The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

The chemistry of the **metal—carbon bond** Volume 5

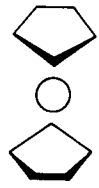
THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of Professor Saul Patai

The chemistry of alkenes (2 volumes)
The chemistry of the carbonyl group (2 volumes)
The chemistry of the ether linkage
The chemistry of the amino group
The chemistry of the nitro and nitroso groups (2 parts)
The chemistry of carboxylic acids and esters
The chemistry of the carbon–nitrogen double bond
The chemistry of amides
The chemistry of the cyano group
The chemistry of the hydroxyl group (2 parts)
The chemistry of the azido group
The chemistry of acyl halides
The chemistry of the carbon–halogen bond (2 parts)
The chemistry of the quinonoid compounds (2 parts)
The chemistry of the thiol group (2 parts)
The chemistry of the hydrazo, azo and azoxy groups (2 parts)
The chemistry of amidines and imidates
The chemistry of cyanates and their thio derivatives (2 parts)
The chemistry of diazonium and diazo groups (2 parts)
The chemistry of the carbon–carbon triple bond (2 parts)
The chemistry of ketenes, allenes and related compounds (2 parts)
The chemistry of the sulphonium group (2 parts)
Supplement A: The chemistry of double-bonded functional groups (2 volumes, 4 parts)
Supplement B: The chemistry of acid derivatives (2 parts)
Supplement C: The chemistry of triple-bonded functional groups (2 parts)
Supplement D: The chemistry of halides, pseudo-halides and azides (2 parts)
Supplement E: The chemistry of ethers, crown ethers, hydroxyl groups and their sulphur analogues (2 parts)
Supplement F: The chemistry of amino, nitroso and nitro compounds and their derivatives (2 parts)
The chemistry of the metal—carbon bond (5 volumes)
The chemistry of peroxides
The chemistry of organic selenium and tellurium compounds (2 volumes)
The chemistry of the cyclopropyl group
The chemistry of sulphones and sulphoxides
The chemistry of organic silicon compounds (2 parts)
The chemistry of enones (2 parts)

UPDATES

The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Nitrones, nitronates and nitroxides
Crown ethers and analogs



The chemistry of the **metal—carbon bond** Volume 5

Organometallic compounds in organic and biological syntheses

Edited by

FRANK R. HARTLEY

Cranfield Institute of Technology, Cranfield, England

1989

JOHN WILEY & SONS

CHICHESTER – NEW YORK – BRISBANE – TORONTO – SINGAPORE

An Interscience ® Publication

Library of Congress Cataloging-in-Publication Data:
Organometallic compounds in organic and biological syntheses / edited by Frank R. Hartley.
p. cm.—(The Chemistry of the metal-carbon bond ; v. 5)
(The Chemistry of functional groups)
'An Interscience publication.'
Bibliography: p.
Includes index.
ISBN 0471915564
1. Organometallic compounds. 2. Chemistry, Organic—Synthesis.
I. Hartley, F. R. II. Series. III. Series: The Chemistry of functional groups.
QD410.C43 1982 vol. 5
[QD411]
547 s—dc20
[547.2] 89-5794
CIP

British Library Cataloguing in Publication Data:
The Chemistry of the metal-carbon bond.
Organometallic compounds in organic and biological syntheses.
1. Organometallic compounds
I. Hartley, F.R. (Frank Robinson), *1942–*
547.05

ISBN 0471915564

Typeset by Thomson Press (India) Ltd, New Delhi
Printed and bound in Great Britain by Courier International, Tiptree, Essex

Volume 5—Contributing authors

David Bremner	Department of Molecular and Life Sciences, Dundee College of Technology, Bell Street, Dundee DDl 1HG, Scotland, UK
Henri Brunner	Institut für Anorganische Chemie, Universität Regensburg, Universitätstrasse 31, D-8400 Regensburg, FRG
Peter J. Craig	School of Chemistry, Leicester Polytechnic, P.O. Box 143, Leicester LEl 9BH, UK
George O. Doak	Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695–8204, USA
W. James Feast	Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK
Leon D. Freedman	Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695–8204, USA
Vernon C. Gibson	Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK
Conor Long	School of Chemical Sciences, National Institute for Higher Education, Dublin 9, Ireland
Gary A. Molander	Department of Chemistry and Biochemistry, University of Colorado at Boulder, Campus Box 215, Boulder, Colorado 80309–0215, USA
Kieran C. Molloy	School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK
Frank Neumann	Institut für Anorganische Chemie, Rheinisch-Westfälische Technische Hochschule Aachen, Templergraben 55, D-5100 Aachen, FRG

Jean-Francois Petrignani — Institut de Petroleochimie et de Synthèse Organique Industrielle, CNRS UA 126, Faculté des Sciences de Saint Jérôme, Université d'Aix Marseille, Rue Henri-Poincaré, 13397 Marseille Cedex 13, France

Gábor Speier — Institute of Organic Chemistry, Veszprém University of Chemical Engineering, Schönherz Z.u. 8, Veszprém 8200, Hungary

Georg Süss-Fink — Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland

Foreword

The Chemistry of the Metal—Carbon Bond is a multi-volume work within the well established series of books covering *The Chemistry of Functional Groups.* It aims to cover the chemistry of the metal—carbon bond as a whole, but lays emphasis on the carbon end. It should therefore be of particular interest to the organic chemist. The general plan of the material is the same as in previous books in the series with the exception that, because of the large amount of material involved, this is a multi-volume work.

The first volume was concerned with (a) the structure and thermochemistry of organometallic compounds, (b) the preparation of organometallic compounds and (c) the analysis and spectroscopic characterization of organometallic compounds. The second volume was concerned with cleavage of the metal—carbon bond, insertions into metal—carbon bonds, nucleophilic and electrophilic attack of metal—carbon bonds, oxidative addition and reductive elimination. It also included a chapter on the structure and bonding of main group organometallic compounds. The third and fourth volumes were concerned with the use of organometallic compounds to create carbon—carbon, carbon—hydrogen and other carbon—element bonds.

The present volume is also concerned with the use of organometallic compounds in organic and biological synthesis. It includes chapters on synthetic techniques such as sonochemistry, photochemistry and phase-transfer catalysis, on synthetic reactions such as asymmetric synthesis, oxidation and metathesis, on synthetic reagents such as metal clusters, organo-lanthanide, -antimony and -bismuth reagents and chapters on biological alkylation and bioorganotin compounds.

In classifying organometallic compounds we have used Cotton's hapto-nomenclature (η-) to indicate the number of carbon atoms directly linked to a single metal atom.

In common with other volumes in *The Chemistry of the Functional Groups* series, the emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. The coverage is restricted in that material included in easily and generally available secondary or tertiary sources, such as *Chemical Reviews* and various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) is not, as a rule, repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore, each of the authors has been asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level. With these restrictions, it is realised that no plan can be devised for a volume that would give a *complete* coverage

of the subject with *no* overlap between the chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner sufficient freedom is given to each author to produce readable quasi-monographic chapters. Such a plan necessarily means that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author.

The publication of the Functional Group Series would never have started without the support of many people. This volume would never have reached fruition without Mrs Baylis's and Mrs Vitale's help with typing and the efficient and patient cooperation of several staff members of the Publisher, whose code of ethics does not allow us to thank them by name. Many of our colleagues in the UK, Israel and elsewhere gave help in solving many problems, especially Professor Z. Rappoport. Finally, that the project ever reached completion is due to the essential support and partnership of our wives and families.

Cranfield, England FRANK HARTLEY

Contents

List of abbreviations used

ac	acrylonitrile
Ac	acetyl
acac	acetylacetone
acacen	bis(acetylacetonato) ethylenediamine
ADP	adenosine diphosphate
aibn	azobisisobutyronitrile
all	allyl
An	actinide metal
an	anisyl
ap	antiplanar
appe	$Ph_2AsCH_2CH_2PPh_2$
Ar	aryl
ATP	adenosine triphosphate
9-bbn	9-borabicyclo[3.3.1]nonane
bda	benzylideneacetone
bipy	2,2′-bipyridyl
bnah	*N*-benzyl-1,4-dihydronicotinamide
btmg	2-*tert*-butyl-1,1,3,3-methylguanidine
Btz	benzothiazolyl
Bu	butyl
Bz	benzyl
cd	circular dichroism
cdt	(*E*,*E*,*E*)-cyclododeca-1,5,9-triene
cht	cycloheptatriene
CI	chemical ionization
coct	cyclooctene
1,5-cod	cycloocta-1,5-diene
cot	cyclooctatetraene
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
ctab	cetyltrimethylammonium bromide
Cy	cyclohexyl
Cyst	cysteine

dabco	1,4-diazobicyclo[2.2.2]octane
dba	dibenzylideneacetone
dbn	1,5-diazabicyclo[4.3.0]non-5-ene
dbu	1,8-diazabicyclo[5.4.0]undec-7-ene
dccd	dicylohexylcarbodiimide
dcpe	1,2-bis(dicyclohexylphosphino)ethane
dcpp	dioctylprotoporphyrinato
ddq	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
def	diethyl fumarate
diars	*o*-bis(dimethylarsino)benzene
dibah, dibal	diisobutylaluminium hydride
dien	$H_2NCH_2CH_2NHCH_2CH_2NH_2$
diop	2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
diphos	1,2-diphenylphosphine
dma	*N*,*N*-dimethylacetamide
dmae	*N*,*N*-dimethylaminoethanol
dmap	4-dimethylaminopyridine
dme	1,2-dimethoxyethane
dmfm	dimethyl fumarate
dmg	dimethyl glyoximate
dmm	dimethyl maleate
dmpe	bis(1,2-dimethylphosphino)ethane
dmpf	1,1′-bis(dimethylphosphino)ferrocene
dmso	dimethyl sulphoxide
DNA	deoxyribonucleic acid
dotnH	bis(diacetylmonoxime)propylene-1,3-diamine
dpm	dipivaloylmethanato
dppb	bis(1,4-diphenylphosphino)butane
dppe	bis(1,2-diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppm	bis(1,1-diphenylphosphino)methane
dppp	bis(1,3-diphenylphosphino)propane
edta	ethylenediaminetetracetic acid
ee	enantiomeric excess
Et	ethyl
eV	electronvolt
Fc	ferrocene
fmn	fumaronitrile
fod	$F_3C(CF_2)_2COCH{=}C(O)C(CH_3)_3$
Fp*	$Fp(\eta^5\text{-}C_5H_5)(CO)(PPh_3)$
FT	Fourier transform
2-Fu	2-furfuryl
Hept	heptyl
Hex	hexyl

c-Hex	cyclohexyl
1,5-Hd	hexa-1,5-diene
hfac	hexafluoroacetone
hfacac	hexafluoroacetylacetonato
hfc	3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato
hmdb	hexamethyl(Dewar)benzene
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hmpa	hexamethylphosphoramide
hmpt	hexamethylphosphorotriamide
is	isomer shift (Mössbauer)
lda	lithium diisopropylamide
Ldbb	lithium 4,4′-di-*tert*-butylbiphenylide
LD_{50}	dose causing lethality amongst 50% of a population
Lhdms	lithium hexamethyldisilazide
LiCA	Lithium *N*-isopropylcyclohexylamide
Ln	lanthanide metal
M	metal
M	parent molecule
ma	maleic anhydride
map	2-methyl-2-nitrosopropane
m-cpba	*m*-chloroperbenzoic acid
Me	methyl
MEK	methyl ethyl ketone
Mes	methanesulphonyl
mes	mesityl (2,4,6-trimethylphenyl)
meSal	*N*-methylsalicylaldiminato
Met	methionine
MNDO	modified neglect of diatomic overlap
ms	millisecond
Ms	mesityl
nadh	nicotinamide adenine dinucleotide
nbd	norbornadiene
nbs	*N*-bromosuccinimide
ncs	*N*-chlorosuccinimide
Neo	$PhMe_2CCH_2$
nmp	*N*-methylpyrrolidone
Non	nonyl
Np	naphthyl
oA	*o*-allylphenyldimethylarsine
Oct	octyl
Ofpp	*meso*-tetrakis (*o*-fluorophenyl)porphyrinato
P or Por	Porphyrinato
Pc	phthalocyanine
Pe	pentenyl
Pen	pentyl

Ph	phenyl
phen	*o*-phenanthroline
phth	phthalimide
pmdeta	pentamethyldiethylenetriamine
ppm	parts per million
Pr	propyl
PRDDO	partial retention of diatomic differential overlap
psi	pounds per square inch
pvc	poly(vinyl chloride)
py	pyridyl
pz	pyrazolyl
qs	quadrupole splitting (Mössbauer)
R	any radical
RNA	ribonucleic acid
RT	room temperature
salen	bis(salicylaldehydo)ethylenediamine
salophen	bis(salicylaldehydo)-*o*-phenylenediamine
salpr	bis(3-salicylideneiminopropyl)amino
Samp	(*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine
sce	saturated calomel electrode
Si	silica (used as a support)
sia	sianyl (3-methyl-2-butyl)
S_NI	substitution nucleophilic internal
sp	synplanar
St	stearate
tba	tribenzylideneacetylacetone
tbab(c, i)	tetra-*n*-butylammonium bromide (chloride, iodide)
tbdms	*tert*-butyldimethylsilyl
tbto	$(Bu_3Sn)_2O$
teba	tetrabenzylammonium chloride
tcne	tetracyanoethylene
teta	5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane
tfa	trifluoroacetic acid
TfO	triflate
tfpp	*meso*-tetrakis(pentafluorophenyl)porphyrinato
thf	tetrahydrofuran
2-thi	2-thienyl
thp	tetrahydropyranyl
thpo	tetrahydropyranyloxy
Thx	thexyl (—CMe_2CHMe_2)
tmed	tetramethylethylenediamine
tmg	1,1,3,3-tetramethylguanidine
tmof	trimethyl orthoformate
tms	trimethylsilyl
tmtu	tetramethylthiourea
Tol	tolyl
tond	1,3,5,7-tetramethyl-2,6,9-trioxobicyclo[3.3.1]nona-3,7-diene
tos	tosyl

tpp	tetraphenylporphyrin
t($\alpha, \beta, \alpha, \beta$-Binap)pp	5^{α}, 10^{β}, 15^{α}, 20^{β}-tetrakis[*o*-(*R*)-hydrafropamido-phenyl]porphyrinato
triphos	$Ph_2PCH_2CH_2P(Ph)CH_2CH_2PPh_2$
tta	thallium(III) acetate
ttfa	thallium(III) trifluoroacetate
ttn	thallium(III) nitrate
tu	thiourea
un	olefin or acetylene
X	halide

Part 1
Synthetic Techniques

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 1

The application of sonochemistry in the formation and reactions of metal—carbon bonds

D. BREMNER

Department of Molecular and Life Sciences, Dundee Institute of Technology, Bell Street, Dundee DD1 1HG, Scotland, UK

I. INTRODUCTION

The use of ultrasound in a number of industrially important processes is well known[1], but it is only relatively recently that great interest has been kindled in the application of ultrasound to chemical reactions[2]. It has been found that some reactions which are sluggish or, sometimes, extremely unreactive can be facilitated by irradiating the reaction mixture with ultrasonic waves. This technique has been applied most successfully to heterogeneous reactions, particularly those involving metals, where transient organometallic species are formed *in situ*. It is the purpose of this chapter to review some of the background to the phenomenon of sonochemistry, indicating the origins of the effect and examining, specifically, recent research involving ultrasound in organometallic and organometalloid reactions.

II. BACKGROUND TO SONOCHEMISTRY

A. Ultrasound

The human ear is sensitive to frequencies between 16 and 16 000 Hz; at frequencies above 16 kHz lies the region of ultrasound. For mainly economic reasons, the most common frequency range used in sonochemistry lies between 20 and 50 kHz and 1 Mhz usually represents the upper frequency limit. Mechanical devices, such as tuning forks and hi-fi speakers, are able to produce audible frequencies with considerable power but are incapable of generating high power in the region of ultrasound. The requirements of 20 kHz and, say, 100 W (the power levels commonly used in sonochemical experiments) are produced by using either piezoelectric crystals or magnetostrictive devices. Most commonly, a piezoelectric material such as lead zirconate titanate ceramic is subjected to a high voltage alternating current and the piezoelectric source expands and contracts in the field. The ultrasonic energy so produced is passed into the reaction vessel using techniques which depend on the type of reactor chosen.

B. Ultrasonic Equipment

An ultrasonic cleaning bath is the most easily accessible source of ultrasound and many successful reactions have been reported wherein a round-bottomed flask containing the reactants has merely been immersed in water in the bath, stirred and irradiated for an appropriate length of time, and the products isolated in the usual manner. Not surprisingly, for a reactor system as simple as this, there are a number of drawbacks: the acoustic intensity is not consistent, the position of the flask in the bath is often critical, and temperature control is difficult. A superior alternative is the cup-horn sonicator[3], which was originally designed for cell disruption, but has been used by several research groups. Finally, an ultrasonic horn can be immersed in the reaction medium[3]. This type of equipment can deliver the greatest amount of energy and temperature control is relatively facile. It does, however, suffer from the problem of pitting of the horn with possible contamination by titanium, particularly if reactive organometallics are used.

C. Ultrasonic Effects

When ultrasonic waves are passed through a liquid a number of effects can occur. Firstly, there is rapid movement of the fluid caused by the variation of sonic pressure which subjects the liquid to compression and rarefaction. Secondly, and by far the most important phenomenon, cavitation occurs when gas bubbles are formed in the liquid by a variation in sonic pressure. The sound waves cause microbubbles to oscillate in size about

an average. Some bubbles only oscillate but others are perturbed so much by the ultrasound that they reach a critical size and then violently implode, generating shockwaves which can give rise to sonoluminescence and electromagnetic radiation. The force of the implosion may also generate, momentarily, localized pressures of several GPa and temperatures, at the centre of the bubble, of 10^4–10^5 K.

The third important effect is microstreaming, where a large amount of vibrational energy is put into a small volume with little resultant heating. The results of the sonication of any liquid are similar to those obtained from pyrolysis and radiolysis.

When a solid–liquid interface is subjected to ultrasound, transient cavitation can still occur but the micro bubbles are no longer spherical but direct themselves towards the surface of the solid. This jet is responsible for pitting (often observed on ultrasonic horn tips), ultrasonic cleaning, and deformation of the solid surface. Highly reactive solids are produced, which are kept clean by constant abrasion, and extreme pressures and temperatures are generated in the cavitating liquid.

These properties, coupled with the effect of microstreaming on the liquid transport from the solid–liquid interface, all contribute to the striking enhancement of reactivity caused by ultrasound. With immiscible liquids these phenomena manifest themselves in increased emulsification and account for the similarity between sonochemical reactivity and phase-transfer catalysis.

D. Sonochemistry—Historical Perspective and Scope

The pioneering work on the use of ultrasound in chemistry, sonochemistry, was carried out by Richards and Loomis in the 1920s[4]. They studied the effects of ultrasound on a variety of solutions, solids, and pure liquids and showed that ultrasound had a number of positive effects. Surprisingly, little follow-up work has been reported and most of the reactions studied in the following 20 years concentrated on aqueous systems. Part of the difficulty at this time was the lack of suitable inexpensive equipment which was capable of delivering the required energy and frequency. In spite of this, the first truly organic reaction carried out in the presence of ultrasound was reported in 1938 by Porter and Young[5]. Benzazide (**1**) was shown to undergo the Curtius rearrangement when irradiated with ultrasound (equation 1).

$$\mathrm{PhCON_3} \xrightarrow[10\text{–}50\ \mathrm{kHz}]{)))} \mathrm{PhNCO} + \mathrm{N_2} \qquad (1)$$

(1)

However, it was not until the early 1950s that suitable equipment became available which allowed routine investigations of ultrasonic effects on chemical reactions. Miyagawa[6] reported that the nitration of *m*-xylene, the saponification of fats, and the hydrolysis of esters were all accelerated by ultrasound.

