCH_2O(CH_2)_8NHC_2H_5 \quad (100\%)$$

Inhibition of *O*-benzyl hydrogenolysis was shown to be due to the presence of an amine, a finding with synthetic utility.

13.3. Vinyl Functions

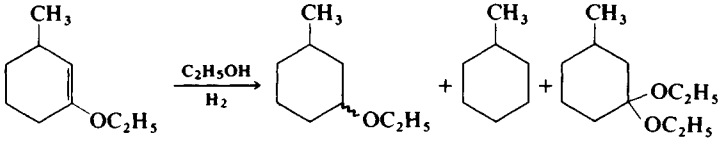
The composition of the products derived from hydrogenation of vinyl functions is determined by the relative rates of two competing reactions.



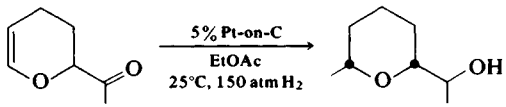
If saturation occurs first, the product will be relatively stable toward further reduction; but if hydrogenolysis occurs first, the resulting olefin is readily reduced. This ratio depends greatly on substrate structure, the catalyst, and environment. Hydrogenolysis is best achieved over platinum, whereas palladium (*77a,82a,122b,162a*), rhodium (*109a*), or ruthenium (*10a,109a*) tend to favor olefin saturation.

A quantitative comparison of metals in the hydrogenation of vinyl ethers has been made. The extent of hydrogenolysis in hydrogenation of 1-ethoxy-3-methylcyclohexene decreased in the order Pt $\gg$ Os > Rh $\sim$ Ir > Pd > Ru (*124e*); in the case of ethyl 4-methyl-1-cyclohexenyl ether, the order was Pt $\gg$ Ir > Rh > Os $\gg$ Ru $\sim$ Pd (*124d*). In ethanol, ketal formation is a

competing reaction that varies greatly with the catalyst. In the reduction of 1-ethoxy-3-methylcyclohexene, the ratio of ketal formation to hydrogenation–hydrogenolysis was Pd (4.5), Rh (3.0), Pt (1.2), Os (0.70), Ir (0.5), Ru (0). The complex relation among solvent, structure, catalyst, and stereochemistry is discussed in these papers. Suffice it to say, a great deal of contol can be exercised by choice of catalyst.

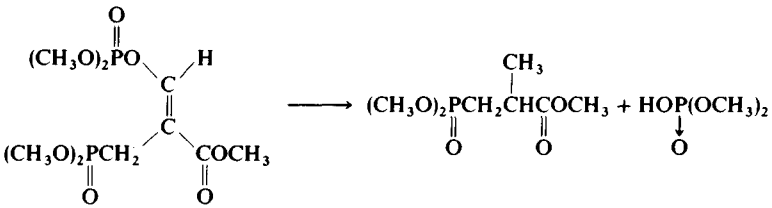


Extensive hydrogenolysis of vinyl ethers does not occur always over platinum. Reduction of **28** proceeded smoothly to **29** (*109*). It is likely that the high pressure and low temperature used in this experiment helped to minimize hydrogenolysis. For effective use of subambient (−30°C) temperatures in stopping hydrogenolysis of vinyl functions, see (*10a*).



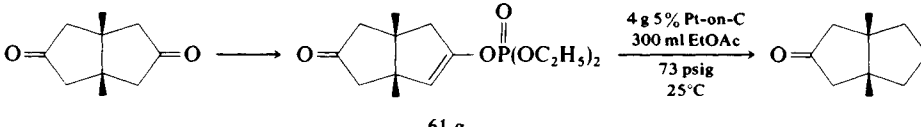
(28) **(29)**

Sometimes the structure is such that the reaction is forced into a single path regardless of catalyst. Hydrogenation of the (*Z*)-enol phosphate **30** over PtO_2, 5% Pd-on-C, or 5% Rh-on-C in EtOAc at 3 atm gave a 95% yield of **31**, obtained by hydrogenolysis followed by hydrogenation (*46a*).



(30) **(31)**

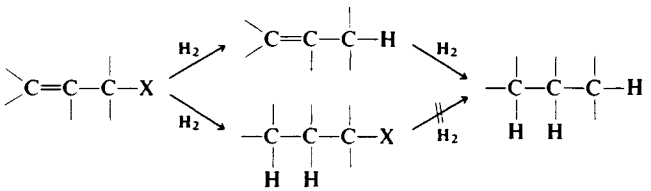
A method for conversion of one of two keto functions to the methylene involves hydrogenolysis of an enol phosphate.



61 g

13.4. Allylic Functions

As with vinyl compounds, the outcome of an allylic hydrogenation is the resultant of two competing reactions.



The rate ratio of hydrogenation to hydrogenolysis varies with the catalyst, substrate structure, and environment in a partially predictable way.

13.4.1. Steric Factors

Steric factors operate by impeding access of one or the other function to the catalyst surface. Allylic compounds substituted by bulky substituents at the olefin or tri- and tetrasubstituted olefins would be expected to, and do, undergo extensive hydrogenolysis (*1,17a,61b,164a*), inasmuch as the olefin is relatively inaccessible to the catalyst. The converse is not true, however; an unhindered approach of the olefin to the catalyst does not assure the absence of extensive hydrogenolysis (*112a,112b,124f*). The extent of hydrogenolysis can also be influenced by structural changes remote from the point of unsaturation (*52a*). Substituents altering access of the catalyst to the oxygen function could be expected to exert a variable influence, depending on whether the catalyst used typically effects hydrogenolysis with inversion or retention (*117*). All in all, steric effects are important but elusive; small structural changes can exert large influences on the composition of the products.

13.4.2. Catalysts and Environment

Comparisons of more than two metals are few, but it appears that hydrogenolysis of allylic functions should increase with metal in the order Ru ~ Rh ≪ Pt < Pd. Trace quantitives of acid or base may drastically alter catalyst performance, with base impeding, and acid accelerating hydrogenolysis (*8a,44,44a,101a,147b,163*). Homogeneous catalysts such as $(Ph_3P)_3RhCl$, have given 95% yield of the saturated product in compounds that underwent 100% hydrogenolysis over palladium-on-carbon (*175a*).

Solvents may exert a marked influence on the products of reduction. The ratio of hydrogenolysis to hydrogenation is expected to increase with increasing polarity and increasing acidity (*31a,124b,124c,159a,168a*). Hydrogenolysis of an allylic carbon–oxygen bond over 10% Pd-on-C during reduction of a 2′,3′-unsaturated *C*-nucleoside was prevented by using THF instead of methanol as solvent (*66*).

13.4.3. Double-Bond Migration

Homoallylic systems may isomerize under hydrogenation conditions to allylic systems, causing hydrogenolysis to occur when it would not have been expected (*39b,45a–45c*). In these cases, if hydrogenolysis is unwanted, it is best to avoid those catalysts and conditions that favor isomerization. Double-bond migration to an allylic position may occur even if the double bond is required to leave a tetrasubstituted position (*26a*).

Isomerization of the double bond in allylic alcohols may result in aldehydes or ketones (*107a*). The reaction can have synthetic value (*8b,73c*). If isomerization is desired, palladium is probably the preferred catalyst, operated best under hydrogen-poor conditions (*147a*). Allylic ethers can be converted to alcohols by isomerization with $(Ph_3P)_3RhCl$ at pH 2 to the vinyl ether, which undergoes hydrolysis (*36a*).

13.5. Hydrogenolysis of the Nitrogen–Nitrogen Bond

Hydrazines (*39,46*) and materials such as azines (*33*) hydrazones, hydrazides, and azo (*17,120,122,152,165,170*) and azoxy compounds that form hydrazines on reduction undergo hydrogenolysis of the nitrogen–nitrogen bond. Usually the rate of reduction of each of these hydrazine precursors is sufficiently greater than the rate of hydrogenolysis so that the first step provides a good synthesis of the hydrazine. Azines and azides are cleaved to amines, providing a good route to various amino compounds.

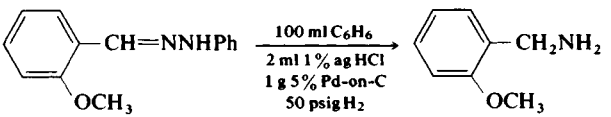
13.5.1. Hydrazones and Hydrazides

Hydrazones can be reduced to the hydrazine, and, if continued, hydrogenolysis of the nitrogen–nitrogen bond ensues. Raney nickel (*14,15,31,133,134, 178,185*), platinum (*42,52,139,155,167*), and rhodium (*130*) have each been

used successfully in the hydrogenolysis of hydrazones, usually in acidic solvent. The reaction is of considerable use in the preparation of amino sugars from osazones and phenylhydrazones (*67*).

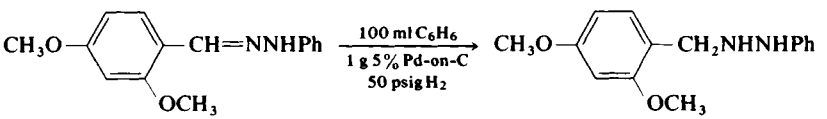
Hydrazines vary in their ease of hydrogenolysis, and it may be difficult to arrest the reduction of a hydrazone at the hydrazine stage if the hydrazine is reduced easily (*15*). Usually, however, there is sufficient difference in the rates of the two steps so that hydrazines can be isolated in good yield (*74*). Hydrogenolysis of optically active hydrazones can be used as a means of preparing optically active amines (*91*). Hydrazones of aromatic carbonyls can be cleaved at the benzyl–nitrogen bond, using palladium; the reaction is useful when carbonyl reagents have been used for purification (*25*).

Reductive cleavage of phenylhydrazones of carbonyl compounds provides a route to amines. The reduction is carried out conveniently in ethanol containing ammonia over palladium-on-carbon. Ammonia is used to minimize formation of secondary amines, derived by addition of the initially formed amine to the starting material (*160*). Alternatively, a two-phase system of benzene, cyclohexane, toluene, or dioxane and aqueous hydrochloric acid can be used.



5g

Without acid present, the major product is a substituted hydrazine.