Aqueous sonochemistry has been extensively studied[2c] probably owing to the interest in the effects of ultrasound on biological systems. During sonication in the presence of water, hydroxyl radicals and hydrogen atoms are produced in a process similar to that observed in radiolysis. The primary products are hydrogen peroxide and hydrogen (equation 2).

$$2\mathrm{H_2O} \xrightarrow{)))} 2\mathrm{HO^{\cdot}} + 2\mathrm{H^{\cdot}} \rightarrow \mathrm{H_2O_2} + \mathrm{H_2} \qquad (2)$$

A considerable number of inorganic oxidations and reductions in aqueous media have also been reported, most of them occurring as a result of the initial formation of H_2O_2 and H_2[2g]. Even organic compounds are not immune from reaction on sonication in the

presence of water. Most products arise from oxidation processes but the yields are low for synthetic use. Amino acids, although relatively stable, decompose under sonication to give a variety of simpler products resulting from both oxidation and reduction processes[7] (equation 3).

$$RCH(NH_2)COOH \xrightarrow[H_2O]{))))} H_2 + CO + NH_3 + HCHO + RCH_2NH_2 + \text{etc.} \quad (3)$$

Ultrasound enhances the rate of acid-catalysed hydrolysis of esters[6,8] and a number of studies have shown that the rate enhancements are inversely proportional to temperature. Base hydrolysis[9] and solvolysis of haloalkanes[10] are also greatly influenced by ultrasonic irradiation.

This brief introduction to sonochemistry sets the scene for the review of the use of ultrasound in the formation and reactions of metal—carbon bonds. Recently there has been a plethora of publications concerning the reactions of metals with organic compounds in the presence of ultrasonic waves. These reactions do not necessarily generate specific discrete isolable organometallic compounds, but certainly involve metal–organo interactions in the reaction scheme. Such reactions will be included together with the reactions of organometallic complexes in homogeneous solution, catalytic reactions, and the generation of reactive metal powders.

III. HOMOGENEOUS REACTIONS INVOLVING METAL COMPLEXES

A. Stoichiometric reactions

In 1981 Suslick *et al.*[11] reported the first example of the effect of ultrasound on iron carbonyls in alkane solutions. The carbonyls were selected because the corresponding thermal and photochemical reactivities had been well characterized. Their study illustrates the unique effects that homogeneous sonication can have on the course of the reaction of an organometallic. Thermolysis of $[Fe(CO)_5]$ above 100 °C gives pyrophoric, finely divided iron powder whereas ultraviolet photolysis produces $[Fe_2(CO)_9]$ via $Fe(CO)_4$, and multiple infrared photolysis in the gas phase yields isolated Fe atoms. Ligand dissociation, generating $Fe(CO)_3$, $Fe(CO)_2$, etc., does not occur in ordinary thermal or photochemical processes, although it has been identified during gas-phase laser photolysis and in low-temperature inert matrices.

Sonication[12] of $[Fe(CO)_5]$, neat or in alkane solutions, yields $[Fe_3(CO)_{12}]$ in an unusual clusterification reaction, together with finely divided iron. The kinetics were found to be first order, which the authors suggested as being consistent with a simple dissociative process activated by the intense local heating generated by acoustic cavitation. This view is supported by the fact that the logarithm of the observed first-order rate coefficient is linear with respect to the solvent vapour pressure. This effect has interesting consequences in that the ratio of the $[Fe_3(CO)_{12}]$ to Fe can be varied with the solvent vapour pressure. The production of $[Fe_3(CO)_{12}]$ is strongly favoured by increasing solvent volatility (heptane gives the best yields). The proposed mechanism by which $[Fe_3(CO)_{12}]$ is formed during sonolysis is shown in Scheme 1 and does not involve $[Fe_2(CO)_9]$ as an intermediate. Sonolysis of $[Fe_2(CO)_9]$ actually yields only $[Fe(CO)_5]$ and finely divided iron.

The production of $[Fe_3(CO)_{12}]$ arises from the initial dissociative loss of CO from cavitational heating of $[Fe(CO)_5]$, followed by secondary reactions with excess $[Fe(CO)_5]$. On the basis of ligand trapping experiments, the authors favour sonochemical production of $Fe(CO)_3$ and reaction with $[Fe(CO)_5]$ but they do not rule out dimerization of $Fe(CO)_4$.

$$[Fe(CO)_5] \xrightarrow{)))} Fe(CO)_{5-n} + nCO \quad (n = 1\text{–}5)$$
$$Fe(CO)_3 + [Fe(CO)_5] \longrightarrow Fe_2(CO)_8$$
$$2Fe(CO)_4 \longrightarrow Fe_2(CO)_8$$
$$Fe_2(CO)_8 + Fe(CO)_5 \longrightarrow [Fe_3(CO)_{12}] + CO$$

SCHEME 1

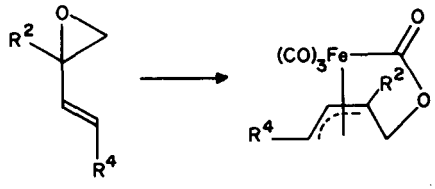
In addition to clusterification, sonochemical ligand substitution also occurs in $[Fe(CO)_5]$ (and in most metal carbonyls). Sonication of $[Fe(CO)_5]$ in the presence of phosphines or phosphites[5] in various alkanes produces $[Fe(CO)_4L]$, $[Fe(CO)_3L_2]$, and small amounts of $[Fe(CO)_2L_3]$. The ratio of the products is independent of the period of sonication and multiply-substituted products increase with increasing initial concentration of L. Interestingly, $[Fe(CO)_4L]$ is not sonochemically converted into $[Fe(CO)_3L_2]$ at a rate comparable to its production from $[Fe(CO)_5]$. The general mechanism proposed to account for these products is shown in Scheme 2.

$$[Fe(CO)_5] \xrightarrow{)))} Fe(CO)_{5-n} + nCO \quad (n = 1\text{–}5)$$
$$Fe(CO)_4 + L \longrightarrow [Fe(CO)_4L]$$
$$Fe(CO)_3 + L \longrightarrow Fe(CO)_3L$$
$$Fe(CO)_3L + CO \longrightarrow [Fe(CO)_4L]$$
$$Fe(CO)_3L + L \longrightarrow [Fe(CO)_3L_2]$$

SCHEME 2

Sonochemical ligand substitution also occurs with other metal carbonyls such as $[Cr(CO)_6]$, $[Mo(CO)_6]$, and $[W(CO)_6]$. In these compounds ligand substitution originates directly from the parent carbonyl and the rates of sonochemical ligand substitution follow their relative volatilities.

A synthetic application of sonochemical substitution has been described (equation 4)[13]. η^3-Allyltricarbonyliron–lactone complexes (**3**) are usually prepared by treatment of alkenyl epoxides (**2**) with coordinatively unsaturated iron carbonyl species under somewhat forcing conditions. However, when nonacarbonyl diiron ($[Fe_2(CO)_9]$) in tetrahydrofuran (thf) is reacted with a series of alkenyl epoxides (**2**) the corresponding iron complexes (**3**) are obtained in moderate to excellent yields. These reaction conditions are satisfactory for most substrates but a complementary process which would allow room temperature reaction was desired. Alkenyl epoxides (**2**) do not react with $[Fe_2(CO)_9]$ in



(4)

(**2**) (**3**)

R^2 = Me, R^4 = H 94%
R^2 = Me, R^4 = Ph 60%
R^2 = Me, R^4 = n-C_6H_{13} 62%

hydrocarbon solvents even after 2 weeks at room temperature but are readily converted into the corresponding complexes (**3**), in acceptable yields, on sonication in a cleaning bath. In this instance the use of thf, in the quiet, actually gives better yields than those obtained by ultrasound, although this is one of the few cases where the ultrasonic technique has been bettered.

In control experiments in hydrocarbon solvents neither $[Fe(CO)_5]$ nor $[Fe_2(CO)_9]$ was found to react with alkenyl epoxides under sonochemical conditions. Exposure of $[Fe_2(CO)_9]$ to sonication gave $[Fe(CO)_5]$, Fe, and CO. The authors[13] were surprised that under their conditions $[Fe(CO)_5]$ and $[Fe_3(CO)_{12}]$ did not undergo substitution reactions and suggested that Suslick's conclusions were debatable. However, Suslick[2h] believes that this is due to the low intensities of ultrasound present in the ultrasonic cleaning bath, which are sufficient to induce cavitation in heterogeneous slurries of $[Fe_2(CO)_9]$ but which are not sufficient in homogeneous solutions of $[Fe(CO)_5]$ or $[Fe_3(CO)_{12}]$.

The sonication of $[Mn_2(CO)_{10}]$ and $[Re_2(CO)_{10}]$ has also been described[14]. These systems were chosen because the thermal and photochemical behaviour of these carbonyl complexes is well known and provides a comparative basis for the study of reactivity under sonication. When phosphines or phosphites are present, ultrasonic irradiation of $[Mn_2(CO)_{10}]$ produces ligand substitution which is independent of the ligand or its concentration and the mechanism does *not* involve metal—metal bond cleavages. Surprisingly, $[Re_2(CO)_{10}]$ does not undergo sonochemical substitution at appreciable rates. Both of these carbonyl complexes do undergo rapid sonochemical halogenation in halocarbon solvents via homolysis of the solvent, resulting in generation of halogen atoms and alkyl radicals. Scheme 3 describes the proposed reaction mechanism which accounts for the observed products.

$$R_3C \xrightarrow{)))} R_3C^{\cdot} + X^{\cdot}$$

$$2R_3C^{\cdot} \longrightarrow R_3CCR_3$$

$$2X^{\cdot} \longrightarrow X_2$$

$$[M_2(CO)_{10}] + 2X^{\cdot} \longrightarrow 2[M(CO)_5X]$$

$$[M_2(CO)_{10}] + X_2 \longrightarrow 2[M(CO)_5X]$$

SCHEME 3

A further example of a secondary sonochemical reaction was described by Suslick[2h]. Lengthy sonolysis of $[Co_2(CO)_8]$ in *n*-alkanes produces acetylene complexes of cobalt carbonyls. Surprisingly, the expected product $[Co_4(CO)_{12}]$ is formed only in small amounts, the principal products being $[Co_2(CO)_6(C_2H_2)]$ and $[Co_4(CO)_{10}(C_2H_2)]$. Isotopic labelling confirmed that the acetylene is produced from the alkane solvent. The rate of formation of the acetylene complexes is relatively slow and comparable to that of acetylenes from alkanes alone[15]. Further, cobalt carbonyls undergo easy thermal reactions with alkynes, so these results indicate that the reaction does *not* proceed via organometallic activation of the alkane but merely by a secondary reaction between sonochemically induced alkane decomposition products and the metal carbonyl. Ley *et al.*[16] described a related reaction, the preparation of $[(\eta^4\text{-diene})Fe(CO)_3]$ complexes by sonolysis of $[Fe_3(CO)_9]$ in the presence of dienes.

The sonochemistry of organometallic compounds *per se* is still in its infancy and few reports exist of the study of such a potentially highly interesting area of organometallic chemistry. The exposure of organotin compounds **4**, **5** and **6** to ultrasonic irradiation has been described [17] and leads to the formation of free radicals. Electron spin trapping, with nitrosodurene, proved to be a reliable method for the detection of alkyl and acyl radicals

generated during the sonolysis. Scheme 4 was proposed to account for the ESR spectra which are obtained.

R_3SnSnR_3 $R^1_2SnR^2_2$ $ClSn(CH_2Ph)_3$

(4) (5) (6)

R = Me, Bu, Ph R^1 = Bu; R^2 = Ph

$R^1 = R^2$ = Me, Et, Bu

$$R_4Sn \xrightarrow{)))} R^{\cdot} + R^{\cdot} + R_3Sn^{\cdot}$$

$$R^{\cdot} + C_6HMe_4NO \longrightarrow (C_6HMe_4)(R)NO$$

$$R_3Sn^{\cdot} + C_6H_6 \longrightarrow R_3SnC_6H_6^{\cdot}$$

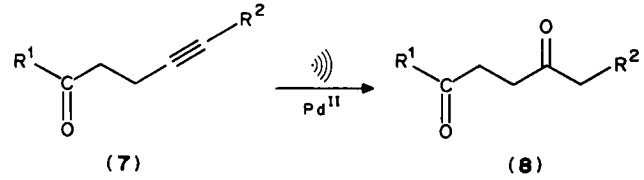
$$R_3SnC_6H_6^{\cdot} + C_6HMe_4NO + [OX] \longrightarrow {}^{\cdot}ON(C_6H_4SnR_3)(C_6HMe_4) + [RED]$$

SCHEME 4

B. Catalytic Reactions

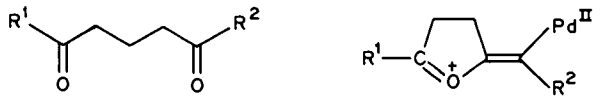
The transient coordinatively unsaturated species produced by sonolysis of metal carbonyls would appear *a priori* to be possible homogeneous catalysts since similar species produced photochemically are highly effective in this role. Sonication[12] of $[Fe(CO)_5]$, $[Fe_2(CO)_9]$, or $[Fe_3(CO)_{12}]$ in pent-1-ene solution produced *trans*- and *cis*-pent-2-ene in a thermodynamic ratio of 3.5:1. The rate of isomerization is enhanced by a factor of 10^5 by ultrasonic irradiation of the iron carbonyls compared with control experiments. Terminal alkenes are readily isomerized, although increasing steric hindrance diminishes the rate. Other metal carbonyls also produce similar isomerizations, although $[Re(CO)_5]$ and $[Ru_3(CO)_{12}]$ produce a higher *trans/cis* ratio. The exact nature of the catalytic species is unknown but the results are indicative of a mechanism similar to that proposed for photo- and thermal catalysis.

An interesting regioselective hydration of alkynones catalysed by palladium occurs in the presence of ultrasonic waves[18]. In acetonitrile–water solution $[PdCl_2(MeCN)_2]$ catalyses the hydration of hept-5-yn-2-one (**7**) to the 1,4-diketone (**8**) in preference to the 1,5-diketone (**9**). Cyclic intermediate **10** is postulated to give rise to the observed regioselectivity. Sodium aurate ($Na[AuCl_4]$) is also effective as a catalyst for similar hydrations of acetylenes (equation 5).



(7) (8)

(5)



(9) (10)

IV. HETEROGENEOUS REACTIONS INVOLVING METALS

A. Stoichiometric Reactions

1. Introduction

The reaction of organic compounds with metals to form organometallics or to produce transient 'organometalloid' species is the area of chemistry in which ultrasound has had the most dramatic impact. Materials which show no evidence of reaction under normal conditions produce high yields of novel organometallics under very mild conditions. Even more noteworthy is the use of ultrasound and metals to form organometallic intermediates which allow a vast range of organic synthetic manipulations to be facilitated. Here the reactions involving metals are sectionalized according to the metal involved and only where an organometallic compound has been isolated and characterized is it described in detail. This section concentrates on the use of organic compounds in the presence of metals and ultrasound in the synthesis of other compounds.

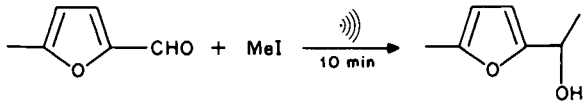
2. Lithium, sodium and potassium

The first use of ultrasound in the synthesis of organometallic compounds was reported in 1950 by Renaud[19], who described the reaction of haloalkanes with lithium, magnesium, and aluminium in undried diethyl ether using ultrasound. Similar reactions with beryllium, calcium, zinc and mercury were unsuccessful. Later in the 1950s, ultrasound was employed in an improved method for the preparation of metal addition complexes with aromatic systems[20]. Even at this early stage solvents such as dioxane and 1,2-dimethoxyethane were identified as being effective in the preparation of sodium addition complexes of the isomeric benzoquinolines. Using ultrasound the preparation time is 45 min whereas a similar reaction in the absence of ultrasound requires 48 h. The authors commented that 'for other reactions involving metals where bond rupture is involved, as in Wurtz or Grignard reactions, the use of ultrasonics should likewise prove useful'. This statement is an impressive prophecy, although it was some 25 years later that these ultrasonic reactions were described[21]. Ultrasonically dispersed sodium was found[22] to be highly effective for the production of phenylsodium from chlorobenzene. A comparison of the reactivities of sodium dispersed mechanically and ultrasonically is illustrated by the steady rate of reaction achieved with ultrasound as opposed to the violent, uncontrollable reaction seen with mechanical dispersions. A similar report on the facile preparation of aromatic anion radicals by ultrasonic irradiation appeared in 1982[23]. Using a common ultrasonic laboratory cleaner, a metallic alkali cube, and commercial thf, naphthalene is readily converted into its radical anion on sonication for 30 min. Naphthalenelithium, anthracenesodium, and biphenylsodium can be prepared in a similar manner in commercial thf. Lithium and naphthalene also react in non-ethereal solvents to afford lithium naphthalide under ultrasonic conditions[24]. The resulting anion can be used to oligomerize isoprene.

The preparation of the useful synthon sodium methyl sulphinyl carbanion is another example of an early use of ultrasonics in an organometallic preparation[25]. When a sodium hydride suspension in mineral oil was stirred in dmso with ultrasonic irradiation, the temperature rose to 50 °C and after 1 h a clear solution of methylsulphinyl carbanion was obtained. This solution is relatively stable when protected by a 1 cm layer of mineral oil. For synthetic work the reagent is drawn off by pipette.

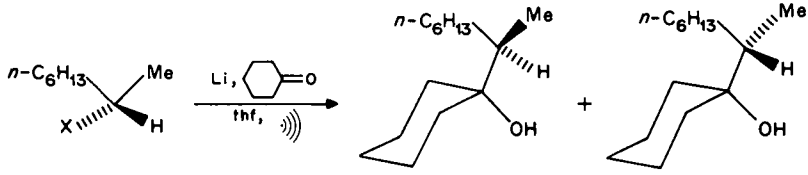
The arrival of ultrasonically assisted reactions as highly useful chemical tools can be dated to the early 1980s and to the work of Luche and coworkers in particular[26,27]. They began a systematic study of the use of metals in conjunction with ultrasound in the synthesis of organic compounds. Surprisingly, their first report[26] on the use of ultrasound on the formation of Grignard reagents was not particularly encouraging. However, they

found that lithium metal in the presence of ultrasound was extremely reactive in the Barbier reaction. The aldehyde **11** is converted into the alcohol **12** in 100% yield after ultrasonic irradiation for 10 min in the presence of lithium metal. Furthermore, ultrasonic reaction provides considerable advantages over normal conditions. Commercial, undried thf can be used and unwanted reduction and enolization are minimised. Also, Wurtz coupling, which is a major problem in non-ultrasonic methods, is eliminated with ultrasound (equation 6).



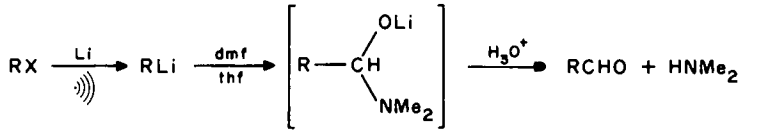
(11) (12) (6)

This type of reaction has been utilized[27] in a study of the mechanistic consequences of the retention of optical activity in Barbier reactions using (*S*)(+)-2-octyl halides. When haloalkanes **13** are reacted with lithium and cyclohexanone in thf with sonication, optically active alcohols **14** are obtained in every case (equation 7). However, the yield of **14** varies, depending on the halide, the temperature, the time, and even the energy of the ultrasonic bath. The optical activity of **14** is attributed to a stereoselective reaction pathway wherein an initial single-electron transfer from the metal to the carbon—halogen bond forms a tight ion pair adsorbed on to the metal surface. The fate of this radical ion pair depends mainly on the halogen and the temperature. This reaction is the first report of stereochemical information being obtained from organometallic reactions starting from chiral alkyl halides and gives a more accurate picture of the complex Barbier reaction mechanism.



[(S)(+)-13] X=Cl, Br, I [(R)(+)-14] [(S)(−)-14] (7)

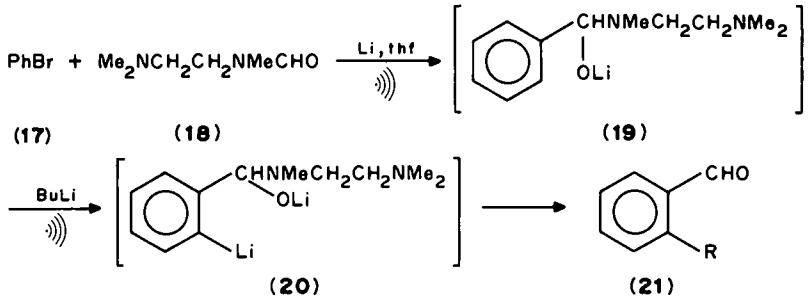
Metallic lithium is also involved in the Bouveault reaction[28]. Aldehydes **16** are readily obtained in high yield via intermediate **15** by ultrasonic treatment of alkyl and aryl halides in the presence of lithium and DMF (equation 8).



(15) (16) (8)

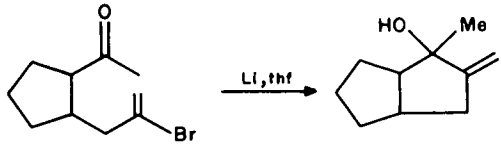
The solvent used for the reaction and the frequency of the ultrasound have a marked

effect on the yield[29]. With diethyl ether as solvent and with a variety of amides, the yield of aldehyde is much lower than when thf or tetrahydropyran is used in a 50 kHz ultrasonic cleaning bath. With 500 kHz ultrasound the reaction in diethyl ether is effected and the yield is increased to ca 75%. When intermediate **15** (R = Ph) is prepared under sonochemical conditions it can be further *ortho*-lithiated[30]. The use of thf as solvent increases the rates and yields of metallation which is achieved by *in situ* generation of alkyllithium. Thus, bromobenzene (**17**) and amide **18** in thf containing lithium metal are sonicated to give the Bouveault intermediate **19**. Treatment of **19** with butyllithium gives the *ortho*-lithiated species **20** which is reacted with dmf or MeI, followed by hydrolysis, to give the *ortho*-substituted aldehyde **21** in 69% yield (Scheme 5).



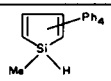
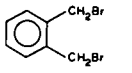
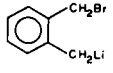
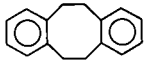
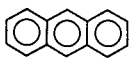
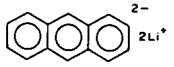
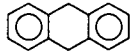
SCHEME 5

This *ortho*-reaction may be further simplified[31] by sonication of the amide, aryl halide, and excess lithium metal for 15 min followed by the addition of 1-bromobutane and sonication for a further 30 min. The butyllithium thus formed *in situ ortho*-lithiates the phenyl ring and reacts readily with an electrophile to give excellent yields of the 2-substituted aldehydes (**21**). An example of the synthetic use of the ultrasonically mediated intramolecular Barbier reaction is provided by the cyclization[32] of ketone **22** to the exomethylene derivative **23**. Conventional methods of organometallic generation with lithium or magnesium failed to give satisfactory results; also, the use of low-temperature halogen–metal exchange (*t*-BuLi, −120 °C) did not yield any closure products.



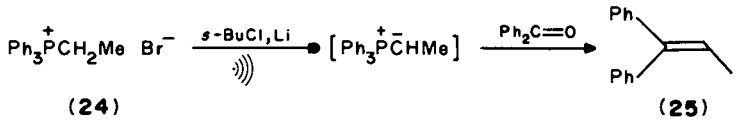
Butyllithium reagents are some of the most useful organometallics in organic synthesis. They are utilized as strong bases, as precursors to lithiated reactive intermediates or other organometallics, and as initiators in many polymerization reactions. Since butyllithium reacts with ethereal solvents it is commonly supplied in hydrocarbon solution and this necessitates standardization and solvent exchange. Einhorn and Luche[33] described the replacement of butyllithium reagents by their inexpensive and safer precursors, the corresponding butyl halides and lithium metal under sonochemical conditions directly in

TABLE 1. Reactions of substrates with lithium

Substrate	Organolithium	Time (min)	Electrophile	Product	Yield (%)
PhC≡CPh	PhC(Li)=CPhCPh=C(Li)Ph	10	$MeHSiCl_2$		68
PhC≡CH	PhC≡CLi	5	MeI	PhC≡CMe	95
		60–90			80
		30–45	H_2O		90
		60–90	MeOH		90

ethereal solvents. It is also possible to generate lithium diisopropylamide (LDA) from diisopropylamine, lithium metal, and butyl halides by sonication at 15 °C in dry thf. Further, the LDA can be reacted *in situ* with a number of species to produce anions which can be further reacted with a variety of electrophiles. For example, the phosphonium salt **24** reacts readily with *s*-BuCl and lithium wire under sonication to form the ylid which may be quenched with benzophenone to give alkene **25** in 87% isolated yield (equation 9).

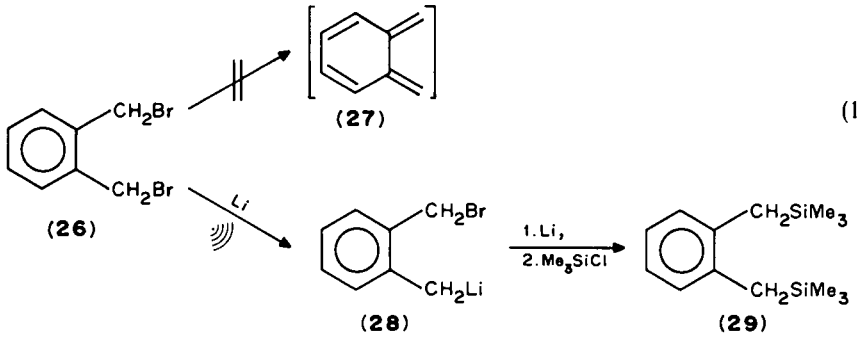
Significant rate enhancements are produced by ultrasound when a number of substrates are treated with lithium (Table 1)[34].



(24) (25) (9)

The reaction of α,α′-dibromo-*o*-xylene (**26**) with lithium is interesting because it does not lead to *o*-xylylene (**27**), the major product when zinc is used[35], but to the ionic intermediate **28** which is trapped as α,α′-bis(trimethylsilyl)-*o*-xylene (**29**) when chlorotrimethylsilane is present (equation 10).

Ultrasound may also be used to couple organic halides in the presence of lithium wire[36]. Alkyl, aromatic, benzylic and benzoyl halides have been successfully coupled in good yields using lithium wire suspended in thf. For chlorobenzene sonication for 12 h is required to give a 70% yield of biphenyl. This type of reaction has been extended to chlorosilanes and chlorostannanes[37], while under similar conditions chlorotriphenylsilane (**30**) can be coupled using lithium dispersed in oil. A catalytic amount of anthracene is added to promote the reaction (equation 11).



(10)

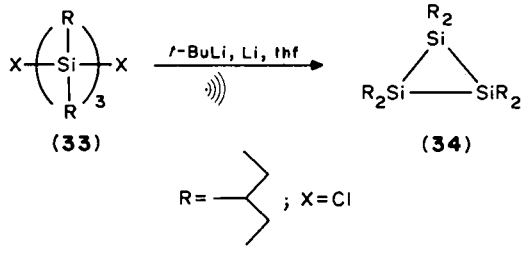
$$Ph_3SiCl \xrightarrow[\text{)))}]{\text{Li, thf}} Ph_3SiSiPh_3 \qquad (11)$$

(30) 73%

The sonochemical reaction of lithium with simple dichlorosilanes (**31**) gives high yields of cyclopolysilanes (**32**) and the hexa-alkyldichlorosilanes (**33**) react with *t*-BuLi, lithium, and naphthalene in a mixture of thf and pentane under sonication to give cyclic trisilanes such as **34** (equations 12 and 13)[38].

$$R_2SiCl_2 \xrightarrow[\text{)))}]{\text{Li}} (R_2Si)_n \qquad (12)$$

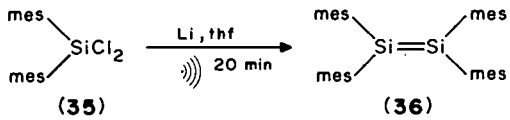
(31) (32) 70–95%



(13)

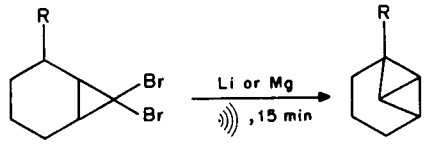
When a solution of **35** in thf is irradiated with ultrasonic waves in the presence of lithium wire, a yellow colour is produced immediately, and within 20 min all of the **35** and most of the lithium is consumed. Thereafter the highly substituted tetramesityldisilene (**36**) is isolated in 90% yield (equation 14)[39].

The use of low-intensity ultrasound also leads to increased yields and a reduction in reaction time from 48 to 6 h in the preparation of tris(phenyldimethylsilyl)methane[40].



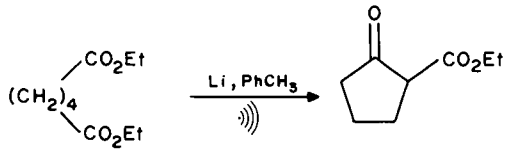
(14)

Lithium, sodium, or magnesium metal are also involved in the generation of cyclopropylidenes (**38**) from *gem*-dihalopropanes (**37**) under the influence of ultrasound[41]. The use of metals to generate carbenoids is well known, as is their subsequent rearrangement into allenes or insertion into C—H bonds. Under sonochemical conditions cyclopropylidenes are generated without induction periods in reasonable yields; the solvent is found to be important, with thf being superior to *n*-pentane (equation 15).



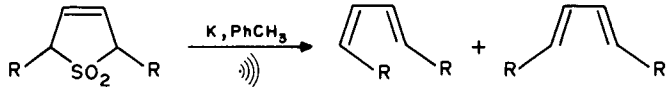
(37) (38) (15)

A number of reports have indicated that in certain instances potassium is superior to other alkali metals in ultrasonic reactions. Potassium, suspended in dry toluene under argon at 10 °C, forms a fine suspension of metal on ultrasonic treatment[42] (no such suspension is observed using thf as solvent). When diethyl adipate (**39**) in toluene is added, rapid cyclization occurs and ethyl 2-oxocyclopentane carboxylate is obtained (equation 16). No similar reaction occurs with lithium or sodium sands.



(39) (16)

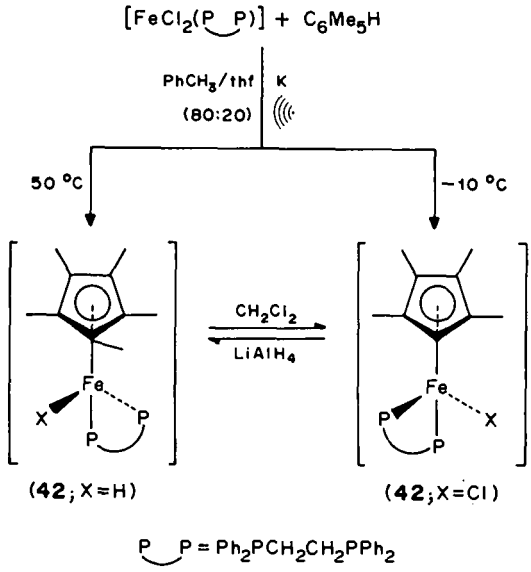
Similarly, ultrasonically dispersed potassium promotes the extrusion of SO_2 from di- and tri-substituted 3-sulpholenes (**40**) to give the corresponding dienes (**41**) stereoselectively[43] (equation 17). Ultrasonically dispersed potassium is also effective in reactions of some brominated hydrothiophene *S,S*-dioxides[44].



(40) (41) (17)

A one-step synthesis of the organometallic [Fe(C_5Me_5) (dppe)X] (**42**) starting from C_5Me_5H, 1,2-bis(diphenylphosphino)ethane (dppe), and potassium under ultrasonic activation has been described[45]. When the reaction is carried out at −10 °C the chloro compound **42** (X = Cl) is obtained in 50% yield, whereas at 50 °C the new iron hydride **42** (X = H) is isolated. Treatment of **42** (X = Cl) with $LiAlH_4$ gives **42** (X = H) and the reverse reaction may be carried out in CH_2Cl_2 (Scheme 6).

Ultrasound can also accelerate the reductive cleavage of phosphorus—carbon bonds using lithium metal[46]. The procedure provides a clean source of dialkylphosphide anions (**44**) from dialkylphenylphosphine (**43**). These anions may be subsequently alkylated with a variety of haloalkanes (equation 18).



SCHEME 6

$$R^1R^2PPh \xrightarrow[)))]{Li,\ thf} R^1R^2P^-Li^+ \xrightarrow{E^+} R^1R^2PE \qquad (18)$$

(43) (44) 70–85%

Dialkylphosphines (**46**) may also be prepared from the reaction of **45** with an alkali metal, under ultrasonic irradiation, followed by alkylation[47] (equation 19).

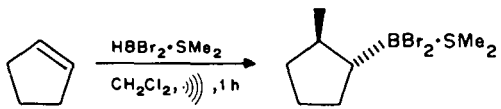
$$Ph_2P(CH_2)_nPPh_2 \xrightarrow[2.\ RX]{1.\ Na,\ thf,\ )))} RPhP(CH_2)_nPPhR \qquad (19)$$

(45) $n = 2$–6 (46)

Treatment of diphenyldiselenide with sodium metal in thf under sonication conveniently produces a suspension of sodium phenylselenide[48]. Transfer by syringe or cannula allows further reactions with sulphonates, halides, and epoxides.

3. Boron

Most organoboranes are readily available from the desired olefins by facile hydroboration. However, some important organoboranes require either long reaction periods or prolonged heating to achieve reasonable yields. Ultrasound dramatically enhances the rates of many slow heterogeneous hydroborations and has a modest accelerating effect on slow homogeneous hydroborations[49]. Alkyldibromoboranes (**47**) are usually prepared by



(20)

(47)

hydroboration of alkenes with $HBBr_2 \cdot SMe_2$. These hydroborations normally require 5–12 h at room temperature or 4–6 h at 40 °C. The application of ultrasound achieves the required reaction in 1–2 h (equation 20).

Brown and Racheria[50] reported the use of ultrasound in the preparation of symmetrical trialkylboranes such as Pr^n_3B and hindered $(1\text{-naphthyl})_3B$. The former is obtained in higher purity than from normal hydroboration. The synthesis of triorganylboranes directly from organic halides with or without ultrasound is not a very effective process. However, such boranes can be prepared in a rapid and quantitative manner by reaction of organic halides with a mixture of magnesium and boron trifluoride diethyrate under ultrasound. In this instance the appropriate Grignard reagent is formed, first, *in situ* (equation 21).

$$3RX \xrightarrow[Et_2O,\ ))),\ 15\text{–}30\,min]{Mg,\ BF_3 \cdot Et_2O} R_3B \qquad (21)$$

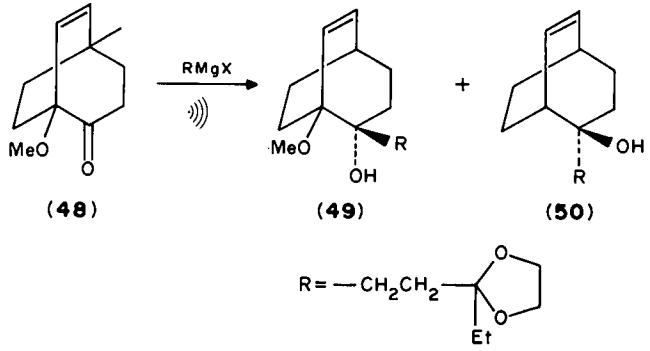
90–100%

4. Magnesium

The effect of ultrasound on the preparation of organomagnesium reagents was first reported by Luche and Damiano[26]. Their results indicated that ultrasound did not significantly affect the rate of formation of the organometallic. However, a later study[51] investigated the effects of absorbed water and alcohol on the magnesium surface. It was found that with standard anhydrous diethyl ether, application of ultrasound markedly reduces the time required for initiation. Even in diethyl ether with larger amounts of water and alcohol, ultrasonic waves promote initiation in less than 8 min. The reaction is not purely thermal but a result of the ultrasound removing the surface-adsorbed water or alcohol. Sonication does not, however, significantly alter yields.

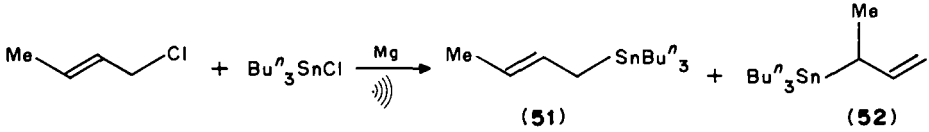
The kinetics of the formation of *n*-butylmagnesium bromide in toluene in the presence of diethyl ether with ultrasonic irradiation have been studied[52]. Under sonication the induction period is reduced considerably and reaction rate greatly increased. The rate constant of the slow step, in particular, is nearly doubled. The dependence of the reaction rate on the molar ratio of diethyl ether and the yield of Grignard reagent do not change under the influence of ultrasound.

An example of a positive effect of ultrasound on a Grignard reaction has been described[53]. Sonication of a solution of ketone **48** with three equivalents of the Grignard reagent derived from 2-(2-bromoethyl)-2-ethyl-1, 3-dioxolane in thf at 25 °C for 1.5 h gives a mixture of isomeric tertiary alcohols **49** and **50** in a combined yield of 93% (equation 22). In the absence of ultrasound the Grignard reaction is slow and gives only a 61% yield.



(48) (49) (50) (22)

The cross-coupling of allylic chlorides with tri-*n*-butyltin chloride, in the presence of magnesium, is promoted by ultrasound[54]. The predominant products are *trans*- or *trans*, *trans*-allystannanes (**51**). In some cases the rearranged olefin **52** is obtained (equation 23).



(**51**) (**52**)

(23)

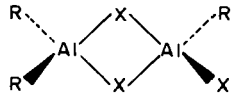
5. *Aluminium*

Organoaluminium compounds prepared from aluminium and mono- and polyhaloalkanes, alkenes, and cycloalkenes are formed only if the aluminium is previously irradiated ultrasonically[55]. Thus, treating allylic bromide **53** with activated aluminium in dioxan gives a 73% yield of **54** (equation 24).

$$3MeCH{=}CHCH_2Br \xrightarrow{\text{Al, dioxane}} (CH_2{=}CHCHMe)_3Al_2Br_3 \qquad (24)$$

(**53**) (**54**)

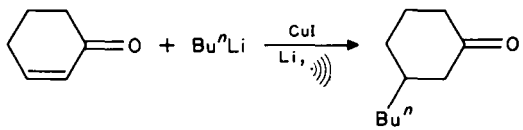
Liou *et al.*[56] found that, with the application of ultrasound, the formation of ethylaluminium sesquibromide (**55**) from ethyl bromide and aluminium could be efficiently achieved within 20 min at room temperature. Similarly, methyl iodide and aluminium powder, when irradiated with ultrasound, form methylaluminium sesquiiodide, which can be subsequently treated with triethylaluminium to give trimethylaluminium in 86% yield and 95% purity[57]; triethylaluminium etherate has also been prepared in this way[58].



(**55**) (R = Et; X = Br)

6. *Transition metals (copper, zinc, manganese)*

Organocopper reagents are notoriously difficult to prepare and react consistently with carbonyls and α, β-unsaturated carbonyls. Formation of organocopper reagents has been shown[59] to occur with remarkable ease using alkyl or aryl halides and ultrasonic irradiation. These lithium organocuprates react *in situ* with enones to give high yields of β-alkylated ketones (equation 25).



90%

(25)

One of the difficulties with organocopper reagents is their thermal instability, but the development of an ultrasonic route to organozinc reagents has now overcome this problem. Reaction of a haloalkane[60,61] with lithium forms an organolithium intermediate which is then converted by *trans*-metallation into an organozinc compound (equation 26).