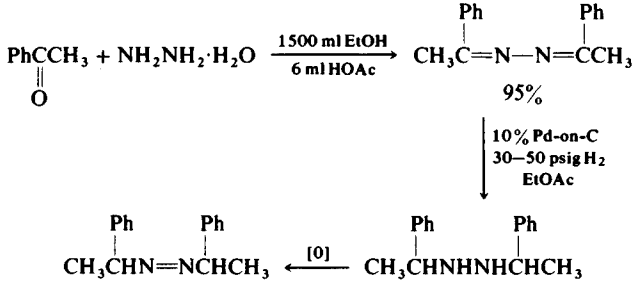
5g

13.5.2. Azines

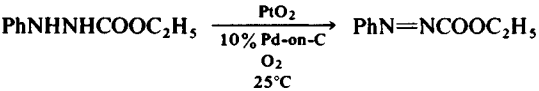
Azines can be reduced catalytically to the disubstituted hydrazines (*24,51*) and then to the amine if the reduction is continued (*108*). The hydrogenolysis chemistry is thus that of hydrazines. The hydrazine can be formed *in situ* by hydrogenation of a mixture of hydrazine and 2 mol of carbonyl compound (*32,103*).

A general method for the preparation of azo compounds is reduction of azines to the hydrazine, followed by oxidation (*12,33,128,132*). Platinum

catalysts in acidic media are usually used for the reduction. Palladium has also been used effectively (*129*). Daub and Cannizzo (*45*) applied the sequence to the synthesis of *meso*-azobis-(α-phenylethane).



In the hydrogenation, 200 g of acetophenone azine, 1000 ml of EtOAc and 5 g of 10% Pd-on-C was shaken at 30–50 psig for 10 h. Hydrogen absorption had ceased. About 7.6 g of phenylethylamine, formed by cleavage of the N—N bond, was obtained as a by-product. Oxidation of hydrazines can be done catalytically. Ethyl 2-arylhydrazine carboxylates were oxidized easily by bubbling air at 25°C through a toluene or dioxane solution in the presence of Pd or Pt (*56*).

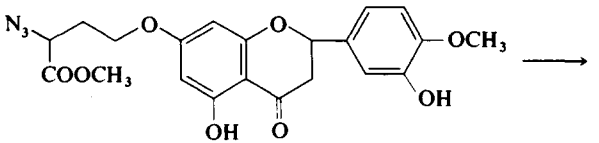


13.5.3. Azides

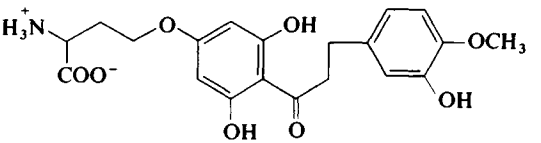
Hydrogenolysis of azides provides a convenient way of introducing an amino nitrogen (*13,77,81,93,104,135,164*). Azides are stable toward a variety of reagents and hydrolytic conditions yet can be easily reduced to an amine, often selectively in the presence of other easily reduced functions (*5,97,135, 175*). Azido compounds are formed with inversion by nucleophilic displacement with an inorganic azide and hydrogenated with retention of configuration (*153*). The azido function has served well as an incipient amine in the synthesis of a number of nucleotides (*60*) and amino sugars (*29,59,76,97,172*).

Palladium, platinum, and Raney nickel (*7,126*) all have been used successfully under mild conditions for hydrogenation of the azido function. In especially sensitive molecules, subambient temperature may prove advantageous. Reduction of methyl 3′,5-dihydroxy-4′-methoxy-7-(3-azido-3-carboxypropoxy)flavanone (**32**) in aqueous alkali proved capricious. The major product (**33**) was contaminated by several other products when reagents were mixed and hydrogenated at room temperature or above, but by the

following procedure nearly quantitative yields of **33**, a potent sweetener, could be obtained. A sample of 10 g of **32** was dissolved, by additions in small portions with stirring under an argon atmosphere, to 112 ml of ice-cold 10% KOH in a Parr hydrogenation bottle. One gram of 5% Pd-on-C was added and the mixture was shaken at 35 psig for 6 h. The isolated yield of **33** was 95% (*49*).



(32)



(33)

There is no pressure drop in the hydrogenation of azides, so reaction completion can not be followed by this means. If a drop does occur, some other function is being reduced as well.

13.6. Hydrogenolysis of the Nitrogen–Oxygen Bond

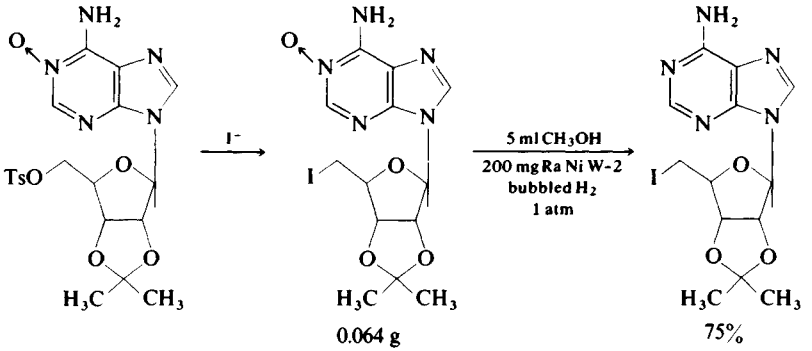
Catalytic cleavage of the nitrogen–oxygen bond occurs very frequently as in reduction of nitro compounds, oximes, and various heterocyclics; these reactions are discussed in separate chapters. Considered here are *N*-oxides, hydroxylamines, and *N*- and *C*-nitroso compounds.

13.6.1. Amine Oxides

Both amine oxides related to pyridines and aliphatic amine oxides (*125*) are easily reduced, the former the more so. Pyridine *N*-oxide has been reduced over palladium, platinum, rhodium, and ruthenium. The most active was rhodium, but it was nonselective, reducing the ring as well. Palladium is usually the preferred catalyst for this type of reduction and is used by most workers (*16,23,84,158*); platinum is also effective (*100,166,169*). Katritzky and Monro (*84*) examined carefully the selectivity of reduction over palladium of a

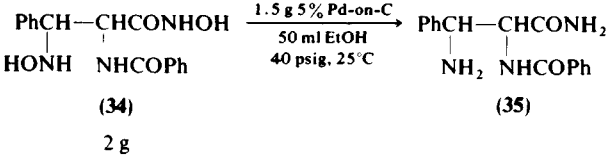
variety of substituted pyridine oxides. Selectivity depends on both the substituent and position.

Nucleoside *N'*-oxides have proved useful in preventing intramolecular cyclizations during manipulation of the sugar moiety. A key step is the reductive removal of the oxide when needed. In the presence of Raney nickel, the oxide can be reduced selectively even when such easily reduced substituents as iodo are present. Azides, however, are reduced concomitantly with the oxide (*105*).

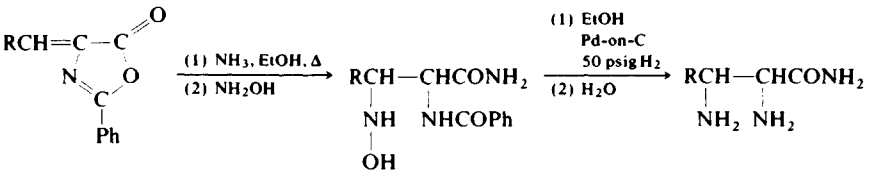


13.6.2. Hydroxylamines

Hydroxylamines are reduced readily to the amine over palladium. The hydroxylaminohydroxamic acid **34** gave **35** in 95% yield under mild conditions (*140*).



A convenient synthesis of α,β-diamino acids from azlactones involves catalytic hydrogenolysis of a hydroxylamino function over palladium-on-carbon (*141*).



13.6.3. *N*-Nitrosoamines

N-Nitrosoamines are reduced easily to the hydrazine and, if continued, to the amine (*62*). Early workers ruled out cleavage of dimethylhydrazine as the source of dimethylamine in hydrogenation of *N*-nitrosodimethylamine since little ammonia was found; the tetramethyltetrazene was implicated in the hydrogenolysis (*131*). Palladium-on-carbon under mild conditions is used for industrial production of dialkyl hydrazines from *N*-nitrosoamines.

Hydrogenolysis can be decreased, if necessary, by the addition of any of a variety of salts that increase the ionic strength of the medium (*162*). Iron salts have been used specifically for this purpose (*102,173*). Yields may depend markedly on the conditions of the reaction (*92*).

13.6.4. *C*-Nitroso Compounds

C-Nitroso compounds with an α-hydrogen atom rearrange readily to the corresponding oxime (*171*) and perhaps to the unsaturated hydroxylamine (*145*). Reduction of these is discussed in the chapter on oximes.

Aromatic nitroso compounds usually are considered to be intermediates in the hydrogenation of a nitroaromatic compound to the aromatic hydroxylamine or amine. However, nitroso compounds do not accumulate in these reductions, suggesting that they are reduced more easily than are nitro compounds. Catalysts effective for the nitro group should also be effective for nitroso.

Formation of azo-type products might be troublesome. These by-products, arising from reduction of aromatic nitro compounds, usually are assumed to be derived from the coupling of intermediate nitroso and hydroxylamine compounds. The coupling problem is accentuated in reduction of nitroso compounds because of much higher concentrations. It can be alleviated by dropwise addition of the substrate to the hydrogenation and use of acidic media.

13.7. Hydrogenolysis of the Carbon–Carbon Bond

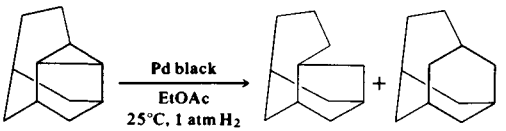
Carbon–carbon bonds are not easily cleaved under mild conditions unless weakened by strain (*3,86,182*) or activation. The most common examples of carbon–carbon bond cleavage occur in cyclopropanes.

13.7.1. Cyclopropanes

Cyclopropanes are now readily available and have become useful, through hydrogenolysis, for synthesis of compounds containing quaternary carbons, *gem*-dialkyl, *t*-butyl, and angular-methyl substituents (*179*), compounds often available only with difficulty otherwise (*27,53,58,150,156*). Cyclopropanes can be formed in good yields by hydrogenation of cyclopropenes (*26*).