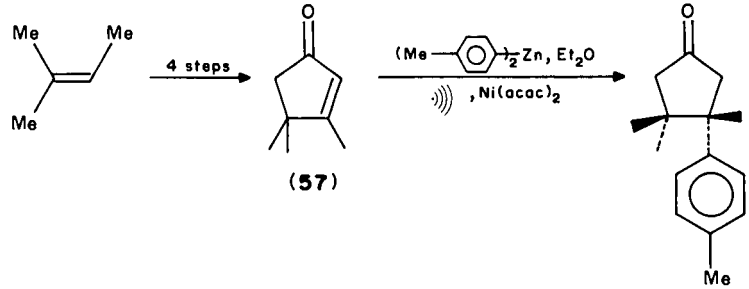
$$RX + Li \xrightarrow{))))} RLi \xrightarrow{ZnBr_2} R_2Zn \qquad (26)$$

Further reactions of this type indicate that temperature, reactive site, and solvents all have to meet specific requirements for successful reaction. Thus, the ultrasonically accelerated reaction of the dialkylzinc derivative **56** with an enone is catalysed by $[Ni(acac)_2]$ in toluene–thf (85:15) solvent mixture (equation 27)[62,63].

$$RX + Li + ZnBr_2 \xrightarrow[))))\text{, 10 min, 0 °C}]{\text{PhMe–thf}} R_2Zn \cdot n LiX \xrightarrow[[Ni(acac)_2]]{\text{enone}} \text{adduct} \qquad (27)$$

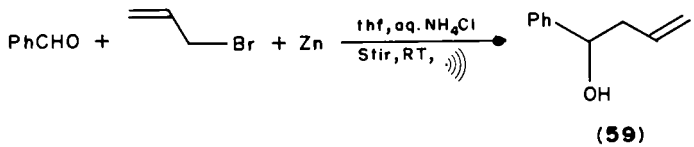
(56)

The synthesis of β-cupranone (**58**) from 2-methylbut-2-ene via the enone **57** using an organozinc intermediate is illustrative[64] of the synthetic potential of such ultrasonic reactions (equation 28). Whereas the enone **57** proved resistant to several copper-assisted conjugate addition techniques for the introduction of the *p*-tolyl group, nickel acetylacetonate-catalysed conjugate addition of di-*p*-tolylzinc (lithium, $C_7H_7Br \cdot ZnBr_2$, diethyl ether, ultrasonic irradiation) proceeded smoothly to give **58** in 67% yield.



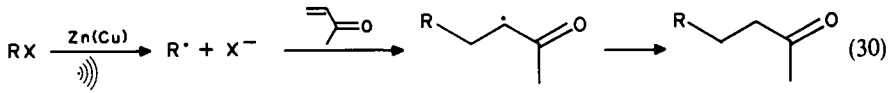
(28)

An unexpected reaction occurs when allylic halides are stirred in the presence of zinc and aldehydes or ketones in aqueous media[65]. Stirring a suspension of benzaldehyde with alkyl bromide and zinc powder in 5 ml of distilled water and 1 ml of thf for 4 h at room temperature produces 1-phenylbut-3-en-1-ol (**59**) in 48% yield. When the solvent system contains saturated aqueous ammonium chloride instead of water, a quantitative yield of **59** is obtained. Use of ultrasound alone leads to reduced yields of **59** (equation 29).



(29)

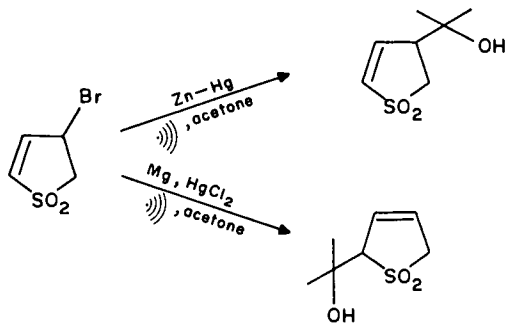
When the reaction is performed using metallic tin instead of zinc under sonication in a water–thf mixture, the desired rearranged homoallylic alcohol is obtained[66] in slightly better yields than with activated zinc and stirring. Also of interest is the fact that aldehydes undergo preferential allylation in the presence of ketones by both the tin- and zinc-mediated method. This early work indicated that the reaction is limited to the addition of allylic groups only and that use of saturated alkyl halides left the reactants, including the metal, unchanged. However, this lack of reactivity has been overcome[67] by alloying the zinc with copper. Surprisingly, such reactions run in anhydrous solvents gave poor results whereas in water without organic solvent a virtually quantitative yield of adduct was obtained. The authors suggested that, in this instance, a free organometallic species is highly improbable and that a radical pathway is most likely (as shown in equation 30).



(30)

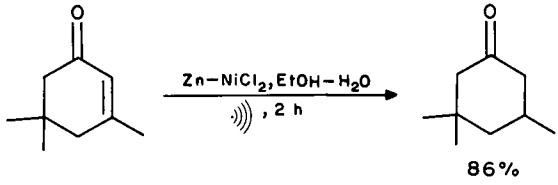
The stereochemical implications of selective allylation of carbonyl compounds in aqueous media have also been discussed[68]. Allylic halides, tin, and aldehydes or ketones in the presence of mannitol or camphoric acid (as chiral inductors) with sonication failed to induce any asymmetry even when the chiral auxiliaries were used in high concentrations. Nevertheless, important improvements in yields are obtained from reactions involving water-soluble carbonyl compounds and, further, there is no need to protect functional groups (such as OH) which are normally incompatible with organometallic reagents.

An interesting difference in regioselectivity occurs in the reaction of 3-bromo-2,3-dihydrothiophene *S*,*S*-dioxide with acetone in the presence of metals and ultrasound[69]. With zinc amalgam, reaction occurs at the 3-position whereas the use of magnesium provides a 2-substituted product (equation 31).



(31)

Use of allylzinc compounds under ultrasonic conditions has been reported in the synthesis of functionalized 1,4-dienes by addition to alkynes with further cyclization to heterocycles and carbocycles[70]. Although not strictly organometallic, an aqueous zinc–nickel chloride system has been used[71] in the ultrasonically improved selective reduction of α,β-unsaturated carbonyl compounds (equation 32).



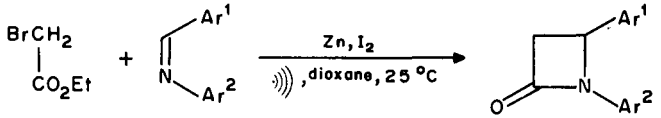
(32)

Other organometallic reactions involving zinc have shown remarkable enhancements when irradiated with ultrasound[72]. The Reformatsky reaction is a generally applicable method for converting aldehydes and ketones to β-hydroxy esters. When mixtures of zinc dust, ethyl bromoacetate, and aldehydes or ketones are irradiated at room temperature with ultrasound for 5–30 min, 90–100% yields of the β-hydroxy esters are obtained (equation 33). Since the reaction is run at room temperature, no dehydrated products are obtained and isolation and purification of the product are simplified.

$$R_2C{=}O + BrCH_2CO_2Et + Zn \xrightarrow[5\text{–}30\,min]{))),\ dioxane} R_2C(OH)CH_2CO_2Et \qquad (33)$$

94–100%

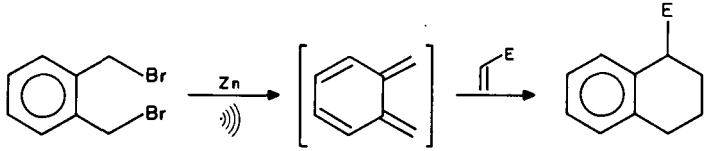
A related modification of this reaction is to utilize an imine (Schiff's base) instead of a ketone[73]. Under the usual conditions ethyl bromoacetate, zinc, and the Schiff base yield only 25–50% of β-lactam but sonication for 4–6 h at room temperature gives a 70–95% yield of the desired β-lactam (equation 34). This type of reaction has been extended to give a stereoselective β-lactam synthesis[74].



(34)

70–95%

When α,α'-dibromo-*o*-xylene (**60**) and zinc powder are irradiated with ultrasonic waves at room temperature in the presence of dienophiles, high yields of cycloaddition products (**60**) are obtained (equation 35)[35]. The reactive intermediate, *o*-xylylene (**27**), is generated *in situ*.

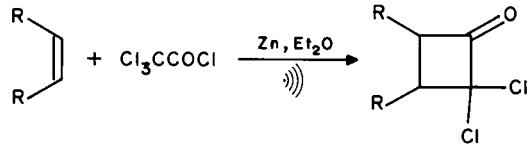


(35)

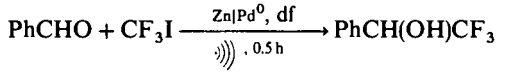
(**26**) (**27**) (**60**)

The Simmons–Smith cyclopropanation does not proceed unless the zinc is first activated[75]. This is normally accomplished by forming zinc–copper or zinc–silver couples and/or by employing iodine or lithium. Even the reaction of zinc with diiodomethane tends to show a delayed exotherm, which can be especially violent with large-scale preparations. Ultrasonic irradiation also activates zinc to such an extent that its reaction with diiodomethane proceeds rapidly but smoothly to give, in the presence of olefins, high yields of cyclopropanated products[75]. Dibromomethane is less expensive and easier to purify and store than diiodomethane and gives yields comparable to CH_2I_2 reactions when ultrasonicated with zinc, copper(I) bromide and the required alkene in diethyl ether[76]. The (2 + 2) cycloaddition of dichloroketene, generated ultrasonically from trichloroacetyl chloride and zinc, to alkenes provides a direct route into cyclobutanones (equation 36)[77].

A number of ultrasonic reactions have been described in which perfluoroalkyl groups in the presence of zinc add to a variety of functional groups. Trifluoromethylation of carbonyl compounds with trifluoromethylzinc generated *in situ* is readily achieved using dimethylformamide as solvent[78] (equation 37).

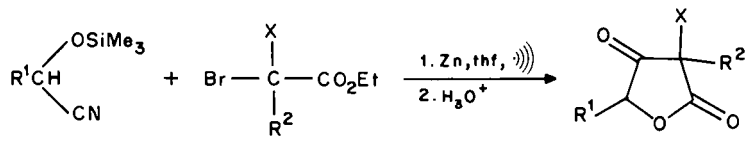


(36)

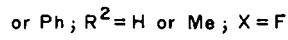


(37)

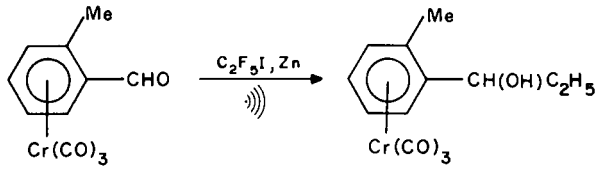
Fluorinated β-keto-γ-butyrolactones are obtained from the ultrasonically mediated cyclization of trimethylsilyl cyanohydrins with fluorinated α-bromoesters in thf in the presence of zinc (equation 38)[79]. Without ultrasound there is no evidence of any reaction.



(38)



Ultrasound has also been shown to promote asymmetric induction with perfluoroalkyl groups by reaction of perfluoroalkyl halides with optically active enamines in the presence of zinc powder and dichlorobis(η^5-cyclopentadienyl)titanium[80]. Similarly, a 30–60% asymmetric induction is obtained during the addition of perfluoroalkyl iodide on a chiral arene–chromium tricarbonyl complex (**61**) using ultrasonically dispersed zinc at room temperature to give both enantiomers of the perfluoroalkylarylcarbinols (**62**) (equation 39)[81].



(39)

(**61**) (**62**)

Perfluoroalkylzinc iodide, generated ultrasonically from zinc and the corresponding perfluoralkyl iodide, has been shown to react with a variety of functional groups[82–85]. These reactions include the palladium-catalysed cross-coupling reactions with allyl, vinyl, or aryl halides (equation 40)[82], the copper iodide-catalysed hydroperfluoroalkylation of alkynes (equation 41)[83], and the ultrasonic-promoted direct carboxylation of perfluoroalkyl iodides (equation 42)[84,85].

A closely related reaction is the preparation of perfluoroalkyl compounds using perfluoroalkyl-manganese or -silver complexes under ultrasound irradiation. The organometallic compounds are useful as potential Grignard-type perfluoroalkylating agents[86]. Perfluoroalkyl alcohols may also be prepared by carrying out a Barbier reaction of fluorinated aldehydes with alkyl or allyl Grignard reagents generated *in situ* with ultrasound (equation 43)[87].

$$CH_2{=}CH_2 + CF_3ZnI \xrightarrow[)))]{Pd} \underset{CF_3}{\overset{I}{\diagup\!\!\diagdown}} \qquad (40)$$

$$R_fI + RC{\equiv}CH \xrightarrow[2.H_3O^+]{1.Zn,CuI,thf,\ ))))} R\diagup\!\!\diagdown\!\!\sim R_f \qquad (41)$$

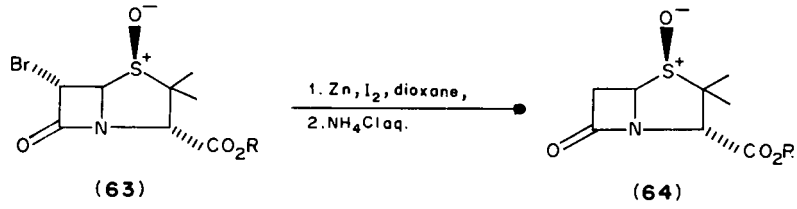
$$F_3C(CF_2)_nI \xrightarrow[)))]{Zn,CO_2} F_3C(CF_2)_nCOOH \quad 75\% \qquad (42)$$

$$CF_3CHO + RX \xrightarrow[2.\ H_3O^+]{1.\ Mg,\ ))))} CF_3CH(R)OH \qquad (43)$$

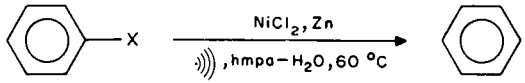
Aldehydes are readily methylenated with zinc–diiodomethane and ultrasonic irradiation. Benzaldehyde is converted to styrene in 70% yield in 20 min but ketones give poor yields (equation 44)[88].

$$PhCHO + CH_2I_2 \xrightarrow[)))\ ,RT]{Zn,\ thf} PhCH{=}CH_2 \quad 70\% \qquad (44)$$

Zinc in conjunction with ultrasound has made possible the reduction of certain organic halides. The penicillanate ester **64**, used as an intermediate in the synthesis of a β-lactamase inhibitor, is readily prepared by debromination of the 6-bromopenicillanate ester **63** with zinc (equation 45)[89]. The usual debrominating agents such as Bu^n_3SnH or $Pd/C–H_2$ are less effective and more expensive. Ultrasound also facilitates the reductive dehalogenation of aromatic halides with nickel chloride and zinc in aqueous hmpa (equation 46)[90].

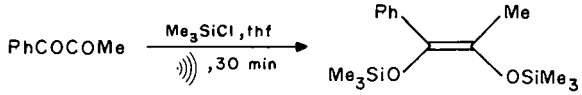


(63) (64) (45)



X = Cl, Br, I (46)

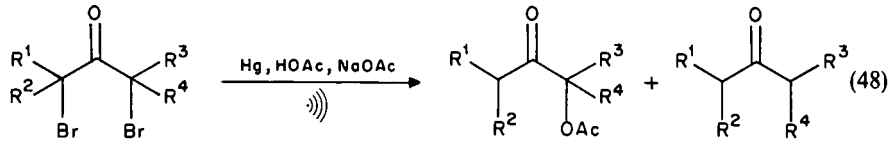
The reductive silylation of diketones with Me_3SiCl and zinc in diethyl ether or thf is significantly accelerated by ultrasound[91]. Thus, the *Z*-silylated compound **66** is prepared from the diketone **65** in 73% yield in less than 30 min with ultrasonic irradiation but in only 45% yield in 3 h without ultrasound (equation 47).



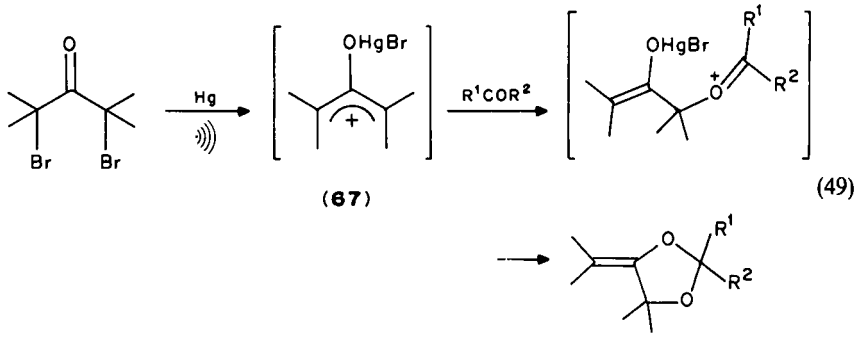
(65) (66) (47)

7. *Mercury*

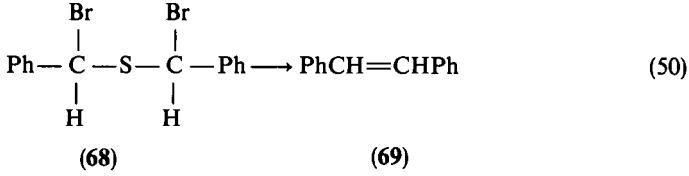
A seminal publication on the use of ultrasound with metals involves the reduction of α,α′-dibromoketones with mercury. In this instance the mercury is dispersed using an ultrasonic cleaner and no reaction occurs in the absence of ultrasound (equation 48)[92,93].



When a similar reaction is carried out in aliphatic ketones as solvent the intermediate is converted into 4-isopropylidene-1,3-dioxolanes (equation 49)[94].



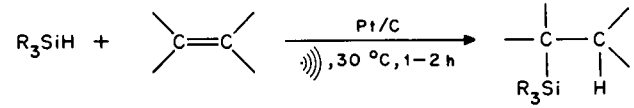
The intermediate **67** can be trapped by other nucleophiles such as alcohols[95]. Ultrasonically dispersed mercury is also utilized in the reduction of the dibromosulphide **68** to *trans*-stilbene (**69**) in excellent yield (equation 50)[96].



(68) **(69)**

B. Catalytic Reactions

It is common practice to activate catalysts prior to hydrogenation reactions but the use of ultrasonic irradiation produces even better results[97]. With continuous irradiation the palladium-catalysed hydrogenation of olefins with formic acid is completed in 1 h whereas in the absence of ultrasound the reactions normally require 2–3 h or heating at 80 °C. The hydrogenation of alkenes can also be achieved with ultrasound using hydrazine in conjunction with Pd/C in ethanol[98]. Further, ultrasonic waves dramatically increase the activity of a Pt/C catalyst in the hydrosilylation of alkenes and alkynes[99]. Prior to the use of ultrasound such reactions required a platinum catalyst at 100–300 °C and pressures of silylating agent of 45–115 psi. However, ultrasound allows the reaction to occur at 30 °C and at atmospheric pressure (equation 51).



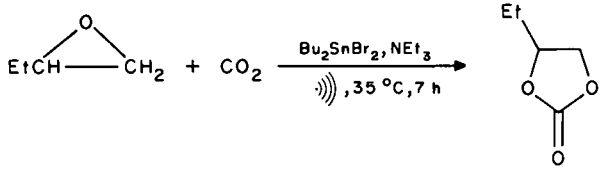
(51)

A number of other heterogeneous catalytic reactions enhanced by ultrasound have been reported. The activity of platinum black, obtained by reduction of chloroplatinic acid with hydrogen under ultrasonic conditions, is higher than that obtained under normal conditions[100]. For the synthesis of ammonia from aqueous mixtures of N_2 and H_2 ultrasound gives 2–6 times higher yields in the presence of platinum, rhodium, or palladium black[101]. Much of the early Russian work on the effect of ultrasound on heterogeneous catalysts and heterogeneous catalytic reactions has been reviewed[102].

Ultrasonic irradiation of nickel powder increases its activity as a hydrogenation catalyst by more than 10^5 as a result of altering the particle aggregation, surface morphology, and thickness of the surface coating[103]. Simple nickel powder is an inactive catalyst for the hydrogenation of alkenes but if it is first irradiated with ultrasound for 1 h hydrogenation of alkenes is rapid and independent of the alkene structure. No reduction of aldehydes or ketones is observed.

Powdered coal is liquefied by hydrogenation with Cu/Zn in the presence of ultrasound[104]. The products include coal gas (24%), light oil (58%), and heavy oil (14%), which compare with 15, 30 and 40%, respectively, in the absence of ultrasound. Alkenes are more efficiently hydroformylated using a two-phase system with a rhodium catalyst. The use of ultrasound increases the efficiency and turnover[105].

Organotin and organoantimony halides catalyse the reaction of carbon dioxide with epoxides[106]. Ultrasound accelerates this reaction giving a 70% total yield of the cyclic carbonate **70** compared with only 46% without ultrasound (equation 52).

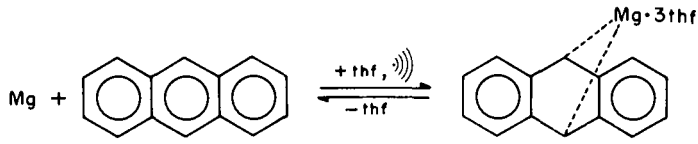


(52)

(70)

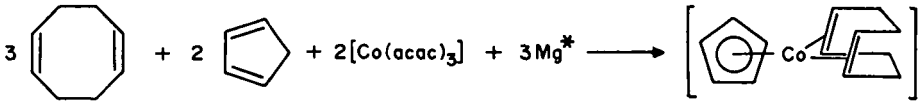
C. Reactive Metals

A more recent use of ultrasound in organometallic chemistry is the production of highly reactive metals often by reduction of transition metal salts. These metal powders have very high surface areas and a large number of surface dislocations, which ensure that the metal is extremely reactive. In addition, the use of ultrasound ensures efficient mass transport to and from the metal surface, and constant cleaning and erosion of the metal. Starting from the observation that addition of a catalytic amount of anthracene to magnesium powder in thf produces the highly reactive organically solvated complex **71** when the mixture is irradiated with low-intensity ultrasound, a simple preparative route to transition metal complexes has been devised[107]. This method (equation 53) allows magnesium powder to be used for the reductive synthesis of all preparatively important transition metal complexes.

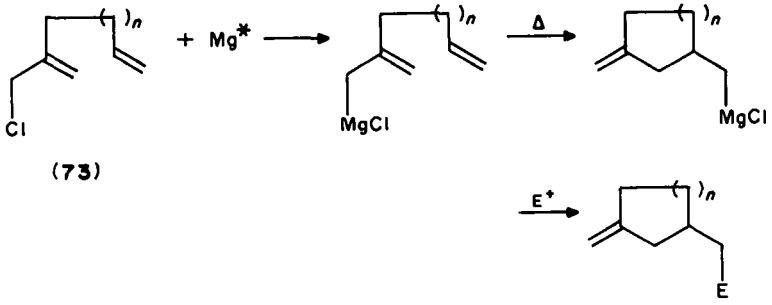


(71) (53)

Complex **71** can be considered to be a source of highly reactive Mg*, which may be utilized in the synthesis of [(cod)CoCp] complex **72** (equation 54)[107] and in the metallo-ene reaction of (2-alkenylallyl)magnesium chlorides (**73**) (equation 55)[108].



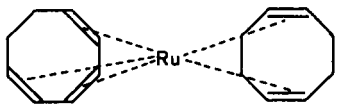
(72) (54)



(73) (55)

Ultrasound also greatly accelerates the lithium reduction of a variety of metal halides to metal powders[109]. Highly reactive metallic zinc, magnesium, chromium, copper, nickel, palladium, cobalt and lead can be prepared by reduction of the metal halide with lithium or potassium under ultrasonic irradiation for less than 40 min. Corresponding reductions without ultrasound require stirring for at least 12 h. The reactivities of these metal powders are significantly greater than those of commercially available powders and appear to rival those produced by the Rieke method[110]. The ultrasonically produced powders show enhanced reactivity in the Reformatsky and Ullman coupling reactions. In the latter case the effectiveness of the coupling of benzyl bromide to bibenzyl is not solely dependent on the powder itself but also on the presence of iodide salts[109]. Improvements in Ullmann coupling reactions are also observed[111] when commercial copper-bronze in dmf is ultrasonicated at 60 °C. Ullmann coupling of aryl sulphonates to biaryls is also catalysed by low-valent nickel complexes generated *in situ* from nickel(II) chloride, PPh_3, sodium iodide and zinc powder under ultrasonic irradiation in dmf[112].

Reduction of ruthenium chloride with zinc dust[113] in the presence of cycloocta-1,5-diene with sonication produces the ruthenium complex **74** in 93% yield. Using an alternative non-ultrasonic method the yield of **74** is only 35%.



(74)

The use of high-intensity ultrasound dramatically enhances the reactivity of transition metal dispersions[114]. The preparation of transition metal carbonyl complexes from the bulk metal is difficult and high pressures of carbon monoxide and high temperatures are normally required. However, the use of ultrasonic irradiation facilitates the reduction of a variety of transition metal salts to such an active form that they react readily with carbon monoxide at low pressures to form simple carbonyl anions. Carbonyl complexes of tungsten, molybdenum, chromium, tantalum, niobium, and vanadium are prepared by sonication of the corresponding chlorides for 100 min with excess sand in thf in the presence of a CO atmosphere. The yields vary from 6 to 54% using 4.4 atm of CO.

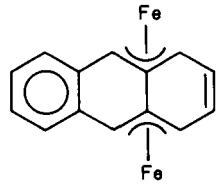
V. MISCELLANEOUS REACTIONS

The intercalation of organic or inorganic molecules into layered inorganic hosts is very slow. Syntheses are often lengthy (weeks) and require elevated temperatures. In the intercalation with organometallic guest molecules the use of ultrasound significantly increases the rates of intercalation reactions[115,116]. Table 2 shows the comparison of thermal and sonochemical conditions for the synthesis of $(guest)_x$ host. The mechanism does not involve enhanced mass transport but, rather, the ability of the ultrasound to generate very small particles.

TABLE 2. Comparison of thermal and sonochemical conditions for intercalation reactions

$(Guest)_x$ host	Thermal	Sonochemical
$(Cp_2Co)_{0.25}ZrS_2$	50 h, 20 °C	2 h, 20 °C
$(Bu^nNH_2)_{0.46}TaS_2$	50 h, 20 °C	15 min, 20 °C
(Pyridine) MoO_3	30 days, 180 °C	3 days, 80 °C

The synthesis using ultrasound of a new diiron–anthracene complex is a rare example of an ultrasonic reaction leading to a product unobtainable via traditional chemistry[117]. When $[Fe_2(CO)_9]$ and an excess of anthracene are suspended in *n*-hexane at −20 °C and subjected to ultrasound for 12 h, two products can be isolated, $[Fe_3(CO)_{12}]$ and the orange complex $[(C_{14}H_{10})Fe_2(CO)_6]$. X-ray crystal data indicate that the 'sawhorse' $Fe_2(CO)_6$ fragment is μ, η^3, η^3-bound to the anthracene, which may be regarded as being divided into two with an isolated carbon—carbon double bond at one end and a benzene ring at the other (**75**).



(75)

VI. CONCLUSION

Ultrasound has become an extremely useful and important technique for the synthetic chemist. Most chemical reactions have their rates enhanced by ultrasonic irradiation, but it is in the area of organometallic chemistry where the most impressive reactions have been

observed. The theory behind the effect of ultrasound on these reactions is only now being developed, although comprehensive studies are hampered by the number of effects involved, particularly at metal surfaces. Metals are altered in a number of ways: particle size is reduced, surface defects are exaggerated, and oxide or impurity layers are rapidly removed. Other contributions include increased mass transport of reactants, cavitation, and generation of considerable local heat. The effects of ultrasound have been compared to that obtained from flash photolysis, photochemistry, and radiolysis but, as research continues, many unique ultrasonic reactions are being discovered and soon ultrasound will be as accepted as these techniques in the chemist's armoury.

VII. REFERENCES

1. A. Shoh, in *Kirk–Othmer Encyclopaedia of Chemical Technology*, 3rd ed., Vol. 23, Wiley, New York, 1983, p. 462.
2. (a) B. Brown and J. E. Goodman, *High Intensity Ultrasonics—Industrial Applications*, Van Nostrand, Princeton, 1965; (b) A. P. Cracknell, *Ultrasonics*, Wykeham, London, 1980; (c) I. E. El'Piner, *Ultrasound: Physical, Chemical, and Biological Effects*, translated by F. L. Sinclair, Consultants Bureau, New York, 1964; (d) M. J. Blandamer, *Introduction to Chemical Ultrasonics*, Academic Press, New York, 1973; (e) P. Boudjouk, *Nachr. Chem. Tech. Lab.*, **31**, 797 (1983); (f) D. Bremner, *Chem. Br.*, **22**, 633 (1986); (g) K. S. Suslick, in *Modern Synthetic Methods*, (Ed. R. Scheffold), Springer, Berlin, 1986, p. 1. (h) K. S. Suslick, *Adv. Organomet. Chem.*, **25**, 73 (1986); (i) A. Henglein, *Ultrasonics*, **25**, 6 (1987); (j) J. P. Lorimer and T. J. Mason, *Chem. Soc. Rev.*, **16**, 239 (1987); (k) J. Lindley and T. J. Mason, *Chem. Soc. Rev.*, **16**, 275 (1987).
3. See ref. 2g for a more comprehensive description of reactor design and configuration.
4. W. T. Richards and A. L. Loomis, *J. Am. Chem. Soc.*, **49**, 3086 (1927).
5. C. W. Porter and L. Young, *J. Am. Chem. Soc.*, **60**, 1497 (1938).
6. I. Miyagawa, *J. Soc. Org. Synth. Chem.*, **7**, 167 (1949); *Chem. Abstr.*, **47**, 4831e (1953).
7. W. H. Staas and L. A. Spurlock, *J. Chem. Soc., Perkin Trans. 1*, 1675 (1975).
8. E. C. Couppis and G. E. Klinzing, *AIChE J.*, **20**, 485 (1974).
9. D. S. Kristol, H. Klotz, and R. C. Parker, *Tetrahedron Lett.*, **22**, 907 (1981).
10. J. P. Lorimer and T. J. Mason, *J. Chem. Soc., Chem. Commun.*, 1135 (1980).
11. K. S. Suslick, P. F. Schubert, and J. W. Goodale, *J. Am. Chem. Soc.*, **103**, 7342 (1981).
12. K. S. Suslick, J. W. Goodale, P. F. Schubert, and H. H. Wang, *J. Am. Chem. Soc.*, **105**, 5781 (1983).
13. A. M. Horton, D. M. Hollingshead, and S. V. Ley, *Tetrahedron*, **40**, 1737 (1984).
14. K. S. Suslick and P. F. Schubert, *J. Am. Chem. Soc.*, **105**, 6062 (1983).
15. K. S. Suslick, J. J. Gawienowski, P. F. Schubert, and H. H. Wang, *J. Phys. Chem.*, **87**, 2299 (1983).
16. S. V. Ley, C. M. R. Low, and A. D. White, *J. Organomet. Chem.*, **302**, C13 (1986).
17. D. Rehorek and E. G. Janzen, *J. Organomet. Chem.*, **268**, 135 (1984).
18. K. Imi, K. Imai, and K. Utimoto, *Tetrahedron Lett.*, **28**, 3127 (1987).
19. P. Renaud, *Bull. Soc. Chim. Fr., Ser. 5*, **17**, 1044 (1950).
20. W. Slough and A. R. Ubbelohde, *J. Chem. Soc.*, 918 (1957).
21. See refs 26 and 35.
22. M. W. T. Pratt and R. Helsby, *Nature (London)*, **184**, 1694 (1959).
23. T. Azuma, S. Yanagida, H. Sukarai, S. Sasa, and K. Yoshino, *Synth. Commun.*, **12**, 137 (1982).
24. T. Fujita, S. Watanabe, K. Suga, K. Sugahara, and T. Katsuya, *Chem. Ind. (London)*, 167 (1983).
25. K. Sjoberg, *Tetrahedron Lett.*, 6383 (1966).
26. J.-L. Luche and J. C. Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980).
27. J. C. de Souza-Barbosa, J.-L. Luche, and C. Petrier, *Tetrahedron Lett.*, **28**, 2013 (1987).
28. C. Petrier, A. L. Gemal, and J.-L. Luche, *Tetrahedron Lett.*, **21**, 3361 (1980).
29. J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, **27**, 1791 (1986).
30. J. Einhorn and J.-L. Luche, *Tetrahedron Lett.*, **27**, 1793 (1986).
31. J.-L. Luche, *Ultrasonics*, **25**, 40 (1987).
32. B. M. Trost and B. P. Coppola, *J. Am. Chem. Soc.*, **104**, 6879 (1982).
33. J. Einhorn and J.-L. Luche, *J. Org. Chem.*, **52**, 4124 (1987).

34. P. Boudjouk, P. Sooriyakumaran, and B.-H. Han, *J. Org. Chem.*, **51**, 2818 (1986).
35. B.-H. Han and P. Boudjouk, *J. Org. Chem.*, **47**, 751 (1982).
36. P. Boudjouk and B.-H. Han, *Tetrahedron Lett.*, **22**, 2757 (1981).
37. P. Boudjouk and B.-H. Han, *Tetrahedron Lett.*, **22**, 3813 (1981).
38. (a) S. Murakami, H. Tobita, and S. Masamune, *J. Am. Chem. Soc.*, **105**, 6524 (1983); (b) S. Masamune, S. Murakami, and H. Tobita, *Organometallics*, **2**, 1464 (1983).
39. P. Boudjouk, B.-H. Han, and K. R. Anderson, *J. Am. Chem. Soc.*, **104**, 4992 (1982).
40. C. Eaborn, P. B. Hitchcock, and P. D. Lickiss, *J. Organomet. Chem.*, **269**, 235 (1984).
41. L. Xu, F. Tao, and T. Yu, *Tetrahedron Lett.*, **26**, 4231 (1985).
42. J.-L. Luche, C. Petrier, and C. Dupuy, *Tetrahedron Lett.*, **25**, 735 (1984).
43. T.-S. Chou and M.-L. Yo, *J. Org. Chem.*, **52**, 2224 (1987).
44. T.-S. Chou and M. M. Chen, *Heterocycles*, **26**, 2829 (1987).
45. C. Roger, P. Marseille, C. Saluts, J.-R. Hamon, and C. Lapinte, *J. Organomet, Chem.*, **336**, C13 (1987).
46. T.-S. Chou, J.-J. Yuan, and C.-H. Tsao, *J. Chem. Res. (S)*, 18 (1985).
47. T.-S. Chou, C.-H. Tsao, and S. C. Hung, *J. Org. Chem.*, **50**, 4329 (1985).
48. S. V. Ley, I. A. O'Neil, and C. M. R. Low, *Tetrahedron*, **42**, 5363 (1986).
49. H. C. Brown and U. S. Racheria, *Tetrahedron Lett.*, **26**, 2187 (1985).
50. H. C. Brown and U. S. Racheria, *Tetrahedron Lett.*, **26**, 4311 (1985).
51. J. D. Sprich and G. S. Lewandos, *Inorg. Chim. Acta*, **76**, L241 (1983).
52. A. Tulmets, M. Horak, and K. Kaubi, *Org. Reactivity*, **23**, 397 (1986).
53. T. Ugehara, J. Yamada, T. Furuta, and T. Kato, *Chem. Lett.*, 609 (1986).
54. Y. Nurata, Y. Nishigaichi, and K. Maruyama, *Chem. Lett.*, 1857 (1986).
55. A. V. Kuchin, R. A. Nurushev, and G. A. Tolstikov, *Zh. Obshch. Khim.*, **53**, 2519 (1983); *Chem. Abstr.*, **100**, 103426f (1984).
56. K. F. Liou, P. H. Yang, and Y. T. Lin, *J. Organomet. Chem.*, **294**, 145 (1985).
57. P. H. Yang, K. F. Liou, and Y.-T. Lin, *J. Organomet. Chem.*, **307**, 273 (1986).
58. Y.-T. Lin, *J. Organomet. Chem.*, **317**, 277 (1986).
59. J.-L. Luche, C. Petrier, A. L. Gemal, and N. Zikra, *J. Org. Chem.*, **47**, 3805 (1982).
60. J.-L. Luche, C. Petrier, J. P. Lansard, and A. H. Greene, *J. Org. Chem.*, **48**, 3837 (1983).
61. C. Petrier, J. C. de S. Barbosa, C. Dupuy, and J.-L. Luche, *J. Org. Chem.*, **50**, 5761 (1985).
62. C. Petrier, J.-L. Luche, and C. Luche, *Tetrahedron Lett.*, **25**, 3463 (1984).
63. J. C. de S. Barbosa, C. Petrier, and J.-L. Luche, *Tetrahedron Lett.*, **26**, 829 (1985).
64. A. E. Greene, J. P. Lansard, J.-L. Luche, and C. Petrier, *J. Org. Chem.*, **49**, 931 (1984).
65. C. Petrier and J.-L. Luche, *J. Org. Chem.*, **50**, 912 (1985).
66. C. Petrier, J. Einhorn, and J.-L. Luche, *Tetrahedron Lett.*, **26**, 1449 (1985).
67. C. Petrier, C. Dupuy, and J.-L. Luche, *Tetrahedron Lett.*, **27**, 3149 (1986).
68. C. Einhorn and J.-L. Luche, *J. Organomet. Chem.*, **322**, 177 (1987).
69. H.-H. Tso, T. Chou, and S. C. Hung, *J. Chem. Soc. Chem. Commun.*, 1552 (1987).
70. P. Knockel and J. F. Normant, *J. Organomet. Chem.*, **309**, 1 (1986).
71. (a) C. Petrier and J.-L. Luche, *Tetrahedron Lett.*, **28**, 2347 (1987); (b) C. Petrier and J.-L. Luche, *Tetrahedron Lett.*, **28**, 2351 (1987).
72. B.-H. Han and P. Boudjouk, *J. Org. Chem.*, **47**, 5030 (1982).
73. A. K. Bose, K. Gupta, and M. S. Manhas, *J. Chem. Soc., Chem. Commun.*, 86 (1984).
74. N. Oguni, T. Tomago, and N. Nagata, *Chem. Express*, 495 (1986); *Chem. Abstr.*, **106**, 13814y (1986).
75. O. Repic and S. Vogt, *Tetrahedron Lett.*, **23**, 2729 (1982).
76. E. C. Friedrich, J. M. Domek, and R. Y. Pong, *J. Org. Chem.*, **50**, 4640 (1985).
77. G. Mehta and H. S. P. Rao, *Synth. Commun.*, **15**, 991 (1985).
78. T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1679 (1981).
79. T. Kitazume, *Synthesis*, 855 (1986).
80. T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, **107**, 5186 (1985).
81. A. Solladie-Cavallo, D. Farkhani, S. Fritz, T. Lazrak, and J. Suffert, *Tetrahedron Lett.*, **25**, 4117 (1984).
82. T. Kitazume and N. Ishikawa, *Chem. Lett.*, 137 (1982).
83. T. Kitazume and N. Ishikawa, *Chem. Lett.*, 1453 (1982).
84. N. Ishikawa, M. Takahashi, T. Sato, and T. Kitasume, *J. Fluorine Chem.*, **22**, 585 (1983).
85. I. Hemer, J. Havlicik, and V. Dadek, *J. Fluorine Chem.*, **34**, 241 (1986).