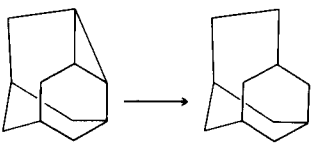
An a priori determination of the direction of ring opening is not always easy, for it is difficult to decide which of several controlling factors is operative. Various generalities concerning the direction of opening have been suggested. Cyclopropanes carrying only phenyl substituents are cleaved exclusively at the bonds adjacent to the phenyl substituent (*87*), whereas alkyl substituents favor cleavage at the bond opposite the substituent (*122a*). Electron-attracting substituents are often cleaved at the bond adjacent to the substituent (*63,79,94,146,154*), but there are exceptions (*113,176*).

More highly substituted nonfunctional cyclopropanes open variously at the carbon with the most hydrogens (*73b,108a*), least hindrance (*39a,147c*), or greatest strain (*51a,122a,156*). Additional strain allows facile ring opening. Hydrogenolysis of the cyclopropane ring in the strained compound **36**, occurred at ambient conditions to give seven parts of 4-homoprotoadamantane (**37**) and one part of **38** (*85*).



(36) (37) (38)

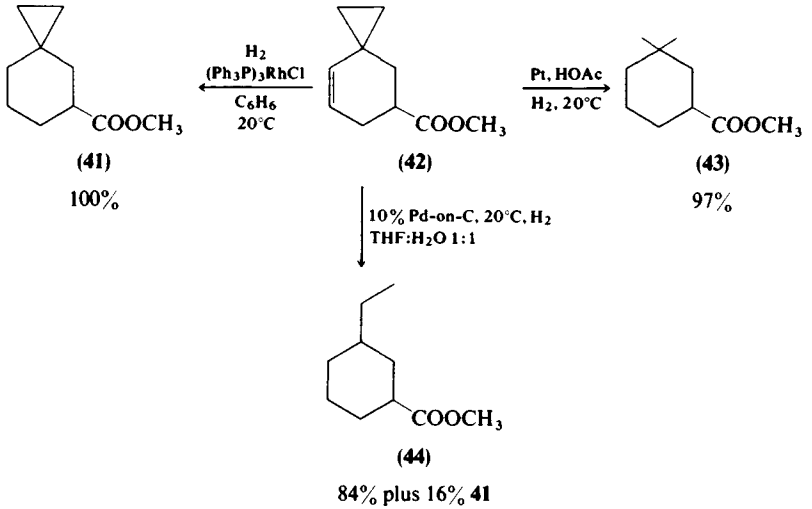
In contrast, hydrogenation of **39** gives only **40**.



(39) (40)

The catalyst exerts some influence on the bonds broken in hydrogenolysis of saturated cyclopropanes (*118*), but in vinyl and alkylidene cyclopropanes the effect is pronounced. Platinum or palladium are used frequently. In one case, Nishimura's (*124a*) catalyst, rhodium–platinum oxide (7:3), worked well where platinum oxide failed (*28*). An impressive example of the marked influence of catalyst is the hydrogenation of the spirooctane **42**, which,

depending on catalyst and solvent, gives **41**, **43**, or **44** in excellent yields (*186*).

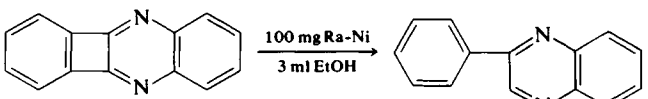


The above results have a precedent. Homogeneous catalysis usually gives hydrogenation and not hydrogenolysis, and ethylcyclohexane is formed over palladium in similar spiro systems in amounts that depend on the solvent (*179a*). Formation of **43** also might be expected since spiro[2.5]octane itself gives 1,1-dimethylcyclohexane (*159b*). Alkylated vinylpropanes usually give extensive hydrogenolysis over palladium (*72a,98a,174a*), whereas platinum or rhodium tend to give hydrogenation initially (*34a,113*).

13.7.2. Cyclobutanes

Cyclobutanes are cleaved less readily than are cyclopropanes, but, nonetheless, fission occurs without difficulty if the ring has additional strain (*113,174b,176*), adjacent unsaturation (*72b,153a*), or aromatic substituents (*26c,82b*).

Hydrogenation of 5,10-diazabenzo[*b*]biphenylene with Raney nickel in hot ethanol gave 2-phenylquinoxaline in 78% yield (*9*). Similar fission of the four-membered ring occurs with biphenylene itself and with substituted biphenylenes (*8*).



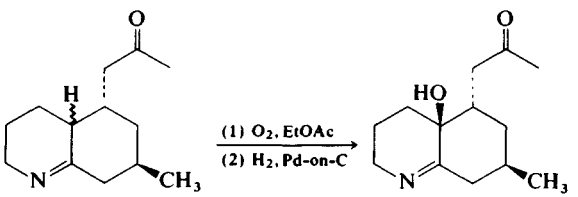
13.7.3 Aromatization

Hydrogenolysis of the carbon–carbon bond occurs readily when one fragment is a good leaving group and, as a result of its loss, the other fragment becomes aromatic (*7e*). Extensive hydrogenolysis is apt to occur when an allyl or, more especially, a benzyl group is attached to a quaternary carbon in a conjugated cyclohexadienone. Polar and hydrogen-bonding solvents favor hydrogenolysis (*7a,26b,115a*).

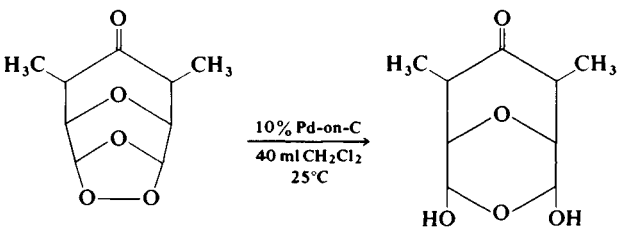
13.8. Hydrogenolysis of the Oxygen–Oxygen Bond

The oxygen–oxygen bonds in peroxides, hydroperoxides, peroxy acids, and ozonides are very easily cleaved by catalytic hydrogenation. In synthetic work, noble-metal catalysts are often used without hydrogen to destroy excess hydrogen peroxide. Hydrogenolysis of the oxygen–oxygen bond is most often done with palladium or platinum catalysts (*35,88,107,110,147,165,177,181*). If the substrate also contains a double bond that is to be preserved, Lindlar catalysts are useful (*2,99*).

Heathcock and Kleinman (*73a*) made interesting use of the hydrogenation of a hydroperoxide as a way of introducing an angular hydroxyl group in an octahydroquinoline during total synthesis of (±)-lycodoline. The diastereomer having the angular oxygen and the neighboring acetonyl trans predominates by 10:1.



The ozonide **45** was reduced easily to diol **46** over 10% Pd-on-C (*41*).



(45) (46)

References

1. R. Adams and M. Gianturco, *J. Am. Chem. Soc.* **78,** 1922 (1956).
1a. P. Aeberli, G. Cooke, W. J. Houlihan, and W. G. Salmond, *J. Org. Chem.* **40,** 382 (1975).
2. E. J. Agnello, R. Pinson, Jr., and G. D. Laubach, *J. Am. Chem. Soc.* **78,** 4756 (1956).
3. I. A. Akhtar, J. J. McCullough, S. Vaitekunas, R. Faggiani, and C. J. Lock, *Can. J. Chem.* **60,** 1657 (1982).
4. P. F. Alewood, J. W. Perich, and R. B. Johns, *Synth. Commun.* **12,** 821 (1982).
5. A. G. Anderson Jr., and R. Lok, *J. Org. Chem.* **37,** 3983 (1972).
6. G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.* **82,** 3359 (1960).
7. R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Org. Chem.* **37,** 1266 (1972).
7a. M. Anteunis and M. Verzele, *Bull. Soc. Chem. Belg.* **68,** 476 (1959).
7b. M. K. Anwer and A. F. Spatola, *Synthesis,* 929 (1980).
7c. M. K. Anwer and A. F. Spatola, *Tetrahedron Lett.* **22,** 4369 (1981).
7d. M. K. Anwer, S. A. Khan, and K. M. Sivanandaiah, *Synthesis,* 750 (1978).
7e. R. Baird and S. Winstein, *J. Am. Chem. Soc.* **79,** 4238 (1957).
8. W. Baker, J. W. Barton, and J. F. W. McOmie, *J. Chem. Soc.,* 2666 (1958).
8a. R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.* **65,** 1984 (1943).
8b. M. F. Barnes and J. MacMillan, *J. Chem. Soc. C,* 361 (1967).
9. J. W. Barton, M. C. Goodland, K. J. Gould, J. Hadley, and J. R. W. McOmie, *Tetrahedron* **34,** 495 (1978).
10. M. Bergmann and L. Zervas, *Ber. Dtsch. Chem. Ges.* **65B,** 1192, 1201 (1932).
10a. W. F. Berkowitz, S. C. Choudhry, and J. A. Hrabie, *J. Org. Chem.* **47,** 824 (1982).
11. C. Berse, R. Boucher, and L. Piche, *J. Org. Chem.* **22,** 805 (1957).
12. J. A. Berson, C. J. Olsen, and J. S. Walia, *J. Am. Chem. Soc.* **84,** 3337 (1962).
13. E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem. Int. Ed. Engl.* **3,** 490 (1964).
14. J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Am. Chem. Soc.* **81,** 2805 (1959).
15. J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.* **81,** 2527 (1959).
16. K. Bodendorf and B. Binder, *Arch. Pharm. (Weinham, Ger.)* **287,** 326 (1954).
17. K. Bodendorf and W. Wössner, *Justus Liebigs Ann. Chem.* **623,** 109 (1959).
17a. V. Boekelheide and M. Y. Chang, *J. Org. Chem.* **29,** 1303 (1964).
18. W. A. Bonner and A. A. Zderic, *J. Am. Chem. Soc.* **78,** 3218 (1956).
19. W. A. Bonner, A. A. Zderic, and G. A. Casaletto, *J. Am. Chem. Soc.* **74,** 5086 (1952).
20. J. Borgulya and K. Bernauer, *Synthesis,* 29 (1983).
21. J. H. Brewster and W. E. Braden, Jr., *Chem. Ind. (London),* 1759 (1964).
22. G. Brooks and E. Hunt, *J.C.S. Perkin Trans. 1,* 115 (1983).
23. E. V. Brown, *J. Am. Chem. Soc.* **79,** 3565 (1957).
24. R. T. Burger, R. T. Standridge, and E. J. Ariens, *J. Med. Chem.* **6,** 221 (1963).
25. J. W. Burnham and E. J. Eisenbraun, *J. Org. Chem.* **36,** 737 (1971).
26. D. N. Butler and I. Gupta, *Can. J. Chem.* **60,** 415 (1982).
26a. L. Canonica, A. Corbella, P. Garboldi, G. Jommi, J. Krepinsky, G. Ferrari, and C. Casagrande, *Tetrahedron* **25,** 3895, 3908 (1969).
26b. J. F. Carson, *J. Am. Chem. Soc.* **73,** 1850 (1951).
26c. M. P. Cava and R. Pohlke, J. Org. Chem. **28,** 1012 (1963).

27. P. N. Chakrabortty, R. Dasgupta, S. K. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *Tetrahedron* **28,** 4653 (1972).
28. B. D. Challand, H. Hikimo, G. Kornis, G. Lange, and P. de Mayo, *J. Org. Chem.* **34,** 794 (1969).
29. C. D. Chang and J. K. Coward, *J. Med. Chem.* **19,** 684 (1976).
30. D. M. Channing, P. B. Turner, and G. T. Young, *Nature (London)* **167,** 487 (1951).
31. G. F. Chittenden and R. D. Guthrie, *J. Chem. Soc. C,* 1508 (1966).
31a. R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.* **81,** 2521 (1959).
32. S. G. Cohen, S. J. Groszos, and D. B. Sparrow, *J. Am. Chem. Soc.* **43,** 2597 (1921).
33. S. G. Cohen, S. J. Groszos, and D. B. Sparrow, *J. Am. Chem. Soc.* **72,** 3947 (1950).
34. D. R. Coleman and G. P. Royer, *J. Org. Chem.* **45,** 2268 (1980).
34a. W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C,* 41, (1966).
35. A. C. Cope, T. A. Liss, and G. W. Wood, *J. Am. Chem. Soc.* **79,** 6287 (1957).
36. A. C. Cope, M. A. McKervey, N. M. Weinshenker, and R. B. Kinnel, *J. Org. Chem.* **35,** 2918 (1970).
36a. E. J. Corey and J. W. Suggs, *J. Org. Chem.* 38, 3224 (1973).
37. D. H. Craig, D. A. Koehler, and R. G. Hiskey, *J. Org. Chem.* **48,** 3954 (1983).
38. J. C. Craig, A. Dinner, and P. J. Mulligan, *J. Org. Chem.* **39,** 1669 (1974).
39. D. J. Cram and J. S. Bradshaw, *J. Am. Chem. Soc.* **85,** 1108 (1963).
39a. S. J. Cristol and G. O. Mayo, *J. Org. Chem.* 34, 2363 (1969).
39b. L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1622 (1957).
40. N. H. Cromwell and R. M. Rodebaugh, *J. Heterocycl. Chem.* **6,** 435 (1969).
41. W. J. Cummins, M. G. B. Drew, J. Mann, J. Walsh, and E. Brian, *J.C.S. Perkin Trans. 1,* 167 (1983).
42. D. Y. Curtin and T. C. Miller, *J. Org. Chem.* **25,** 885 (1960).
43. B. P. Czech and R. A. Bartsch, *J. Org. Chem.* **49,** 4076 (1984).
43a. H. Dahn, U. Solms, and P. Zoller, *Helv. Chim. Acta* 37, 565 (1954).
43b. H. Dahn, J. A. Garbanino, and C. O. Murchú, *Helv. Chim. Acta* 53, 1370 (1970).
44. S. Danishefsky and D. Dumas, *Chem. Commun.*, 1287 (1968).
44a. M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).
45. G. H. Daub and L. F. Cannizzo, *J. Org. Chem.* **47,** 5034 (1982).
45a. W. G. Dauben and D. P. Hance, *J. Am. Chem. Soc.* 77, 2451 (1955).
45b. W. G. Dauben, W. K. Hayes, J. S. P. Schwarz, and J. W. McFarland, *J. Am. Chem. Soc.* 82, 2232 (1960).
45c. W. G. Dauben, J. S. P. Schwarz, W. H. Hayes, and P. D. Hance, *J. Am. Chem. Soc.* 82, 2239 (1960).
46. G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.* **84,** 1724 (1962).
46a. R. M. Davidson and G. L. Kenyon, J. Org. Chem. **45,** 2698 (1980).
47. K. M. Dean and R. S. Varma, *J.C.S. Perkin Trans. 1,* 1193 (1982).
48. G. E. DuBois, G. A. Crosby, and P. Saffron, *Synth. Commun.* **7,** 49 (1977).
49. G. E. DuBois, G. A. Crosby, G. V. McGarraugh, S. Y.-W. Ng, R. C. Stephenson, and R. E. Wingard, Jr., *J. Org. Chem.* **47,** 1319 (1982).
49a. B. El Amin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.* 44, 3442 (1979).
49b. P. W. Erhardt, *Synth. Commun.* 13, 103 (1983).
49c. A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meinhofer, *J. Org. Chem.* 43, 4194 (1978).
50. T. L. Fields, A. S. Kende, and J. H. Boothe, *J. Am. Chem. Soc.* **83,** 4612 (1961).
51. H. H. Fox and J. T. Gibas, *J. Org. Chem.* **20,** 60 (1955).

51a. P. K. Freeman, T. D. Ziebarth, and V. N. M. Rao, *J. Org. Chem.* 38, 3823 (1973).
52. M. Freifelder, W. B. Martin, G. R. Stone, and E. L. Coffin, *J. Org. Chem.* **26,** 383 (1961).
52a. E. Galantay, A. Szabo, and J. Fried, *J. Org. Chem.* **28,** 98 (1963).
53. E. Galantay, N. Paolella, S. Barcza, and R. V. Coombs, *J. Am. Chem. Soc.* **92,** 5771 (1970).
54. E. W. Garbisch, Jr., *J. Org. Chem.* **27,** 3363 (1962).
54a. E. W. Garbisch, Jr., *Chem. Commun.*, 806 (1967).
55. E. W. Garbisch, Jr., L. Schreader, and J. J. Frankel, *J. Am. Chem. Soc.* **89,** 4233 (1967).
56. G. Gaviraghi, M. Pinza, and G. Pifferi, *Synthesis*, 608 (1981).
57. U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.* **34,** 3739 (1969).
58. U. R. Ghatak, P. C. Chakraborti, B. C. Ranu, and B. Sanyal, *J.C.S. Chem. Commun.*, 548 (1973).
59. R. P. Glinski, M. S. Khan, R. L. Kalamas, C. L. Stevens, and M. B. Sporn, *Chem. Commun.*, 915 (1970).
60. R. P. Glinski, M. S. Khan, and R. L. Kalamas, *J. Org. Chem.* **38,** 4299 (1973).
61. R. A. Gobao, M. L. Bremmer, and S. M. Weinreb, *J. Am. Chem. Soc.* **104,** 7065 (1982).
61a. J. C. Godfrey, D. S. Tarbell, and V. Boekelheide, *J. Am. Chem. Soc.* **77,** 3342 (1955).
61b. E. H. Gold, W. Chang, M. Cohen, T. Baum, S. Ehrreich, G. Johnson, N. Prioli, and E. J. Sybertz, *J. Med. Chem.* **25,** 1363 (1982).
62. A. F. Graefe, *J. Org. Chem.* **23,** 1230 (1958).
63. A. P. Gray, H. Kraus, D. E. Heitmeier, and R. H. Shiley, *J. Org. Chem.* **33,** 3007 (1968).
64. T. W. Greenlee and W. A. Bonner, *J. Am. Chem. Soc.* **81,** 4303 (1959).
65. R. B. Greenwald and C. L. Zirkle, *J. Org. Chem.* **33,** 2118 (1968).
66. U. Hacksell and G. D. Daves, Jr., *J. Org. Chem.* **48,** 4144 (1983).
67. G. S. Hajivarnava, W. G. Overend, and N. R. Williams, *J.C.S. Perkin Trans. 1*, 205 (1982).
68. S. S. Hall, D. Loebenberg, and D. P. Schumacher, *J. Med. Chem.* **26,** 469 (1983).
69. S. Hanessian, T. J. Liak, and B. Vanasse, *Synthesis*, 396 (1981).
70. K. Harada, T. Okawara, and K. Matsumoto, *Bull. Chem. Soc. Jpn.* **46,** 1865 (1973).
71. K. Harada and Y. Kataoka, *Tetrahedron Lett.*, 2130 (1978).
72. W. H. Hartung and R. Simonoff, *Org. React.* **7,** 263 (1953).
72a. H. D. Hartzler, *J. Am. Chem. Soc.* **83,** 4990 (1961).
72b. R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.* **29,** 2510 (1964).
73. T. Hayakawa and K. Shimizu, *Bull. Chem. Soc. Jpn.* **46,** 1886 (1973).
73a. C. H. Heathcock and E. F. Kleinman, *J. Am. Chem. Soc.* **103,** 222 (1981).
73b. J. B. Henderickson and R. K. Boeckman, Jr., *J. Org. Chem.* **36,** 23 (1971).
73c. W. Herz, P. S. Subramanian, and T. A. Geissman, *J. Org. Chem.* **33,** 3743 (1968).
74. M. L. Heyman and J. P. Snyder, *Tetrahedron Lett.*, 2859 (1973).
75. R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.* **83,** 4798 (1961).
76. J. Hobbs, H. Sternbach, and F. Eckstein, *Biochem. Biophys. Res. Commun.* **46,** 1509 (1972).
77. R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.* **87,** 1772 (1965).
77a. H. E. Holmquist, F. D. Marsh, J. C. Sauer, and V. A. Engelhardt, *J. Am. Chem. Soc.* **81,** 3681 (1959).
77b. H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.* **84,** 3139 (1961).
78. B. S. Huegi, A. M. Ebnöther, E. Rissi, F. Gadient, D. Hauser, D. Roemer, R. C. Hill, H. H. Buescher, and T. J. Petcher, *J. Med. Chem.* **26,** 42 (1983).
79. W. J. Irwin and F. J. McQuillin, *Tetrahedron Lett.*, 2195 (1968).
80. Y. Isowa and M. Ohmori, *Bull. Chem. Soc. Jpn.* **47,** 2672 (1974).
81. G. A. Ivanovics, R. J. Rousseau, M. Kawana, P. C. Srivastava, and R. K. Robins, *J. Org. Chem.* **39,** 3651 (1974).