86. T. Kitazume and N. Ishikawa, *Nippon Kagaku Kaishi*, 1725 (1984); *Chem. Abstr.*, **102**, 131228c (1984).
87. N. Ishikawa, M. G. Koh, T. Kitazume, and S. K. Choi, *J. Fluorine Chem.*, **24**, 419 (1984).
88. J. Yamashita, Y. Inoue, T. Kondo, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **57**, 2335 (1984).
89. J. Brennan and F. H. S. Hussain, *Synthesis*, 749 (1985).
90. J. Yamashita, Y. Inoue, T. Kondo, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **58**, 2709 (1985).
91. P. Boudjouk and J. Ho So, *Synth. Commun.*, **16**, 775 (1986).
92. A. J. Fry and D. Herr, *Tetrahedron Lett.*, **19**, 1721 (1978).
93. A. J. Fry and G. S. Ginsburg, *J. Am. Chem. Soc.*, **101**, 3927 (1979).
94. A. J. Fry, G. S. Ginsburg, and R. A. Parente, *J. Chem. Soc., Chem. Commun.*, 1040 (1978).
95. A. J. Fry and S. S. Hong, *J. Org. Chem.*, **46**, 1962 (1981).
96. A. J. Fry, K. Ankner, and V. Hana, *Tetrahedron Lett.*, **22**, 1791 (1981).
97. P. Boudjouk and B.-H. Han, *J. Catal.*, **79**, 489 (1983).
98. D. H. Shin and B.-H. Han, *Bull. Korean Chem.* Soc., **6**, 247 (1985).
99. B.-H. Han and P. Boudjouk, *Organometallics*, **2**, 769 (1983).
100. W.-C. Li, A. N. Mal'tsev, and N. I. Kobozev, *Zh. Fiz. Khim.*, **38**, 439 (1964); *Chem. Abstr.*, **60**, 13916 (1964).
101. A. N. Mal'tsev and I. V. Solov'eva, *Zh. Fiz. Khim.*, **44**, 1092 (1970); *Chem. Abstr.*, **73**, 39022 (1970).
102. A. N. Mal'tsev, *Zh. Fiz. Khim.*, **50**, 16412 (1976); *Chem. Abstr.*, **85**, 182827k (1976).
103. K. S. Suslick and D. J. Casadonte, *J. Am. Chem. Soc.*, **109**, 3459 (1987).
104. M. Nakanishi, Jpn. Pat., 81, 127 684 (1981); *Chem. Abstr.*, **96**, 71736n (1982).
105. B. Cornils, H. Bahrmann, W. Lipps, and W. Konkol, *Ger. Offen. D. E.*, 3 511 428 (1986); *Chem. Abstr.*, **106**, 52105q (1987).
106. A. Ninagawa, T. Suzuki, and H. Matsuda, *Chem. Express*, 169 (1986); *Chem. Abstr.*, **106**, 50089p (1987).
107. H. Bonnemann, B. Bogdanovic, R. Brinkman, D. W. He, and B. Spliethoff, *Angew. Chem., Int. Ed. Engl.*, **22**, 728 (1983).
108. W. Oppolzer and P. Schneider, *Tetrahedron Lett.*, **25**, 3305 (1984).
109. P. Boudjouk, D. P. Thompson, W. H. Ohrbom, and B.-H. Han, *Organometallics*, **5**, 1257 (1986).
110. R. D. Rieke, *Acc. Chem. Res.*, **10**, 301 (1977).
111. J. Lindley, J. P. Lorimer, and T. J. Mason, *Ultrasonics*, **24**, 292 (1986).
112. Y. Inoue, J. Yamashita, Y. Kondo, and H. Hashimoto, *Nippon Kagaku Kaishi*, 197 (1987); *Chem. Abstr.*, **107**, 197686 (1987).
113. K. Itoh, N. Nagashima, T. Ohshima, N. Ohshima, and N. Nishiyama, *J. Organomet. Chem.*, **272**, 179 (1984).
114. K. S. Suslick and R. E. Johnson, *J. Am. Chem. Soc.*, **106**, 6856 (1984).
115. K. S. Suslick, D. J. Casadonte, M. L. H. Green, and M. E. Thompson, *Ultrasonics*, **25**, 56 (1987).
116. K. Chatakondo, M. L. H. Green, M. E. Thompson, and K. S. Suslick, *J. Chem. Soc., Chem. Commun.*, 900 (1987).
117. M. J. Begley, S. G. Puntambekar, and A. H. Wright, *J. Chem. Soc., Chem. Commun.*, 1251 (1987).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER **2**

The photochemistry of organometallic compounds

CONOR LONG

School of Chemical Sciences, National Institute for Higher Education, Dublin 9, Ireland

I. INTRODUCTION

The photochemistry of organometallic compounds continues to be an important area of research because of the wide variety of chemical transformations which can be photoinduced. Indeed, many such transformations can be achieved at low temperatures, and this permits the study of compounds which are thermally unstable. However, the particular

techniques required to induce these reactions are not those which are normally available to the experimental organic chemist, and for the most part photochemical methods remain exotic. The purpose of this chapter is to outline some of the reaction types that can be achieved photochemically, and to indicate the present theories as to their mode of operation. As a result, this chapter is not intended to be a comprehensive review of the photochemistry of organometallic chemistry, but rather to outline the general reactivity of a range of organometallic compounds and attempts to classify the types of reactions which can be photoinduced. For a comprehensive treatment of the area of organometallic photochemistry the reader is referred to the reviews of the topic which will be cited here, and also the excellent book by Geoffroy and Wrighton[1].

The chapter is divided into two sections. The first deals with the photochemistry of the various classes of organometallic compounds, from metal carbonyls to compounds containing metal to metal bonds, and describes the general photochemistry observed for these systems. The second part outlines some classes of reactions which can be photoinduced. In particular, those reactions which induce a change in the organic moiety on the metal will be discussed, and this rather than the nature of the metal will form the basis of the classification. Those reactions which simply result in ligand-exchange processes will not be covered, even though such reactions may be of fundamental importance to the understanding of organometallic photochemistry.

II. THE PHOTOCHEMISTRY OF COMPOUND TYPES

A. The Photochemistry of Metal Carbonyl Compounds

One of the most widely studied areas of organometallic photochemistry is that of the metal carbonyl compounds. Indeed, it was with the mononuclear metal carbonyls that the early workers realised the considerable photosensitivity of this class of compound[2]. In general, the primary photoinduced reaction of metal carbonyls involves the monodecarbonylation process (reaction 1)[3].

$$[M(CO)_x] \xrightarrow{h\nu} [M(CO)_{x-1}] + CO \qquad (1)$$

Although such a reaction has little importance as far as the transformation of organic ligands is concerned, its importance lies in the high quantum efficiency of these processes[4], and also in the reactive nature of the decarbonylated complex[5]. The high quantum efficiency can be explained in simple terms by examining the nature of the bonding between the metal and the carbon monoxide ligand (Fig. 1). From a simplified molecular orbital diagram it can be seen that the highest occupied orbital set are principally the metal-based t_{2g} orbital sub-set, and the lowest unoccupied orbitals are strongly antibonding with respect to the σ-interaction of the carbonyls. The photoinduced promotion of an electron from the t_{2g} orbital sub-set to the σ^* orbital removes electron density from those orbitals contributing to the back-bonding interaction (Fig. 2) and populates an orbital which is strongly antibonding with respect to the carbonyl σ interaction. The net result of this is the efficient labilization of the metal–carbonyl interaction.

One such system which has received considerable attention is that of the Group 6 hexacarbonyls[5-10]. These studies have indicated that the coordinatively unsaturated metal pentacarbonyl species produced following photolysis of the parent hexacarbonyl is capable of binding relatively inert compounds such as alkanes[9,10] and also dinitrogen[11]. It is the exceptional reactivity of the 16-electron species that makes their study of such importance to many transformations of organic materials such as olefin isomerization and hydrogenation (see Section III.C). Indeed, picosecond flash photolysis studies on

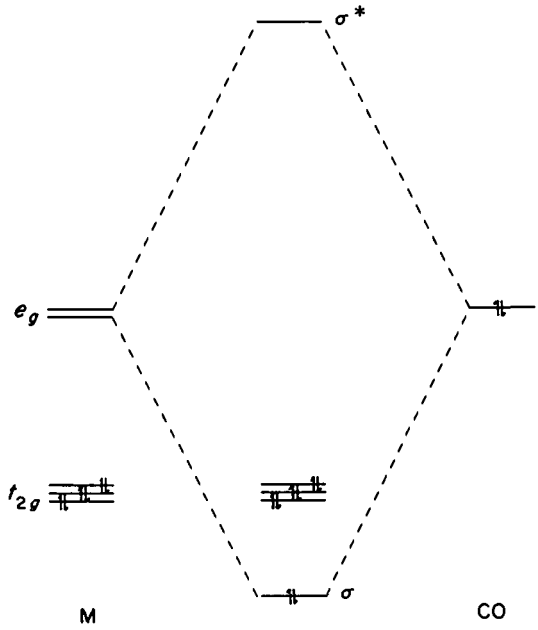


FIGURE 1. A simplified molecular orbital energy diagram indicating the interaction of a carbon monoxide molecule with a d^6 metal

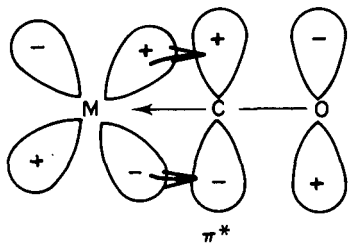


FIGURE 2. Diagrammatic representation of the interaction of a carbonyl ligand with a metal centre

$[Cr(CO)_6]$ indicated that the expulsion of the carbon monoxide ligand occurs within 25 ps of excitation[5]. The reactivity of the metal pentacarbonyl complex has been investigated by flash photolysis[10] and liquified noble gas techniques[11]. $[Cr(CO)_5]$ has been shown to react with carbon monoxide, dinitrogen and alkanes with rate constants which approach the diffusion-controlled limit.

Vibrational spectra of the $[M(CO)_5]$ species (M = Cr, Mo, or W) in low-temperature matrices confirmed that they have square pyramidal symmetry[12,13]. The significant spectral differences observed for the $[M(CO)_6]$ and $[M(CO)_5]$ species in the ultraviolet–visible region can be explained in terms of the simplified energy level diagram (Fig. 3)[14]. The lowest energy absorption band has been assigned to the $^1A_1(e^4b_2^2) \rightarrow {}^1E(e^3b_2^2a_1^1)$ transition. In a low-temperature matrix the reverse carbonylation of the $[M(CO)_5]$ species can be photoinduced (reaction 2)[15], but the quantum efficiency of the

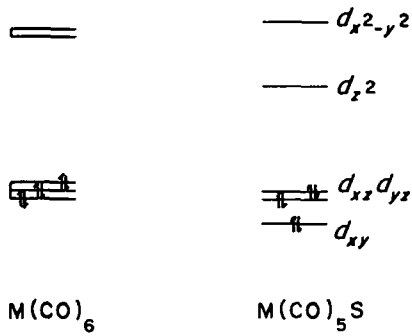


FIGURE 3. An energy level diagram for both a Group 6 metal hexacarbonyl and a monosubstituted derivative of a Group 6 metal carbonyl

forward and reverse reactions depends on the nature of the isolating matrix. This suggests that the isolating material affects the efficiency of the reverse photochemical reaction and further highlights the considerable reactivity of the coordinatively unsaturated $[M(CO)_5]$ species.

$$[M(CO)_6] \xrightarrow{h\nu} [M(CO)_5] + CO \tag{2}$$

The photochemistry of monosubstituted derivatives of the Group 6 hexacarbonyls is strongly influenced by the nature of the unique ligand. In compounds such as $[M(CO)_5L]$ (L = pyridine or substituted pyridine), the direction and efficiency of the photochemical processes depend on the electronic nature of any substituent on the pyridine ring system[16]. For substituents which do not affect the energy of the π^* orbital on the pyridine ligand, the lowest energy transition is thought to be principally a metal-centred ligand-field transition. Population of the ligand-field state in these materials tends to result in the efficient photoexpulsion of the unique ligand. In the case of substituents which lower the π^* orbital energy, the lowest energy transition assumes some metal-to-ligand charge-transfer character (MLCT). In general, population of MLCT states in organometallic compounds results in photochemical reactions of low quantum efficiency.

The photochemistry of other mononuclear carbonyls has also been investigated, and in particular an excellent review of the photochemistry of $[Fe(CO)_5]$ has been published[17]. Low-temperature matrix photochemistry of $[Fe(CO)_5]$ indicated that $[Fe(CO)_4]$ is formed efficiently, and this species is assumed to have a ground-state triplet configuration. $[Fe(CO)_4]$ is less reactive to alkanes than is $[Cr(CO)_5]$[18,19]. Nickel carbonyl also exhibits considerable carbonyl photolability, and its photochemistry has been studied in the gas phase[20], in solution[21], and in low-temperature matrices[22]. The quantum yield for the decarbonylation of nickel carbonyl is high, but does exhibit some variation with excitation wavelength, being 0.22 at 366 nm and 0.5 at 240 nm[23]. The matrix isolation experiments confirm that the structure of $[Ni(CO)_3]$ has C_{3v} symmetry.

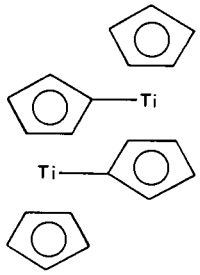
B. The Photochemistry of Metal Alkyl Compounds

1. Simple metal alkyls which do not contain carbonyl groups

The photochemistry of simple metal alkyl systems continues to attract interest principally because of the thermal stability of the metal—carbon bond. Alkyl groups which contain no β-hydrogens have no low-energy route to thermal decomposition.

However, photochemical reactions of such compounds do present interesting templates for mechanistic studies. In this section, the principal photoreactions of some simple metal alkyls will be introduced. Again, this is by no means a comprehensive treatment of the topic[1,24].

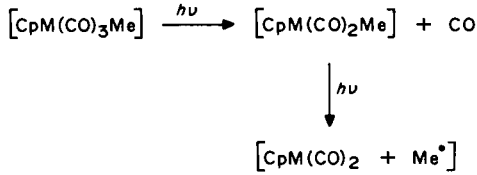
The analysis of the gaseous alkane products formed following photolysis of $[Cp_2Ti(CH_3)_2]$ indicated the formation of methane[25]. It is tempting to suggest that this reaction involves a simple homolytic cleavage of the metal—carbon bond, producing free methyl radicals which can abstract a hydrogen atom from the solvent to produce methane. However, analysis of the metal-containing product of this reaction indicated that the complex had a dimeric structure (**1**)[26]. Deuteration studies confirmed that the hydrogen abstraction occurred exclusively from the Cp ring[27,28]. Such studies indicate that the product observed following homolytic cleavage of a metal—carbon bond reflects the stability of the radical species produced, and have their ability to escape from the radical pair cage. As a further example, photolysis of $[AgBu^n(PBu^n)_3]$ produced principally but-1-ene, presumably via a β-hydrogen elimination reaction process (see Section III.B), but also significant amounts of butane and octane[29]. The octane is produced as the result of the combination of two butane radicals which have escaped the radical pair cage. These experiments indicate that while homolytic cleavage of the metal—carbon bond usually results following irradiation of metal alkyl compounds, the nature of the products depends on the stability of the radicals produced.



(**1**)

2. *Metal alkyl compounds containing carbonyl groups*

Photolysis of metal alkyls containing carbonyl groups usually results in carbonyl expulsion as the primary photochemical reaction. However, photolysis of $[CpM(CO)_3Me]$ (M = Cr, Mo, or W) produced methane as the gaseous product[30]. The methane production probably arises from a secondary photochemical reaction, possibly involving the dicarbonyl compound (Scheme 1)[31], or perhaps a dimeric species formed by



SCHEME 1

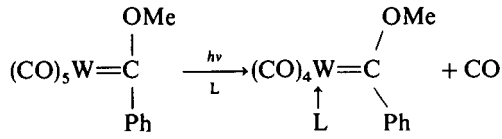
the reaction of the dicarbonyl with the parent tricarbonyl compound. Such a dimerization has been observed following photolysis of the isoelectronic $[CpMn(CO)_3]$ complex[32]. One example of an apparent homolytic cleavage of the metal—carbon bond following irradiation of a metal alkyl compound containing carbonyl ligands is obtained from the photochemical reactions of $[Os(CO)_4Me_2]$[33]. In this case the methane is assumed to arise from the homolytic cleavage of the metal—carbon bond, followed by hydrogen abstraction from the alkene solvent.

C. The Photochemistry of Metal Carbene Compounds

The interest in the photochemistry of metal carbene compounds lies not in the photochemistry of the carbene chromophore, but rather in the chemistry induced following loss of other ligands such as carbonyls from metal carbene complexes. For instance, the ultraviolet–visible absorption spectrum of $[M(CO)_5$ (carbene)] (M = Cr, Mo, or W) exhibits an intense band near 400 nm[34–37], with a shoulder on the high-energy side. This band is thought to have a considerable MLCT character, and in general such transition do not induce efficient photochemical processes. The shoulder, however, is thought to arise from a ligand-field (LF) transition and population of this state induces a decarbonylation reaction (reaction 3).

$$[M(CO)_5(C(OMe)Ph)] \xrightarrow{h\nu} [M(CO)_4\{C(OMe)Ph\}] + CO \qquad (3)$$

The quantum efficiency of this reaction is low ($\Phi = 0.01$–0.02) and this presumably results from the efficient internal conversion from the LF to the inactive MLCT state. In the presence of an entering ligand (L), the *cis*-substituted product is formed following photolysis (reaction 4)[36].

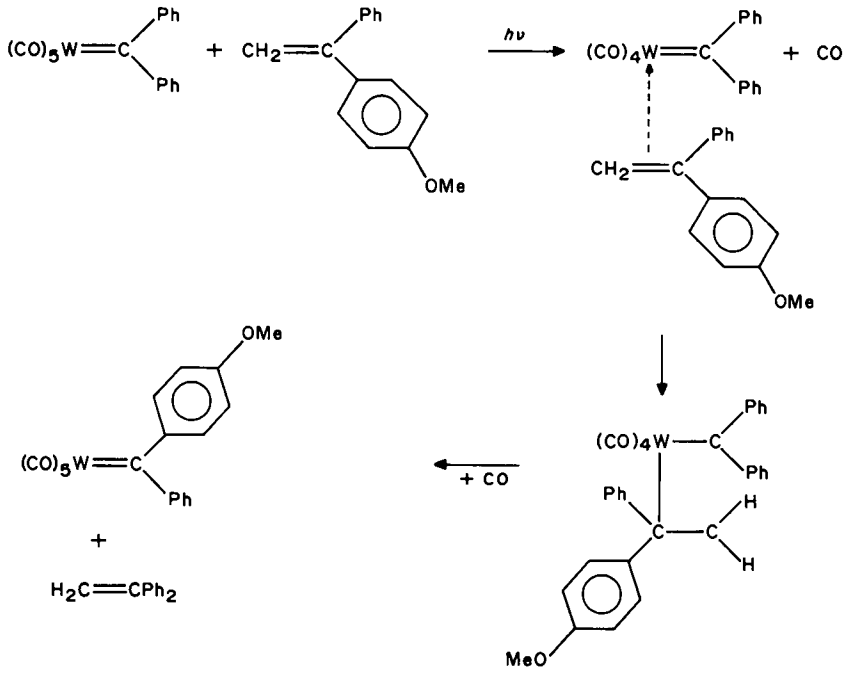


(4)

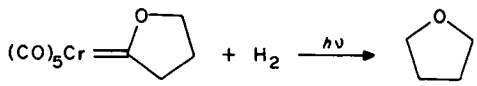
The vacant coordination site *cis* to the carbene moiety provides an ideal environment for thermal chemistry of the carbene with added ligands. One such example is given in Scheme 2[37], in which metathesis of the olefinic species is observed. Also in the presence of dihydrogen the hydrogenation of the carbenic ligand can occur, although in low yield[38]. As a result, photolysis of **2** under a hydrogen atmosphere produced principally tetrahydrofuran (reaction 5). Interestingly, the synthesis of β-lactams has also been reported following photolysis of chromium carbene complexes in the presence of imines (reaction 6)[39].

D. The Photochemistry of Carbyne Compounds

The photoinduced reactions of metal carbynes has not attracted a great deal of attention[24]. Their chemistry is dominated by the presence of a low-energy MLCT transition which in general has a relatively long lifetime[40]. Population of this MCLT state has been shown to induce protonation of the carbyne ligand[41], carbyne rearrangement[42], and also photoinduced carbonylation[43,44]. For instance, photolysis of the carbyne **3** results ultimately in the formation of **4**[44]. The proposed mechanism is outlined in Scheme 3.