81a. A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976).
82. J. N. Jacobs and D. E. Nichols, *J. Med. Chem.* **25,** 526 (1982).
82a. H. I. Jacobson, M. I. Griffin, S. Preis, and E. V. Jensen, *J. Am. Chem. Soc.* **79,** 2608 (1957).
82b. F. R. Jensen and W. E. Coleman, *J. Am. Chem. Soc.* **80,** 6149 (1958).
83. D. A. Jones, Jr., *Tetrahedron Lett.*, 2853 (1977).
84. A. R. Katritzky and A. M. Monro, *J. Chem. Soc.*, 1263 (1958).
85. T. Katsushima, K. Maki, R. Yamaguchi, and M. Kawanisi, *Bull. Chem. Soc. Jpn.* **53,** 2031 (1980).
86. T. Katsushima, R. Yamaguchi, and M. Kawanisi, *Bull. Chem. Soc. Jpn.* **55,** 3245 (1982), and references therein.
87. B. A. Kazanskii, M. Y. Lukina, and I. L. Safonova, *Dokl. Akad. Nauk SSSR* **130,** 322 (1960).
88. A. S. Kende and J. Y.-C. Chu, *Tetrahedron Lett.*, 4837 (1970).
89. A. M. Khan, F. J. McQuillin, and I. Jardine, *J. Chem. Soc.*, 136 (1967).
90. A. P. G. Kieboom, J. J. deKreuk, and H. van Bekkum, *J. Catal.* **20,** 58 (1971).
91. S. Kiyooka, K. Takeshima, H. Yamamoto, and K. Suzuki, *Bull. Chem. Soc. Jpn.* **49,** 1897 (1976).
92. K. Klayer, E. M. Wilson, and G. K. Helmkamp, *Ind. Eng. Chem.* **52,** 119 (1960).
93. L. Krbechek and H. Takimoto, *J. Org. Chem.* **29,** 1150 (1964).
94. M. E. Kuehne and J. C. King, *J. Org. Chem.* **38,** 304 (1973).
95. R. Kuhn and H. J. Haas, *Ann. Chem.* **611,** 57 (1958).
96. K. Kuromizu and J. Meinhofer, *J. Am. Chem. Soc.* **96,** 4978 (1974).
97. H. Kuzuhara, O. Mori, and S. Emoto, *Tetrahedron Lett.*, 379 (1976).
98. J. M. Lacombe and A. A. Pavia, *J. Org. Chem.* **48,** 2557, 2564 (1983).
98a. S. B. Laing and P. J. Sykes, *J. Chem. Soc. C*, 421 (1968).
99. G. D. Laubach, U.S. Patent No. 2,794,033 (1957).
100. W. M. Lauer and W. S. Dyer, *J. Am. Chem. Soc.* **64,** 1453 (1942).
101. B. H. Lee and M. J. Miller, *J. Org. Chem.* **48,** 24 (1983).
101a. S. D. Levin, R. E. Adams, R. Chen, M. L. Cotter, A. F. Hirsch, V. V. Kane, R. M. Kanojia, C. Shaw, M. P. Wachter, E. Chin, M. Huetteman, P. Ostrowski, J. L. Mateos, L. Noreiga, A. Guzman, A. Mijarez, and L. Tovar, *J. Am. Chem. Soc.* **101,** 3404 (1979).
102. D. A. Lima, U.S. Patent No. 3,154,538 (1964).
103. H. L. Lochte, J. R. Bailey, and W. A. Noyes, *J. Am. Chem. Soc.* **43,** 2597 (1921).
104. D. F. Loncrini and H. M. Walborsky, *J. Med. Chem.* **7,** 369 (1964).
105. M. MacCoss, E. K. Ryu, R. S. White, and R. L. Last, *J. Org. Chem.* **45,** 788 (1980).
106. J. R. D. McCormick and E. R. Jensen, U.S. Patent No. 3,019,260 (1962).
107. A. F. McKay, J.-M. Billy, and E. J. Tarlton, *J. Org. Chem.* **29,** 291 (1964).
107a. J. McQuillin, *Tech. Org. Chem.* **9,** 498 (1963).
108. A. Maihle, *C. R. Acad. Sci.* **170,** 1265 (1920).
108a. Z. Majerski and P. von R. Schleyer, *Tetrahedron Lett.*, 6195 (1968).
109. R. Malherbe, G. Rist, and D. Bellus, *J. Org. Chem.* **48,** 860 (1983).
109a. J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *J. Org. Chem.* **31,** 943 (1966).
110. N. P. Marullo and J. A. Alford, *J. Org. Chem.* **33,** 2368 (1968).
111. P. J. Mauer and M. J. Miller, *J. Am. Chem. Soc.* **104,** 3096 (1982).
112. J. Meinhofer and K. Kuromizu, *Tetrahedron Lett.*, 3259 (1974).
112a. J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.* **82,** 5253 (1960).
112b. J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.* **80,** 6303 (1958).
113. J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.* **85,** 582 (1963).
114. R. B. Merrifield, *J. Am. Chem. Soc.* **85,** 2149 (1963).
115. A. I. Meyers, R. J. Himmelsback, and M. Reuman, *J. Org. Chem.* **48,** 4053 (1983).
115a. B. Miller and L. Lewis, *J. Org. Chem.* **39,** 2605 (1974).

116. S. Mitsui and Y. Nagahisa, *Chem. Ind. (London)*, 1975 (1965).
117. S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 1354 (1963).
118. S. Mitsui, S. Imaizumi, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 233 (1964).
119. S. Mitsui, M. Fujimoto, Y. Naghisa, and T. Sugegawa, *Chem. Ind. (London)*, 241 (1969).
119a. S. Mitsui, Y. Sugi, M. Fujimoto, and K. Yakoo, *Tetrahedron* **30,** 31 (1974).
120. J. A. Moore and F. J. Marascia, *J. Am. Chem. Soc.* **81,** 6049 (1959).
121. T. Moriya, N. Yoneda, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.* **47,** 94 (1982).
121a. C. O. Murchú, *Tetrahedron Lett.*, 3231 (1969).
122. W. Nagai, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.* **38,** 1972 (1973).
122a. J. Newham, *Chem. Rev.* **63,** 123 (1963).
122b. M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.* **67,** 233 (1945).
124. R. Y. Ning, I. Douvan, and L. H. Steinbach, *J. Org. Chem.* **35,** 2243 (1970).
124a. S. Nishimura, *Bull. Chem. Soc. Jpn.* **33,** 566 (1960).
124b. S. Nishimura and K. Mori, *Bull. Chem. Soc. Jpn.* **32,** 102 (1959).
124c. S. Nishimura, S. Onoda, and A. Nakamura, *Bull. Chem. Soc. Jpn.* **33,** 1356 (1960).
124d. S. Nishimura, T. Ichino, A. Akimoto, and K. Tsuneda, *Bull. Chem. Soc. Jpn.* **44,** 166 (1971).
124e. S. Nishimura, K. Kunihiro, and N. Sato, *Bull. Chem. Soc. Jpn.* **51**(11), 3330 (1978).
124f. W. E. Noland, J. H. Cooley, and P. A. McVeigh, *J. Am. Chem. Soc.* **8,** 1209 (1959).
125. E. Ochiai, M. Ishikawa, and M. Katada, *Yakugaku Zasshi* **63,** 307 (1943).
126. S. Ogawa, M. Oya, T. Toyokuni, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.* **56,** 1441 (1983).
127. K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway, and W. L. Kennell, *Can. J. Chem.* **60,** 3005 (1982).
128. C. G. Overberger and H. Gainer, *J. Am. Chem. Soc.* **80,** 4556 (1958).
129. C. G. Overberger and I. Tashlick, *J. Am. Chem. Soc.* **81,** 2805 (1959).
130. C. G. Overberger, L. C. Palmer, B. S. Marks, and J. S. Bradshaw, *J. Am. Chem. Soc.* **77,** 4100 (1955).
131. C. Paal and W.-N. Yao, *Ber. Dtsch. Chem. Ges.* **63B,** 57 (1930).
132. C. A. Panetta and S. C. Bunce, *J. Org. Chem.* **26,** 4859 (1961).
133. C. A. Panetta and A.-U. Rahman, *J. Org. Chem.* **36,** 2250 (1971).
134. R. P. Panzica and L. B. Townsend, *J. Org. Chem.* **36,** 1594 (1971).
135. D. S. Pearce, M. S. Lee, and H. W. Moore, *J. Org. Chem.* **39,** 1362 (1974).
136. W. M. Pearlman, *Tetrahedron Lett.*, 1663 (1967).
137. M. L. M. Pennings and D. N. Reinhoudt, *J. Org. Chem.* **48,** 4043 (1983).
138. N. Pourahmody, E. H. Vickery, and E. J. Eisenbraun, *J. Org. Chem.* **47,** 2590 (1982).
139. N. Rabjohn, R. Havens, and J. Rutter, *J. Heterocycl. Chem.* **2,** 67 (1965).
140. M. A. Rakhshinda and N. H. Khan, *Synth. Commun.* **8,** 497 (1978).
141. M. Rakhshinda and N. H. Khan, *Synth. Commun.* **9,** 351 (1979).
142. V. S. Rao and A. S. Perlin, *Can. J. Chem.* **61,** 652 (1983).
143. O. Ribeiro, S. T. Hadfield, A. F. Clayton, C. W. Vose, and M. M. Coombs, *J.C.S. Perkin Trans. 1*, 87 (1983).
144. R. M. Roberts, K. H. Bantel, and C. E. Low, *J. Org. Chem.* **38,** 1903 (1973).
145. W. E. Rosen and M. J. Green, *J. Org. Chem.* **28,** 2797 (1963).
146. J. A. Roth, *J. Catal.* **26,** 97 (1972).
147. G. A. Russell and F. R. Mayo, U.S. Patent No. 2,794,055 (1957).
147a. P. N. Rylander, "Catalytic Hydrogenation in Organic Syntheses," p. 7. Academic Press, New York, 1979.
147b. P. N. Rylander and N. Himelstein, *Engelhard Ind. Tech. Bull.* **5,** 43 (1964).
147c. R. R. Sauers and A. Shurpik, *J. Org. Chem.* **33,** 799 (1968).
148. J. M. Schlatter and R. H. Mazur, *Tetrahedron Lett.*, 2851 (1977).