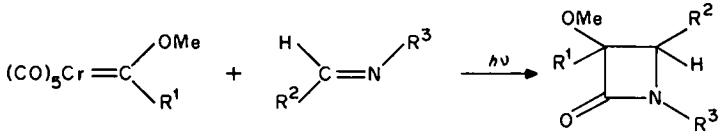


SCHEME 2



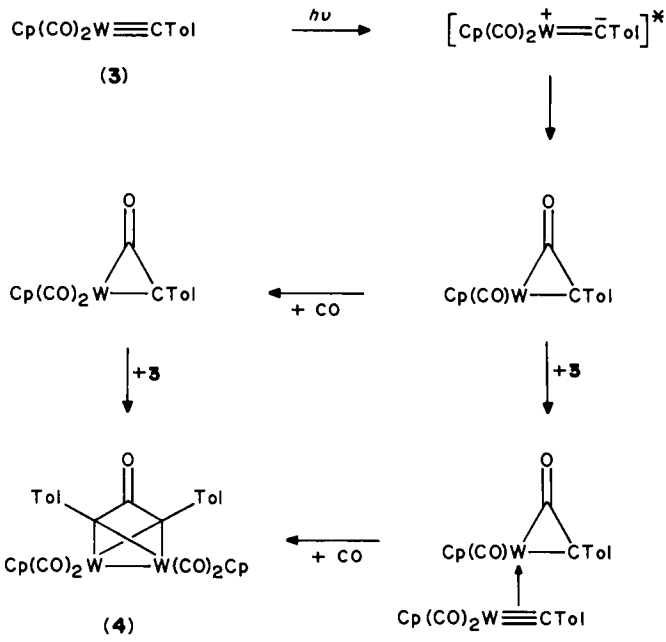
(5)

(2)

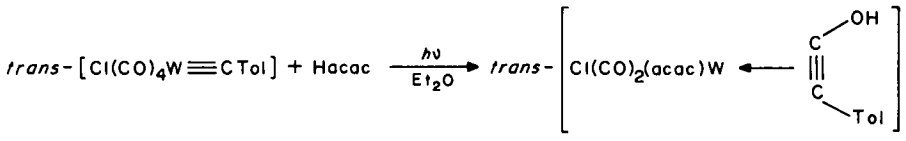


(6)

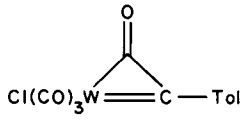
These results may be useful in elucidating the mechanism for the photoinduced conversion of a carbyne to the hydroxyalkyne derivative (reaction 7)[45]. Such a reaction may involve the formation of the η^2-ketenyl intermediate **5**, which ultimately yields the hydroxyalkyne compound.



SCHEME 3



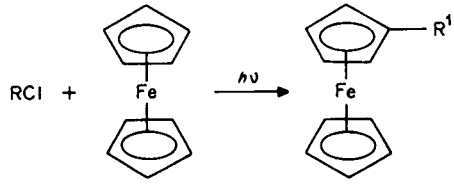
(7)



(5)

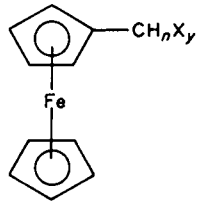
E. The Photochemistry of Cyclopentadienyl-containing Compounds

The photolysis of $[Cp_2Fe]$ in halocarbon–ethanol mixtures induces substitution into the Cp ring and formation of $[Cp_2FeCl]$ (reaction 8)[46-48]. The reaction is thought to proceed via the initial photochemical formation of the halocarbonsubstituted ferrocenè derivative **6** followed by ethanolysis (Scheme 4). There has been a great deal of interest in the photochemistry of substituted ferrocene derivatives and, in general, the chemistry of these systems simply involves the normal photochemistry of the substituent groups. However, the ferrocene moiety can influence the observed chemistry if the organic



(8)

$R = CCl_3, CHCl_2, CH_2Cl$; $R^1 = CO_2Et, CHO, CH_2OEt$

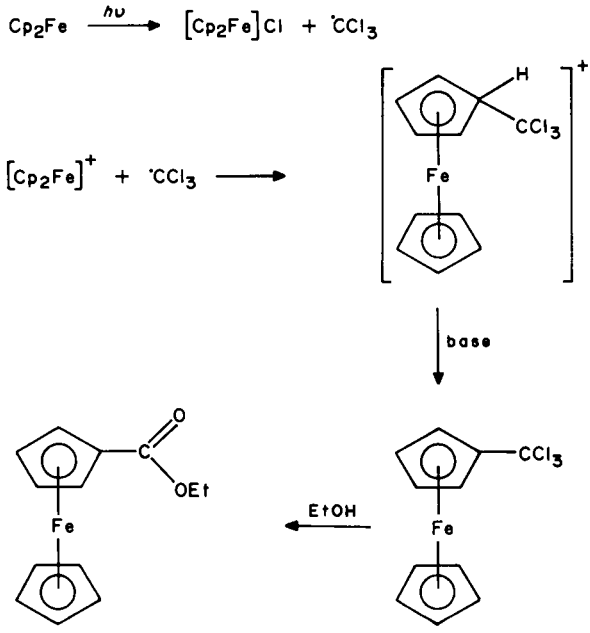


(6)

$n = 0, 1, 2$

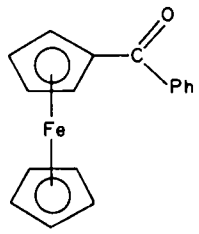
$Y = 1, 2, 3$

X = halogen



SCHEME 4

chromophore can be conjugated with the cyclopentadienyl ring. For instance, the photochemistry of 7, which is the ferrocene derivative of benzophenone, does not undergo the transformation to the pinicol derivative[49].



(7)

F. The Photochemistry of Compounds Containing Metal to Metal Bonds

A typical example of a simple compounds containing a metal to metal bond is $[Mn_2(CO)_{10}]$. The near-ultraviolet absorption of this compound exhibits polarization along the M—M bond axis and is assigned to a σ–σ^* transition[50,51]. In general, irradiation into such bands induced the homolytic cleavage of the M—M bond producing $M(CO)_5^{\cdot}$ species (reaction 9).

$$[Mn_2(CO)_{10}] \xrightarrow{h\nu} 2Mn(CO)_5^{\cdot} \tag{9}$$

The d^7 species thus produced is very substitution labile. This is presumably because of the electron configuration in which the e_g orbital subset is populated (Fig. 4). The d_{z^2}orbital has directed σ^* character with respect to the carbonyl interactions, thus rendering $M(CO)_5^{\cdot}$ labile to ligand substitution processes (Scheme 5)[52].

In the presence of donor solvents such as pyridine, ionic products can be isolated following photolysis of $[Mn_2(CO)_{10}]$. It is tempting to propose a direct heterolytic cleavage of the M—M bond to explain these observations. However, a more complex mechanism involving homolytic cleavage and a 19-electron intermediate is more probably correct (Scheme 6)[53,54].

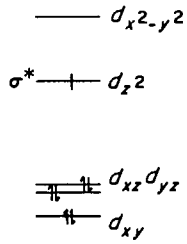


FIGURE 4. A molecular orbital energy diagram for $[Mn(CO)_5^{\cdot}]$ indicating the partial population of a σ antibonding orbital

$$[Mn_2(CO)_{10}] \xrightarrow{h\nu} 2Mn(CO)_5^{\cdot}$$

$$Mn(CO)_5^{\cdot} + L \longrightarrow [Mn(CO)_4L] + CO$$
$$Mn(CO)_5^{\cdot} + [Mn(CO)_4L] \longrightarrow [Mn_2(CO)_9L]$$
$$[Mn(CO)_4L] + [Mn(CO)_4L] \longrightarrow [Mn_2(CO)_8L_2]$$

SCHEME 5

$$[Mn_2(CO)_{10}] \xrightarrow{h\nu} 2Mn(CO)_5^{\cdot}$$

$$Mn(CO)_5^{\cdot} + S \longrightarrow [Mn(CO)_4S] + CO$$
$$[Mn(CO)_4S] + S \longrightarrow [Mn(CO)_3S_2] + CO$$
$$[Mn(CO)_3S_2] + S \longrightarrow [Mn(CO)_3S_3]$$
$$[Mn(CO)_3S_3] + [Mn_2(CO)_{10}] \longrightarrow [Mn(CO)_3S_3]^+ + [Mn_2(CO)_{10}]^-$$
$$[Mn_2(CO)_{10}]^- \longrightarrow [Mn(CO)_5]^- + Mn(CO)_5^{\cdot}$$

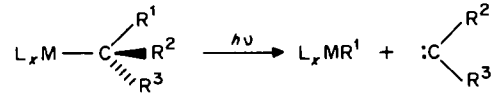
S = amine solvent

SCHEME 6

III. PHOTOCHEMICAL REACTION TYPES

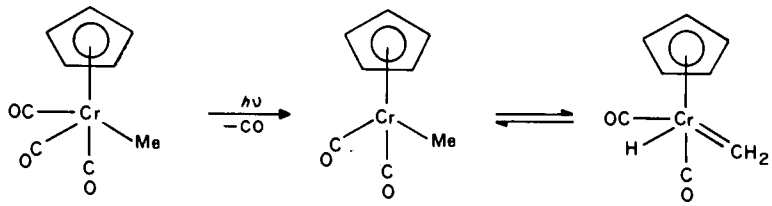
A. α-Elimination Reactions

In general, α-elimination reactions are not very common in organometallic photochemistry. This reaction involves the elimination of a substituent α to the metal atom, producing a carbene fragment which may remain attached to the metal (reaction 10)[55]. There are a few examples of such processes which can be photochemically induced, and these systems have considerable uses in syntheses[56].



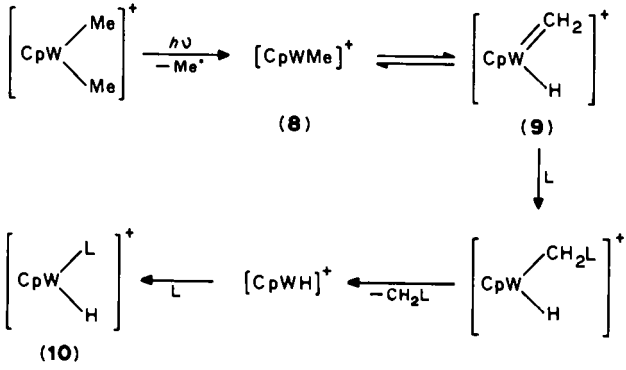
(10)

An α-hydride elimination reaction has been observed following photolysis of $[CpCr(CO)_3(CH_3)]$ in low-temperature matrices (Scheme 7)[57]. Spectroscopic investigations in the carbonyl stretching region of the infrared spectrum indicated that the methylene and hydride ligands are in the *trans* position relative to each other.



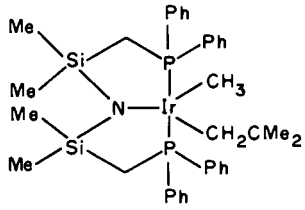
SCHEME 7

A reversible α-hydride transfer is thought to be involved in the photochemistry of $[CpWMe_2][PF_6]$[58]. In this case the primary photoproduct is the coordinatively unsaturated complex **8** which is in equilibrium with the carbene hydride **9** (Scheme 8). The carbene can react with any added ligand (L = PMe_2Ph), ultimately producing the hydride **10**.

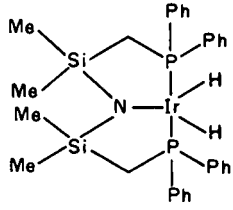


SCHEME 8

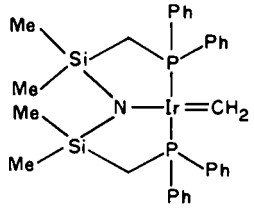
α-Hydrogen elimination can be promoted following irradiation of the iridium(III) dialkyl derivative **11**[59]. Two iridium complexes were isolated from this reaction in the ratio 55:45 (compounds **12** and **13**, respectively), together with 3-methylbut-1-ene and neopentane. X-ray structural information on these materials was also presented[60,61].



(11)



(12)



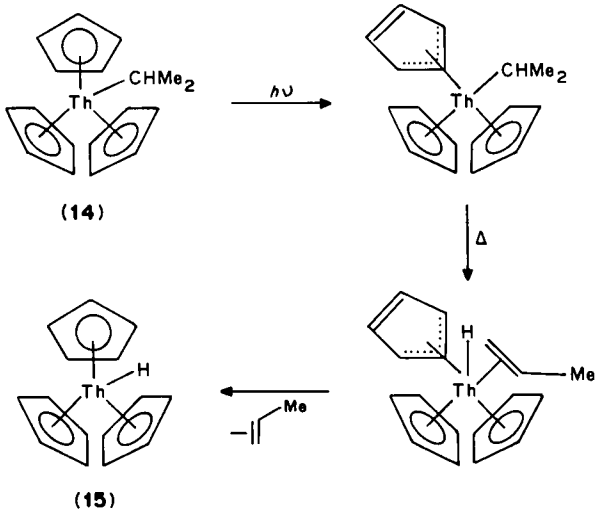
(13)

B. β-Elimination Reactions

There are numerous examples of β-elimination reactions in organometallic photochemistry[55]. The general mechanism is presented in reaction 11.

$$[L_xMCX_2CY_2Z] \xrightarrow{h\nu} [L_xMZ] + X_2C{=}CY_2 \qquad (11)$$

One example of this reaction class involves the irradiation of $[Cp_3ThR]$ (**14**), which exhibits considerable thermal stability ($R = CHMe_2$). Photolysis of this complex results in the formation of $[Cp_3Th]$, propane and prop-1-ene[62,63]. The mechanism proposed involves an initial hapticity change of one of the Cp ligands, following irradiation into the Cp—M charge transfer band. This opens a vacant coordination site on the metal and permits the β-hydride transfer (Scheme 9). The quantum yield of this process was found to be greater than unity, inferring a further reaction of the hydride (**15**) with **14**, liberating the alkene and generating two molecules of $[Cp_3Th]$. The photochemistry of the corresponding $[Cp_3UR]$ compounds also induces β-hydride elimination[62]. However, the mechanism in this case seems to be more complicated than that proposed for the thorium analogue. Here the hydrogen atoms of the Cp ring are susceptible to extraction, as are the hydrogen atoms in the solvent molecules.

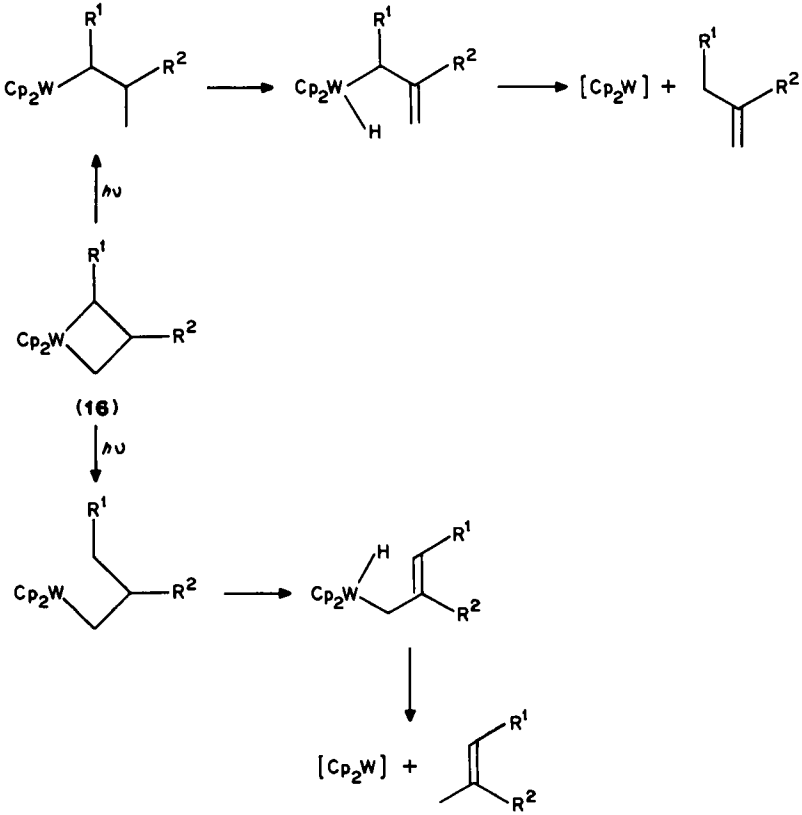


SCHEME 9

Similar β-hydride elimination processes were observed in the photochemical reactions of $[CpW(CO)_3R]$[64,65] and $[CpFe(CO)_2R]$[66] compounds (R = alkyl group). Again, the initial photochemical process involves the opening of a vacant site on the metal by the loss of a carbonyl group. The β-hydride transfer can then occur, producing the appropriate alkene hydride complex. Confirmation that the β-hydride only was involved in the transfer was obtained by partial deuteration studies. In the case of $[CpW(CO)_3(CD_2Me)]$, only $[CpW(CO)_3H]$ is obtained following photolysis[67]. The production of alkanes from these systems is thought to involve a second photochemical reaction of the metal hydride with the parent compound (reaction 12).

$$[CpW(CO)_3(H)] + [CpW(CO)_3(alkyl)] \xrightarrow{\Delta} \text{alkane} + [Cp_2W_2(CO)_6] \qquad (12)$$

A β-hydride elimination process is also thought to be involved in the photochemical decomposition of some tungsten metallacycle compounds[68,69]. For example, photolysis of **16** yields both 1,2- and 2,3-disubstituted-prop-1-ene. The mechanism is thought to involve the initial homolytic cleavage of one M—C bond, followed by a hydride transfer and reductive elimination of the olefin producing 'tungstenocene' (Scheme 10).



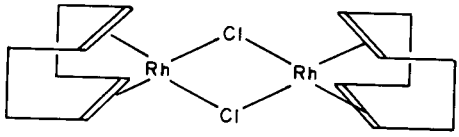
SCHEME 10

C. Photochemical Reactions of Metal Olefin Compounds

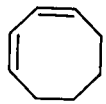
1. Olefin rearrangement reactions

There is a large body of data on the photochemical reactions of olefin complexes with rhodium and copper. Many system exhibit photocatalytic behaviour, involving hydrogenation and rearrangement reactions, in which the metal–olefin interaction plays an important role in the observed chemistry. One system which has received extensive investigation is that of the rhodium complexes of cycloocta-1,5-diene. In the case of the cycloocta-1,5-diene–rhodium chloride dimer (**17**), photolysis in diethyl ether solution

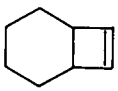
($\lambda = 353$ nm) resulted in the deposition of a brown material, while the supernatant contained three isomers of cyclooctadiene (**18–20**) in addition to the cycloocta-1,5-diene[70]. Addition of excess of cycloocta-1,5-diene to the solution prior to photolysis resulted in the formation of the same organic products, while the precipitation of the brown inorganic material was suppressed. This confirmed that the photochemical process involved the metal complex and did not arise from the direct photolysis of the diene.



(17)

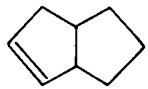


(18)



(19)

(20)

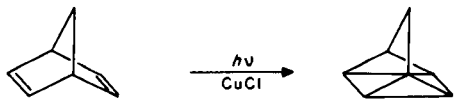


(21)

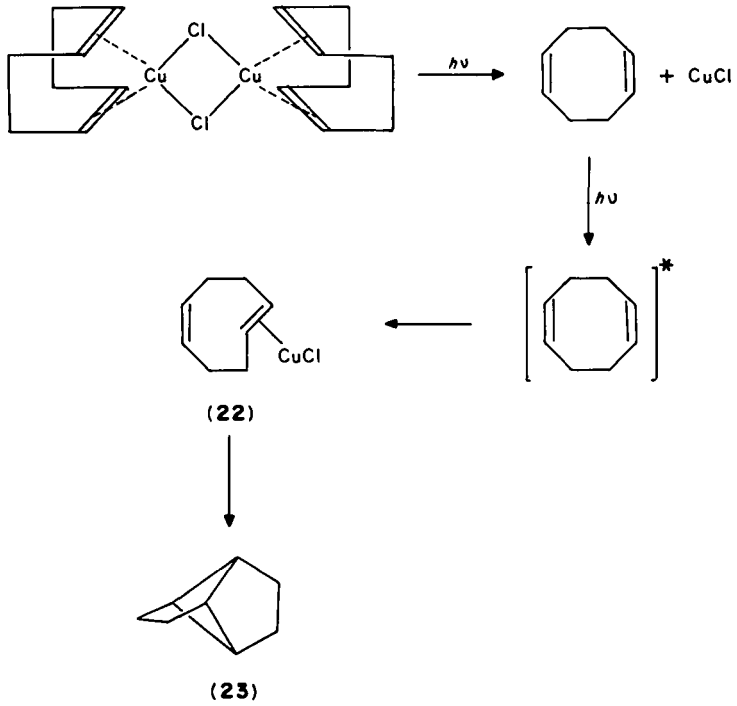
A closer examination of this system revealed that the bicyclic product **21** and also cyclooctene were produced[71]. The mechanism of these rearrangements was further investigated by examining the rate of disappearance of the cycloocta-1,5-diene when photolysed in the presence of rhodium chloride[72]. The disappearance of the 1,5-diene was accompanied by the formation of the 1,4-isomer, confirming that the 1,4-isomer is the primary product and that the other isomers produced are the result of further rearrangements of this isomer. Deuterium labelling experiments confirmed that the mechanism of the isomerization involved an intramolecular 1,3-hydride shift. The positive deuterium effect confirmed that rupture of the allylic C—H bond is involved in the rate-determining step.