150. P. von R. Schleyer and E. Wiskott, *Tetrahedron Lett.*, 2845 (1967).
151. U. Schmidt, A. Lieberknecht, H. Griesser, and J. Talbiersky, *J. Org. Chem.* **47,** 3261 (1982).
152. E. Schmitz and R. Ohme, *Ber. Dtsch. Chem. Ges.* **94B,** 2166 (1961).
153. B. Schönecker and K. Ponsold, *Tetrahedron* **31,** 1113 (1975).
153a. R. C. Schreyer, U.S. Patent 3,092,654 (1963).
154. A. L. Schulz, *J. Org. Chem.* **36,** 383 (1971).
155. W. Schulze and G. Letsch, *J. Prakt. Chem.* **21**(5–6), 272 (1963).
156. M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.* **30,** 2425 (1965).
157. Y. Senda and S. Mitsui, *Nippon Kagaku Zasshi* **83,** 847 (1962).
158. E. Shaw, *J. Am. Chem. Soc.* **71,** 67 (1949).
159. M. J. Shiao, *J. Org. Chem.* **47,** 5189 (1982).
159a. C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957).
159b. R. W. Shortridge, R. A. Craig, K. W. Greenlea, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.* **70,** 946 (1948).
160. A. A. Siddiqui, N. H. Khan, M. Ali, and A. P. Kidwai, *Synth. Commun.* **7,** 71 (1977).
161. A. K. Sinhababu and R. T. Borchardt, *Synth. Commun.* **12,** 983 (1982).
161a. K. M. Sivanandaiah and S. Gurusiddappa, *J. Chem. Res. Synop.*, 108 (1979).
162. G. W. Smith and D. N. Thatcher, *Ind. Eng. Chem. Prod. Res. Dev.* **1,** 117 (1962).
162a. P. Z. Smyrniotis, H. T. Miles, and E. R. Stadman, *J. Am. Chem. Soc.* **80,** 2541 (1958).
163. O. Spitzner, *Tetrahedron Lett.*, 3349 (1978).
164. C. E. Spivak, and F. L. Harris, *J. Am. Chem. Soc.* **94,** 2494 (1972).
164a. R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Med. Chem.* **7,** 117 (1964).
165. C. L. Stevens and R. J. Gasser, *J. Am. Chem. Soc.* **79,** 6057 (1957).
166. T. E. Stevens and J. P. Freeman, *J. Org. Chem.* **29,** 2279 (1964).
167. C. L. Stevens, B. T. Gillis, J. C. French, and T. H. Haskell, *J. Am. Chem. Soc.* **80,** 6088 (1958).
167a. Y. Sugi and S. Mitsui, *Tetrahedron* **29,** 2041 (1973).
168. H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Am. Chem. Soc.* **85,** 2381 (1963).
168a. D. Taub, C. H. Kuo, H. L. Slates, and N. J. Wendler, *Tetrahedron* **19,** 1 (1963).
169. E. C. Taylor and J. S. Driscoll, *J. Org. Chem.* **25,** 1716 (1960).
170. E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.* **80,** 421 (1958).
171. T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," p. 169. Oxford Univ. Press (Clarendon), London, 1945.
171a. F.-S. Tjoeng and G. A. Heavner, *J. Org. Chem.* **48,** 355 (1983).
172. P. F. Torrence, J. A. Waters, and B. Witkop, *J. Am. Chem. Soc.* **94,** 3638 (1972).
173. W. B. Tuemmler and H. J. S. Winkler, U.S. Patent No. 2,979,050 (1961).
174. Y. Ueda, C. E. Damas, and B. Belleau, *Can. J. Chem.* **61,** 1996 (1983).
174a. E. F. Ullman, *J. Am. Chem. Soc.* **81,** 5386 (1959).
174b. A. F. Vellturo and G. W. Griffin, *J. Am. Chem. Soc.* **87,** 3021 (1965).
175. D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.* **37,** 1876 (1972).
175a. S. C. Welch, C. P. Hagen, D. H. White, and W. P. Fleming, *Synth. Commun.* **4**(6), 373 (1974)
176. K. B. Wiberg and R. P. Ciula, *J. Am. Chem. Soc.* **81,** 5261 (1959).
176a. K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.* **76,** 5367 (1954).
177. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73,** 2188 (1951).
178. M. L. Wolfrom, F. Shafizadeh, J. O. Wehrmuller, and R. K. Armstrong, *J. Org. Chem.* **23,** 571 (1958).
179. C. W. Woodworth, V. Buss, and P. von R. Schleyer, *Chem. Commun.*, 569 (1968).
179a. M. T. Wuesthoff and B. Rickborn, *J. Org. Chem.* **33,** 1311 (1968).
180. H. Yajima, K. Kawasaki, Y. Kinomura, T. Oshima, S. Kimoto, and M. Okamato, *Chem. Pharm. Bull.* **16,** 1342 (1968).

181. M. Yamazaki, H. Fujimoto, and T. Kawasaki, *Tetrahedron Lett.*, 1241 (1975).
182. P. Yates, P. H. Helferty, and P. Mahler, *Can. J. Chem.* **61,** 78 (1983).
183. J. A. Zderic, W. A. Bonner, and T. W. Greenlee, *J. Am. Chem. Soc.* **79,** 1696 (1957).
184. J. A. Zderic, M. E. C. Rivera, and D. C. Limon, *J. Am. Chem. Soc.* **82,** 6373 (1960).
185. I. Ziderman and E. Dimont, *J. Org. Chem.* **31,** 223 (1966).
186. F. Zutterman and A. Krief, *J. Org. Chem.* **48,** 1135 (1983).
187. F. Zymalskowski, T. Schuster, and H. Scherer, *Arch. Pharm (Weinheim, Ger.)* **302,** 272 (1969).

Index of Compounds and Methods

A

Acetal formation, 68
Acetophenone, 10, 118
Acetophenone azine, 170
Acetylacetone, 14, 71
Acetylenes, 53–62
Acetylenic aldehydes, 62
Acetylenic amines, 61
Acetylenic carbinols, 59
Acetylenic epoxides, 60
Acetylenic esters, 59
Acetylenic glycols, 59
Acetylenic ketones, 62
Acetylenic nitro compounds, 109–110
N-Acetylindoles, 134
3-Acetylpyridine, 136
Acid, 78–80
Acid chlorides, 154
Acidity, effect of, 10
α-(Acylamino)acrylic acids, 15
Adipic acid, 79
Agitation, effect of, 31
Air-sensitivity, 104
L-Alanyl-L-proline, 85
Alcoholysis, 139
Aldehydes, 66–75
Alkali, 160
Alkoxyanilines, 126
ω-Alkylaminovaleraldehydes, 136
Alkylation, reductive, 11
Alkylidene cyclopropanes, 174
N-Alkylpyridinium salts, 136
Allenes, 37
π-Allyl intermediates, 30
Allylic compounds, 41–44
Allylic functions, 167
Amine oxides, 171–172
α-Amino acids, 89
Amino benzyl alcohols, 69
β-Amino ketones, 69
β-Amino nitriles, 97
Amino sugars, 105
Aminoacetaldehyde dimethylacetal, 83
o-Aminobenzamide, 110
1-Amino-2-cyanonaphthalene, 110
2-Amino-4,5-dimethoxyindanone hydrochloride, 69
3-(1-Aminoethyliden)-5-methyl-2-oxopiperidine, 142
2-Amino-2'-fluorobenzophenone, 151
2-Amino-1-indanol, 100
4-Amino-2-nitro-1-(*N*-piperidyl)benzene, 112
Aminophenols, 140
p-Aminophenol, 107
Ammonium formate, 162
1,4-Androstadiene-3,17-dione, 40
4-Androsten-3,17-dione, 40–41
Anhydrides, 78–80
Anilines, 90, 123–126
o-Anisidine, 106
Aromatic hydroxylamines, 106–107
Aromatization, 6, 36, 71, 89, 176
L-Ascorbic acid, 66
Asperuloside tetraacetate, 42
Asymmetric hydrogenation, 13–14, 74–75
Autodecomposition temperature, 21
Axial alcohols, 73–74

Azaindoles, 111
Azides, 170–172
Azines, 169–170
Azlactones, 172
meso-Azobis-(α-phenylethane), 170

B

(*Z*)-2-Benzamide(acetamido)-3-(2-thienyl)-2-propenoic acid, 48
Benz[*a*]anthracene, 121
Benzene, 119
Benzoic acid, 117
Benzonitriles, 97
Benzyl groups, 157–165
Benzyl hydroxamates, 158
Benzylamines, 97–98
N^4Benzyl-N^1-(*t*-butoxycarbonyl)spermidine, 97
Benzylic oxygenated substituents, 158
4-Benzylpiperidine, 135
4-Benzylpyridine, 135
Biacetyl, 71
Bibenzyls, 153
Bicyclopentadienes, 153
o, o'-Biphenol, 129
Biphenyl, 119, 153
Biphenylene, 175
Bipyridyls, 119, 135
Bis-(4-aminophenyl)-methane, 125
(R)-[*(S)*-1',2-Bis(diphenylphosphino)ferrocenyl]ethyl alcohol, 74
3,6-Bis(morpholinomethyl)catechol, 159
Blocking group, 152
BPPM, 47
Bromo esters, 80
1-β-Bromosantanolide "c," 149
1,4-Butanediol, 79
N-[*N*-(*t*-Butoxycarbonyl)-3-aminopropyl]-*N*-(3-cyanopropyl)benzylamine, 97
4-*t*-Butylcyclohexanol, 74
4-*t*-Butylcyclohexanone, 68
4-*t*-Butylcyclohexene epoxides, 138
1-*t*-Butylnaphthalene, 120
Butyrolactones, 79
γ-Butyrolactones, 43
Butyronitriles, 97

C

CAMP, 119
Carane, 35
Carbobenzyloxy compounds, 160–163
Carbon–carbon bond formation, 61
2-Carene, 35
Carene-3, 35
Carvomenthene, 36
Catalyst(s), 1–7
  activity, effect of, 31
  age, 160
  aging, 34
  choosing, 2–3
  concentration, effect of, 31
  cost, 24
  deactivation, 67, 142
  induction period, 86
  life, 6, 24–25
  loading, 12–13
  poison and inhibitors
    alkali, 118
    ammonia, 125
    ammonium dihydrogen phosphate, 124
    o,o'-azoxyanisole, 106
    o-chloronitrobenzene, 106
    o,o'-dichloroazobenzene, 106
    halide ion, 149
    o,o'-hydrazoanisole, 106
    hydrogen chloride, 106, 149
    o-nitrophenol, 106
    sulfur, 162
    water, 97
  preparation of, 22–23
  prereduction, 6, 32, 67, 86, 133
  pretreatment, 160
  promoters and modifiers, 158–160
    acetic acid, 16, 86
    acidic carbons, 86
    alkali, 73, 138
    amines, 56, 96, 125
    ammonia, 96, 125
    aniline, 56
    benzene, 34
    boron trifluoride, 162
    cadmium, 54
    carbonates, 96, 125
    chlorobenzene, 56

diethylaniline, 56
dimethylsulfoxide, 106
ethanolamine, 108
ethylenediamine, 54, 108
N-ethylmorpholine, 108
ferrous chloride, 67
ferrous sulfate, 40
gold, 55
hydrobromic acid, 135
hydrochloric acid, 86, 158
hydroxides, 56, 96, 125
iron, 68
iron salts, 173
lead, 55
N-methylmorpholine, 108
morpholine, 108
perchloric acid, 158–159
piperazine, 108
piperidine, 56
potassium acetate, 40
potassium hydroxide, 59, 61
pyridine, 56
pyrroline, 86
quinoline 54–57
quinoline-sulfur, 154
ruthenium, 55
silver, 55
sodium bromide, 14, 75
sodium cyanide, 43
sodium hydroxide, 43, 61
sodium nitrite, 42–43
stannous chloride, 67
sulfur compounds, 56
sulfuric acid, 158
tartaric acid, 14, 75
tertiary amines, 86, 159
tin, 55
triethylamine, 35, 54–55
water, 118
zinc, 55
zirconium, 54
purchased, 23
recycle, 24
regeneration, 67, 124
regulated, 154
reuse of, 7, 25, 124
support, choosing, 4
use, economics of, 23–25
2-Chloroaniline, 150
Chloroanilines, 86, 107–109
2-Chlorobenzoxazole, 128
4-Chloro-2,6-di-*t*-butylphenol, 127
α-Chloroethynyl compounds, 55
9-Chloromethyltriptycene, 149
Chloronitroaromatics, 86
5α-Cholestan-3β-ol, 72, 74
5α- and 5β-Cholestan-3-ones, 68, 72–74
Chuangxinmycin, 44
Cinnamaldehyde, 40
Cinnolines, 113
Citronellol, 38
Concentration, effect of, 151
Conditions, choosing of, 5
Coronopilin, 32
Coupling reactions, 153
β-Cyano ethers, 97
2-(β-Cyanoethyl)cyclohexanone, 99
trans-2-[6-Cyanohex-2(*Z*)-enyl]-3-(methoxycarbonyl)cyclopentanone, 58
Cyclobutanes, 175
Cyclohexadiene, 163
1,4-Cyclohexanedione, 71, 128
Cyclohexanone, 126
Cyclohexene, 8, 17, 163
Cyclohexenols, 45
4-Cyclohexylcyclohexanol, 129
4-Cyclohexylcyclohexyl methyl ether, 129
(R)-α-Cyclohexylglycine, 117
p-Cyclohexylphenol, 129
Cyclopropanes, 174
Cyclopropenes, 174
(R)-Cycphos, 15

D

Damsin, 33
"Dead-end" complex, 48
Debenzylation, 58
Decahydroquinoline, 99
cis- and *trans*-Decalin, 38
cis-β-Decalone, 6
cis-2-Decalone, 9
Decarbonylation, 40, 154
Decarboxylation, 137
Dehydrohalogenation, 80, 108, 148–155

Dehydronicotine, 6
6-Demethyl-6-deoxytetracycline, 90
Deoxygenation, 69–70, 137–139
  without ring reduction, 128
2,5-Diacetoxy-2,5-dimethyl-3-hexene, 59
2,5-Diacetoxy-2,5-dimethyl-3-hexyne, 59
Dialkyl hydrazines, 173
3,5-Dialkyl-$\Delta^{3,4}$-dehydroindolizidine alkaloids, 45
2,2'-Diaminobiphenyl, 113
Diaminobiphenyls, 113
Diaminotoluene, 111
5,10-Diazabenzo[*b*]biphenylene, 175
Dibenzylamine, 97, 164
2,6-Di-*t*-butylcyclohexanone, 127
1,4-Di-*t*-butylnaphthalene, 120
3,3-Dicarbethoxy-5,8-dimethoxy-1-tetralone, 69
3,4-Dichloronitrobenzene, 20
3,4-Dichlorophenylhydroxylamine, 21
Dicyclohexyl ether, 130
Dicyclohexylamine, 125
Dielectric constant, 8
Dienes, 36–39
Dienones, 62
1,1-Diesters, 79
Diffusion, resistance, 57
Dihydro-2-benzazepine, 149
Dihydrocoronopilin, 32
13,14-Dihydroeremophilone, 40
Dihydropyrazines, 101
4,5-Dihydropyrene, 121
Dihydroresorcinol, 127
Dihydrothebaine, 43
Dihydrothebainol, 43
Dihydrothebainone, 43
1,8-Dihydroxynaphthalene, 127
3,5-Dihydroxyphenylacetic acid, 127
3,4-Dihydroxyphenylalanine, 47
1,8-Diisopropylnaphthalene, 120
Diketones, 71–72
β-Diketones, 69
1,4-Diketones, 69
1,5-Diketones, 69
4,5-Dimethoxy-2-aminoindan, 100
4,5-Dimethoxy-2-oximino-1-indanone, 100
Dimethylbicyclo[2.2.1]heptane-2,5-diene-2,3-dicarboxylate, 17
2,5-Dimethyl-2-acetoxy-4-hexene, 59
Dimethylamine, 173
1,1-Dimethylcyclohexane, 175
5,5-Dimethyl-1,3-cyclohexanedione, 72
3,3-Dimethylcyclohexanone, 72
2,4-Dimethylcyclohexanone, 127
Dimethylhydrazine, 173
3,5-Dimethylisoxazole, 140
3,5-Dimethylisoxazolo[5,4-*b*]pyridine, 142
3,5-Dimethylmorpholine, 108
2,4-Dimethylphenol, 127
2,4-Dinitroalkylbenzenes, 112
2,4-Dinitroaniline, 111
2,4-Dinitroanisole, 112
2,2'-Dinitrobiphenyls, 113
2,4-Dinitrophenol, 112
2,4-Dinitro-1-(*N*-piperidyl)benzene, 112
2-β-Dinitrostyrenes, 109, 113
DIOP, 47
Dioxane, 12
1,6-Dioxaspiro[4,5]decanes, 60
1,6-Dioxaspiro[4,4]nonanes, 60
DIPAMP, 47
Diphenyl ether, 130
erythro-2,3-Diphenylbutan-2-ol, 138
cis-2,3-Diphenylbut-2-ene epoxide, 138
Diphenylethylene, 54
Diphenylethyne, 54
Diphenylmethane, 119
Dipropylamine, 97
Disproportionation, 13, 36
Double-bond migration, 29–37, 118, 168
Dropwise addition, 95, 173
  portion-wise addition, 139

E

Edible hydrogenated fats, 34
Electronic factors, 107
Electrophilicity, 107
Enalapril maleate, 85
Enol phosphate, 166
Enynones, 62
Epilaurallene, 151
Epimerization, 140
Epinephrine hydrochloride, 74
1,2-Epoxydecane, 138
(*Z*)-1,2-Epoxydec-4-ene, 60
1,2-Epoxydec-4-yne, 60
Eremophilone, 40

Esters, 78–80
O-(Ethoxycarbonyl)-3-methoxymandelonitrile, 95
Ethoxycyclohexanols, 138
1-Ethoxy-3-methylcyclohexene, 165–166
Ethyl adipate, 80
Ethyl *p*-aminobenzoate, 124
Ethyl 2-arylhydrazine carboxylates, 170
Ethyl 4-methyl-1-cyclohexenyl ether, 165
Ethyl orsellinate, 129
Ethyl 2-Oxo-4-phenyl butanoate, 85
Ethyl pyrrole-3-acetate, 70
Ethyl pyrrole-3-glyoxalate, 70
Ethyl *p*-tolyl ether, 129
Ethyl-4-aminocyclohexane carboxylate, 84
Ethylbenzene, 118–119
Exocyclic olefins, 36

F

Fatty acids, 37
Fixed-bed processes, 2
  flooded-bed, 2
  trickle-bed, 2
Fluoroaniline, 107
Formic acid, 17, 163
Furans, 133–134
Fused rings, 120–121

G

Glucose, 67
Glyoxylic acid, 89
L-Gulono-1,4-lactone, 66

H

Half-hydrogenated states, 31
Halonitro aromatics, 108
Halonitro compounds, 153
Haptophilicity, 45, 72
(Z,Z,Z)-3,6,9-Heneicosatrienol, 54
Heterocycles, 133–147
Hexahydrobenzoic acid, 117
Hexahydromandelic acid, 16
Hexamethylene glycol, 80
1,6-Hexanediol, 79
Homoallylic systems, 168
Homobenzylic oxygenated substituents, 158
Homogeneous catalysis, 13–16, 32–33, 36–41, 46–47, 54, 79, 112, 153, 167–168, 175
4-Homoprotoadamantane, 174
Hydrazides, 168–169
Hydrazine, 107, 163, 169
  hydrate, 112
Hydrazones, 168–169
Hydrogen
  availability, 8, 30, 57
    effect of, 31
  elimination, 32
  transfer, 74, 107, 128, 162–163
    agents, 163
      cyclohexadiene, 163
      cyclohexene, 163
      formic acid, 163
      hydrazine, 163
    reduction, 16–17
Hydrogenation, reactors, 17–21
  materials of construction, 21
  safety of, 20–21
    rupture disks, 21
Hydrolysis, 100
Hydroperoxides, 176
Hydroquinone, 128
N-Hydroxyamino acids, 158
1-Hydroxyazetidine, 158
o-(2-Hydroxycyclohexyl)phenol, 129
4-Hydroxydodec-2-ynoic acid, 55
Hydroxylamines, 100, 172
N^6-Hydroxylysine, 158
9,10-Hydroxymethyltriptycene, 121
2-Hydroxy-3-nitronpropanoic acid, 105
8-Hydroxy-1-tetralone, 127

I

Impurities, influence of, 105
cis- and *trans*-Indanone, 46
Indenones, 46
Indoles, 134
  N-acetylindoles, 134
Induction periods, 6
Inhibitors, effect of, 31, *see also* Catalysts
1-Iodoeicosane, 153
Isocoronopilin, 32
Isodamsin, 33
Isoflavan, 164
Isomerization, 31, 45, 118, 123, 168

Isoprene, 38
Isoquinuclidine, 84
Isoquinuclidone, 84
Isoxazoles, 140
Isoxazolines, 140–142

J

dl-cis-Jasmanate, 56

K

Ketal, formation of, 11, 68, 166
β-Keto amides, 69
β-Keto esters, 69
Ketones, 66–75

L

Labeling, 13
Leaving group, 128, 158, 176
Leukotrienes, 60
Ligand synthesis, 14–15
Limonene, 36
d-Limonene, 17
Lock-and-key concept, 48
(±)-Lycodoline, 176

M

Maleic anhydride, 79
Mandelic acid, 15–16
Mandelonitrile, 95
Mannich bases, 159
Masked functions, use during alkylation, 88
Metal concentration, *see also* Catalysts
  choosing, 4–5
  effect of, 31
Methoxatin, 89
p-Methoxyaniline, 126
Methoxycyclohexanols, 138
5-(Methoxymethoxy)-2-pentenal, 57
2-(*m*-Methoxyphenylethylamine), 95
4-(4-Methoxyphenyl)-3-(2-nitro-4-methoxyphenyl)-1-pentene, 33
4-Methoxypyridine, 41
Methyl 3′,5-dihydroxy-4′-methoxy-7-(3-azido-3-carboxypropoxy)flavanone, 170
Methyl hardwickiate, 133
Methyl hexahydrohardwickiate, 133
Methyl 3-hydroxyalkanoates, 75
Methyl indole-4-carboxylate, 113
Methyl 3-oxoalkanoate, 75
(*S*)-α-Methylbenzylamine, 85
1-Methyl-4-*t*-butylcyclohexene, 17
Methylcyclohexane, 33, 35, 41
1-Methylcyclohexene, 17
2-Methylcyclohexene, 33
3-Methylcyclohexene, 33
4-Methylcyclohexene, 33
4-Methyl-1-cyclohexenyl ether, 41
4-Methyl-3-cyclohexenyl ethyl ether, 35
4-Methylcyclohexyl ethyl ether, 35
Methylcyclohexylcarbinol, 118
5-Methyldihydrothebaine, 43
Methylenecyclohexane, 33
Methylenediisoxazoles, 140
1-Methyl-4-isopropyl-cyclohexene, 17
8-Methyl-1-naphthoic acid, 157
2-Methyl-2-phenylaziridine, 139
Methylphenylcarbinol, 118
8-Methyl-1,2,3,4-tetrahydro-1-naphthoic acid, 157
5-Methylthebaine, 43
Mevinolin, 38
Minocycline, 90
Molecular queuing, 53
2-Morpholinoisoflav-3-ene, 164
p-(*N*-Morpholino)nitrobenzene, 109

N

Naphthalene, 119
2-Naphthol, 129
Natural oils, 34
Neighboring-group assistance, 149
Nicotine, 6
Nicotyrine, 6
Nitriles, 94–101
Nitro compounds, 104–114
Nitroaldehydes, 110–111
o-Nitroaniline, 6
o-Nitroanisole, 105–106
Nitrobenzene, 107
2-Nitro-1,4-benzenediamine, 111
4-Nitro-1,2-benzenediamine, 111
o-Nitrobenzonitrile, 110

o-Nitrobenzyl ketones, 111
1-(2-Nitrobenzyl)pyrrol-2-aldehyde, 111
Nitroenamines, 113
Nitroketones, 110–111
α-Nitroketones, 111
γ-Nitroketones, 111
3-Nitro-2-methylbenzoic acid, 113
Nitronitriles, 110
2-Nitrophenylacetaldehyde oximes, 109
Nitropyridines, 111
C-Nitroso compounds, 173
N-Nitrosoamines, 173
β-Nitrostyrene, 95, 109
3-Nonyn-1-ol, 60
Norepinephrine, 87
Nucleophilicity, 41
Nucleoside *N*-oxides, 172

O

Octadeca-3,6-diynol, 54
Octadecahydro-9-chloromethyltriptycene, 149
$\Delta^{1,9}$-Octalin, 37
$\Delta^{9,10}$-Octalin, 37
β-Octalone, 9
Octane, 31
Olefinic epoxides, 60
Olefinic nitro compounds, 109–110
Olefinic sulfur compounds, 44–48
Olefins, hydrogenation of, 29–48
  mechanisms of, 29–30
Osazones, 169
Oxazoles, 143–144
Oxazolines, 143–144
Oxidation, 127–128, 169–170, 176
Oximes, 94–101
Oximino ketones, 69
α-Oximino ketones, 101
2-Oximino-1-indanone, 100
Oxiranes, 137–139
4-Oxo-*trans,trans*-7,10-dodecadiene-2-ynamide, 56
2-Oxo-4-phenylbutanoate, 85
Ozonides, 176

P

PAMPO, 119
Parr hydrogenator, 18–20
1,3-Pentadiene, 37
2,4-Pentanediol, 14
Peptides, 162
Perhydrorosin, 117
Peri strain, 120, 157
Peroxides, 176
Peroxy acids, 176
α-Phellandrene, 17
4,7-Phenanthroline, 135
Phenols, 90, 126–130
Phenylacetaldehyde oxime, 109
Phenylacetic acid, 118
Phenylalanine, 17
1-Phenyl-5-chlorotetrazole, 128
Phenylcyclohexane, 118–120
5-Phenyl-2-(3,4-dimethoxybenzyl)-2--oxazoline, 144
o-Phenylenediamine, 6
Phenylethanol, 10
1-Phenylethanol, 139
Phenylethylamine, 170
β-Phenylethylamines, 95, 109
(R)-α-Phenylglycine, 111
Phenylhydrazones, 169
Phenylhydroxylamine, 107
Phenylisocyanate, 128
exo-2-Phenyl-9-oxabicyclo[3.3.1]nonan-2-ol, 159
p-Phenylphenol, 129
2-Phenylquinoxaline, 175
1-Phenyltetrazolyl ether of tyrosine, 17
Pheromones, 55
Phoracantholide I, 150
Phosphinic acid, 107
Piperazines, 111
Polycyclic systems, 119–120
Polyenes, 36–39
Polyhalo compounds, 151–152
Porphobilinogen, 98
Portion-wise addition, 139
Pressure, effect of, 31, 39–41, 47, 94, 109, 120, 129–130, 135–137
Progargylamines, 61
Propionitrile, 97
Propylene, 37
Prostaglandins, 55
  $F_{2\alpha}$, 142
Protecting group, 80

Pupukeanone, 31–32
Pyrazines, 111
Pyridine, 135–137
3-Pyridinecarboxylic acids, 137
Pyridoxine, 96
Pyrrolidines, 111

Q

Quarternization, 164

R

Racemization, 128
Reactive solvents, 10–11
Reductive alkylation, 11, 82–91
Reductive hydrolysis, 94–96, 126
Regulated catalysts, 154
Resorcinol, 127, 140
Ring hydrogenolysis, 137
Ring saturation, 133–137
Ring strain, 117–119, 137, 174
Rosenmund reduction, 153–155
Rosin, 117
Runaway reactions, 99
Rupture disks, 21
Ruthenium tetraoxide, 128
Ruthenium trichloride, 128

S

Safety
  in catalytic hydrogenations, 11–13
  runaway reactions, 99–100
Selectivity, 41
  influence of solvent on, 8–10
  measurement of, 7
Solvent(s)
  effect of, 8–11, 13, 31, 33–34, 41, 46–47, 56–58, 67–70, 73, 87, 95–96, 100, 105, 109, 120, 125–127, 134–135, 138–142, 149, 158–161, 164, 168–169, 175–176
  reactive, 10–11
Sorbitol, 67
Space-time yield, 25
Spirooctane, 174
Spiro[2.5]octane, 175
Stereochemistry, 15, 35–41, 43, 46–47, 54, 57–59, 66, 72–75, 85–91, 99–101, 118, 126, 138–141, 160, 164–165
Stereoselectivity, 57
Steric factors, 3, 35–45, 58, 70, 79, 82, 91, 112, 119, 167
Steric hinderance, 152
Steroids
  1-4-diene, 41
  3-oxo-4-ene, 41
Δ^5 Steroids, 72
Styrene oxide, 139
N-Substituted iminolactones, 43
Substrate purity, effect of, 45, 59
Succinic anhydride, 79
Synergism, 7, 78, 101

T

Temperature, effect of, 5–6, 13, 31, 41–42, 47–48, 59, 94, 113, 118–120, 125–127, 154, 161–162, 166, 170
Tertiary amines, 159
Tetracontane, 153
Tetrahydrofuran, 79
(R)-Tetrahydrofuran-2-carboxaldehyde, 85
Tetrahydroisoquinolines, 84
Tetrahydropyrazino[2,1-*a*]-isoindol-6(2*H*)-one, 95
Tetrahydropyrene, 121
1,2,3,6-Tetrahydropyridines, 139
Tetrasubstituted double bonds, 43
Tetrasubstituted olefins, 34
β-Tetronic acid, 151
Thebaine, 43
Thermodynamic selectivity, 57
Toluene, 119
Toluene diisocyanate, 111
Trans hydrogenation, of alkynes, 54
Tricarbonylchromium complexes, 37
2,4,6-Trichloro-*s*-triazines, 128
Triethylammonium formate, 153
1,1,4-Trimethylcycloheptane, 35
Triphenylacetyl chloride, 154
Tripropylamine, 97
Tritium labeling, 60

U

Unsaturated carbonyl compounds, 40–41

Unsymmetrical amines, 95

V

Valeronitrile, 97
Venting, 125
α-Vinyl carbonyl compounds, 55
Vinyl cyclopropanes, 174
Vinyl ethers, 134, 165
Vinyl functions, 165–166
Vinylic compounds, 41–44
Vinylogous amide, 66, 136, 140–142, 161

Z

Zoapatanol, 42