Two mechanisms can be postulated for the production of the 1,4-isomer. In one case an oxidative addition of the allylic CH to the rhodium atom may be the primary route, and the rhodium simply acts as a hydride transfer agent. The second mechanism would involve the cleavage of a rhodium—olefin bond, producing a highly reactive coordinatively unsaturated complex which would yield the 1,4-diene by a reductive elimination pathway. Studies on acyclic dienes have confirmed the latter dissociative mechanism[72].

The mechanism of olefin rearrangements using copper salts appears to differ significantly from those of the rhodium systems. Here, photoinduced rearrangements occur predominantly by intramolecular pathways. One important example of such a reaction is that of the transformation of norbornadiene to quadricyclene (reaction 13)[73–76]. This reaction has received considerable attention as a possible chemical store for photochemical energy. The photocatalytic transformation of norbornadiene (nbd) to quadricyclene in the presence of $[Cu(PPh_3)_2]BH_4$ compounds is thought to involve a sensitization process rather than a mechanism involving a direct coordination of the nbd to a copper atom[76].

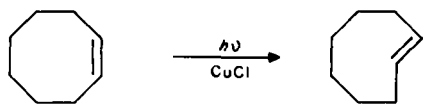


(13)

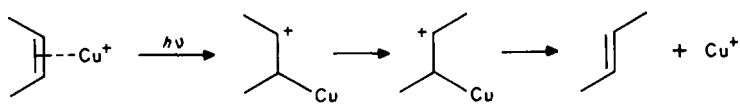


SCHEME 11

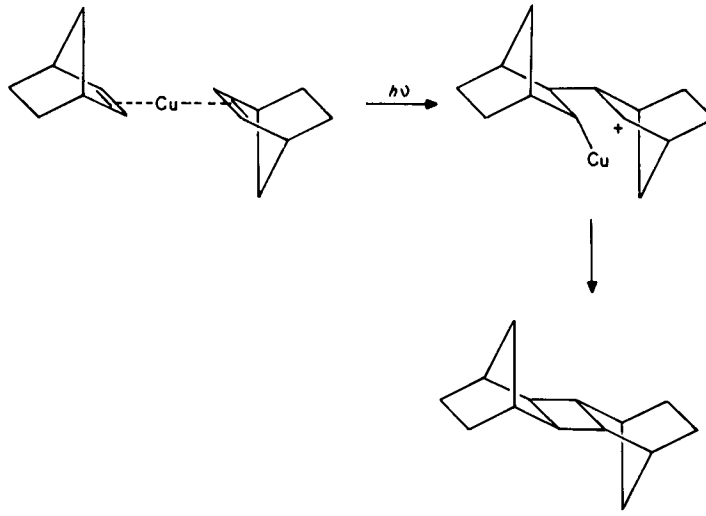
Photolysis of the cycloocta-1,5-diene salt of Cu^{I} has been investigated in both diethyl ether solution[70] and pentane suspension[77]. These studies indicate that the photochemical conversion of the diene to the tricyclooctane **23** occurs via the initial dissociation of the copper complex. The copper salt acts as a template to stabilize the excited state of the diene, upon which further photochemical or thermal reactions may occur (Scheme 11). Both *cis–trans* and *trans–trans* isomers of **22** have been isolated[77]. Indeed, the stability of [(*trans*-cyclooctene)CuCl] has been demonstrated by its use in the conversion of *cis*- to *trans*-cyclooctene (reaction 14)[78]. The mechanism of this transformation might best be explained in terms of the formation of a copper–carbenium ion (Scheme [12])[79]. Such a mechanism can also be used to explain the photodimerization of two olefins coordinated to a single copper(I) ion (Scheme 13), and also the formation of tricyclooctane from cycloocta-1,5-diene (Scheme 14)[80,81].



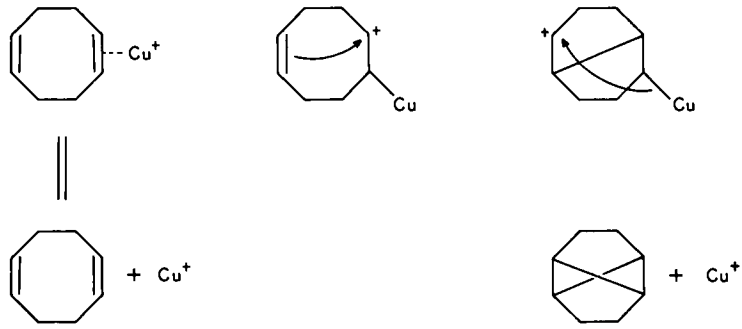
(14)



SCHEME 12



SCHEME 13

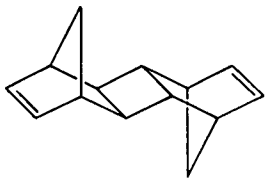


SCHEME 14

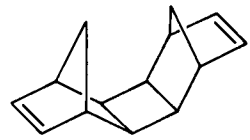
Evidence has been presented for the photoinduced cycloadditions of dienes to cyclic alkenes. These reactions occur in the presence of Cu^{I} salts such as copper(I) trifluoromethanesulphonatbenzene adduct [CuTfO)][79,82]. In general, such reactions are analogous to vapour-phase photoreactions sensitized by mercury. However, some reactions are not observed in mercury-sensitized systems; thus, methylenecyclopropanes such as **24**, when photolysed in the presence of [Cu(TfO)], produce the corresponding cyclobutene compound (**25**). Other olefin isomerization reactions have been observed following photolysis in the presence of copper(I) salts[83].

(24) **(25)**

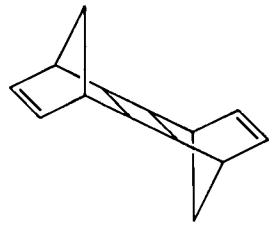
Metal carbonyl complexes have also been investigated as useful agents in olefin isomerization and other transformations such as dimerization[84]. Norbornadiene has again been studied and a variety of compounds have been investigated for their usefulness in its dimerization. For instance, the thermal reaction of norbornadiene with $[Ni(CO)_4]$[85], $[(PPh_3)_2Co_2(CO)_6]$[86], $[Fe(NO)_2(CO)_2]$[87], $[Co(CO)_3(NO)]$[87], and $[Fe_2(CO)_9]$[88] induced dimerization, while the photoinduced dimerization can be achieved in the presence of $[Fe(CO)_5]$[89]. Photolysis of norbornadiene in the presence of $[Cr(CO)_6]$ produced the $[(nbd)Cr(CO)_4]$ compound as the primary photoproduct[90]. A secondary photochemical reaction is involved in the dimerization process which produced three isomers of the dimer, **26**, **27**, and **28** in the ratio 1.8:1.0:1.4.



(26)

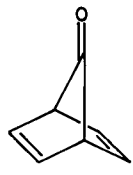


(27)

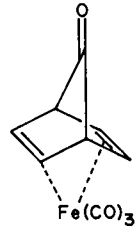


(28)

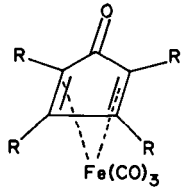
Many photoassisted olefin reactions with derivatives of $[Fe(CO)_5]$ can result in carbonylation or decarbonylation of the organic ligand[91]. For instance, the unstable norbornadiene-7-one compound **29** can be synthesized as the iron tricarbonyl derivative (**30**). Irradiation of **30** induces decomplexation, producing **29**, which rapidly undergoes a disrotatory ring cleavage extruding carbon monoxide and producing benzene[92]. Examples in which carbonylation occurs following photolysis of the olefin in the presence of iron carbonyls are common. The photolysis of diphenylacetylene in the presence of $[Fe_3(CO)_{12}]$ or $[Fe_2(CO)_9]$ results in the formation of the cycloaddition product **31**[93], while the photolysis of the dimethylacetylene with $[Fe(CO)_5]$ results in the production of the quinone derivative **32**[94].



(29)

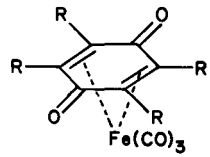


(30)



(31)

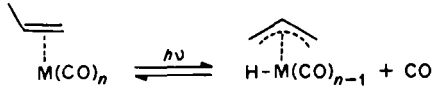
R=Ph



(32)

R=Me

Isomerization reactions of simpler diene compounds can be achieved via the formation of the $[M(CO)_5(diene)]$ complexes (M = Cr, Mo, or W)[95]. The overall process in forming these complexes and the subsequent isomerization process requires two photons. This is consistent with observations on several metal–olefin systems, in which photolysis results in the transformation of the olefin[90,96–98]. It seems likely that in the excited state of the metal–olefin complex the C=C bond order in the olefin is significantly reduced, allowing the isomerization to proceed. Whether the mechanism follows the course involving the η^3-allyl hydride species **33** (reaction 15) or the formation of a σ-bonded diradical is a matter of some doubt. It is most likely that the mechanism will depend on the nature of the olefin as some olefins which do undergo isomerization do not possess allylic hydrogens (e.g. stilbene), which would preclude reaction 15 in their case.

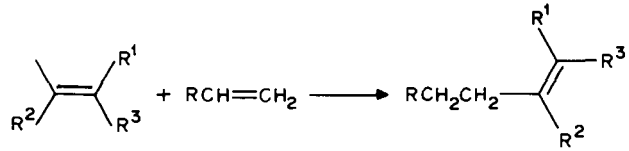


(15)

(33)

Catalytic isomerization of pent-1-ene was also observed following substitution of *cis*-cyclooctene in (*cis*-cyclooctene)iron tricarbonyl by pent-1-ene in neat pent-1-ene at temperatures above $-50\,°C$[98]. Turnover numbers in excess of 2000 can be achieved, producing both *cis*- and *trans*-pent-2-ene. This observation, coupled with the activity towards isomerization of the photoproducts of $[Fe(CO)_5]$, confirmed that light is not required in the catalytic reaction[98–100]. The reaction does require a vacant site on the metal, which can either be photogenerated or produced by loss of a labile ligand such as *cis*-cyclooctene.

There has been some discussion as to the catalytic activity of polynuclear metal compounds towards olefin transformations[101]. Such materials are thought to exhibit some structural features similar to metallic surfaces. Evidence for the hydrogenation of alkynes to *trans*-olefins has been presented, in which a dirhodium catalyst was utilized[102,103]. The effectiveness of the dirhenium carbonyl derivative (μ-hydrido) (μ-alkenyl)dirhenium octacarbonyl as an agent for olefin dimerization has also been demonstrated[103]. Ethylene dimerization produced but-1-ene whereas propylene produced hex-2-ene (reaction 16). There is no evidence that the product olefin further reacts



(16)

with the dirhenium centre to produce polymeric materials, presumably because of the reduced reactivity of the product olefin, possibly for steric reasons.

In all cases of olefin transformation mentioned so far, the olefin at some stage of the reaction is thought to bind directly to the metal centre. However, isomerization reactions can be induced in ligands whose mode of interaction with the metal is not through the olefin moiety. The photochemistry of [$W(CO)_4$(*trans*-4-styrylpyridine)] has been investigated and found to differ significantly from that of the simple pyridine derivatives[104]. Isomerization from the *trans*- to the *cis*-styrylpyridine occurs if the complex is irradiated with light with a wavelength of 313 nm. This isomerization is thought to proceed via an intra-ligand excited state. Irradiation of [$ReX(CO)_3L_2$] (X = Cl or Br; L = *trans*-3-styrylpyridine) induced *trans* to *cis* isomerization, which is thought to proceed via a triplet intra-ligand excited state, which is relatively unperturbed by coordination to the metal[105].

2. *Hydrogenation of olefins*

Stromeier and coworkers[106–115] have investigated the activity of a variety of [$IrCl(CO)L_2$] complexes (L = phosphine-containing ligand) towards the hydrogenation of various olefins. The activity of the catalyst was found to depend strongly on the nature of the ligand L. In all cases the activity of the catalyst was enhanced by irradiation, and this increased activity was found to continue after the light source had been removed. The efficiency of these catalysts is impressive and in the case of the hydrogenation of cyclohexa-1,3-diene to cyclohexane using [$IrCl(CO)(PPh_3)_2$] a turnover of approximately 100 000 was obtained[116]. The mechanism of the photoreaction is not clear, but it is known that photolysis of [$IrCl(CO)(PPh_3)_2$] does not result in a simple decarbonylation, and there is some evidence that PPh_3 loss is the primary photochemical process[117].

Chromium hexacarbonyl has been shown to be a good catalyst for the light-induced hydrogenation of olefins[118]. For example, 2,3-dimethylbutadiene and cyclohexa-1,3-diene can be hydrogenated to 2,3-dimethylbut-2-ene and cyclohexane, respectively. The hydrogenation occurs exclusively on the 1,4-position. The rate of hydrogenation was found to be fastest for those dienes which contain carbon—carbon double bonds which are capable of binding to the same metal centre[119]. Thus, cyclohexa-1,3-diene can be rapidly hydrogenated to cyclohexane whereas the equivalent reaction with 1,3-cyclooctadiene did not proceed, also the *trans*, *trans* isomer of hexa-2,4-diene can be selectivity hydrogenated in a mixture of hexa-2,4-dienes[120,121]. Again, these reactions were shown to require photoinitiation and once the initial photochemical step, i.e. production of [$Cr(CO)_5$], has been achieved the subsequent reaction with the diene to form [$Cr(CO)_4$(diene)] proceeds thermally (Scheme 15). It is possible, however, that a further photon is required to activate the [$Cr(CO)_4$ (diene)], producing a vacant coordination site and permitting the H_2 to bind to the metal.

$$[Cr(CO)_6] \xrightarrow[-CO]{h\nu} Cr(CO)_5 \xrightarrow{\text{diene}} [Cr(CO)_5(\text{diene})] \xrightarrow{-CO} [Cr(CO)_4(\text{diene})]$$

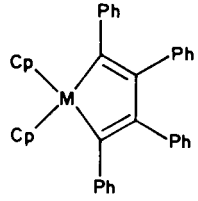
SCHEME 15

The nature of the hydrogenation process has been investigated by a number of workers[122–125]. A number of possible routes exist for this process, one involving the photojection of another CO ligand from the [$Cr(CO)_4$ (diene)], producing [$Cr(CO)_3$ (H_2)(diene)] from which the hydrogenation reaction can proceed[122]. This reaction sequence seems to be supported by the observation that [$Cr(CO)_3(CH_3CN)_3$] exhibited

catalytic action in the hydrogenation of 1,3-dienes. This suggested that the $Cr(CO)_3$ nucleus in involved in the hydrogenation process. However, there is some evidence which supports the opening of the norbornadiene chelate in [$Cr(CO)_4$ (norbornadiene)] as the principal photochemical reaction[125].

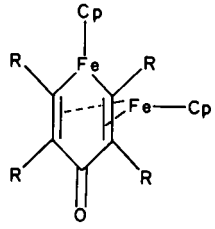
D. Coupling and Insertion Reactions with Alkynes

Apart from simple coupling reactions which occur following homolytic cleavage of metal—alkyl or metal—aryl bonds,[126,127] photolysis of some organometallic compounds in the presence of acetylenes can produce metallacylic compounds formed by the coupling of the acetylene molecules. For instance, photolysis of [$Cp_2M(CH_3)$] (M = Ti, Zr, or Hf) in the presence of diphenylacetylene produced the metallacycle **34**[128]. A similar reaction using [$Cp_2Hf(CO)_2$] also afforded **34** (M = Hf) in good yield (> 50%)[129].

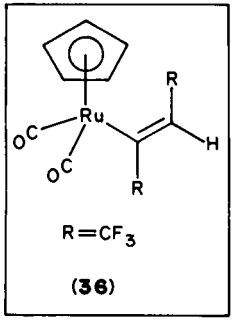


(34)

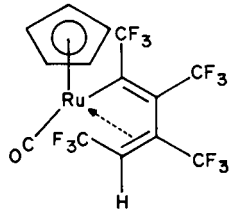
Other reactions involving alkynes to produce insertion products have been described. For example, irradiation of [$Cp_2Fe_2(CO)_2$]$_2$ in the presence of hexafluorobut-2-yne produces a ferrocyclohexadienone compound (**35**)[130], whereas in the case of the ruthenium analogue the monomeric products **36** and **37** were formed. However, photolysis of



(35)

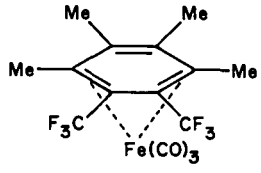


(36)

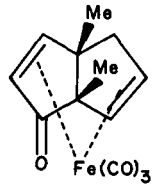


(37)

[(tetramethylcyclobutadiene)Fe(CO)$_3$] in the presence of $CF_3C{\equiv}CCF_3$ involved the cyclobutadienyl ligand in the final insertion product. In this case compounds **38** and **39** are formed[131]. Pruitt *et al.*[132] conducted some experiments designed to elucidate the mechanism of the insertion reactions of (cyclobutadienyl)Fe(CO)$_3$ compounds.

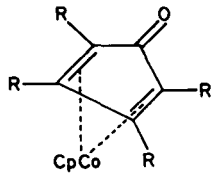


(38)

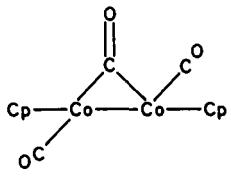


(39)

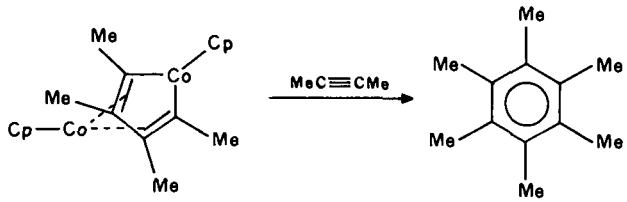
A cyclicdienone derivative (**40**) was produced following irradiation of [CpCo(CO)$_2$] in the presence of substituted acetylenes[133]. The primary photochemical reaction was shown to be the decarbonylation of the dicarbonyl, allowing coordination of the acetylene. This is followed by an insertion into the metal—CO bond coordination of a second acetylene molecule. A binuclear species (**41**) was also observed following photolysis of [CpCo(CO)$_2$]. This compound, in the presence of dimethylacetylene, forms the metallacycle **42**, which acts as a catalyst for the trimerization of alkynes (reaction 17).



(40)



(41)

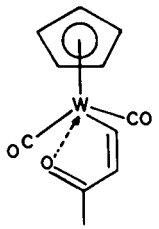


(17)

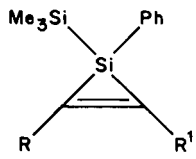
(42)

Alt and coworkers[134–137] examined the photoinduced reactions of [CpW(CO)$_3$CH$_3$] in the presence of acetylenes. The primary photoproduct is the dicarbonyl compound, which coordinates the alkyne and, following two insertion reactions, yields the methyl vinyl ketone derivative **43**.

Irradiation of $(Me_3Si)_3SiPh$ in the presence of acetylenes yields the silacyclopropane derivative **44**[138]. Further irradiation of **44** produces **45** by a 1,2-hydrogen shift from the carbon to the cyclic silicon.



(43)



(44)

R= *n*-Bu or Me_3Si; R^1=H

RC≡CSi(H)(Ph)$SiMe_3$

(45)

E. Photoinduced Polymerization Reactions

Tetraneopentyltitanium has been shown to initiate polymerization of both styrene and methyl methacrylate to produce polymers with a bimodal distribution of molecular weight[139]. This indicated that two different propagation mechanism are in operation. The evidence presented suggested that the propagating species is a caged radical (Scheme 16). The addition of radical scavengers such as diphenylpicrylhydrazyl increased the rate of polymerization by suppressing the termination process represented in reaction 18.

$$(Neo)_3TiP_n \rightleftharpoons [(Neo)_3Ti^{\cdot} + P_n^{\cdot}]$$

$$(Neo)_3TiP_{n+1} \rightleftharpoons [(Neo)_3Ti^{\cdot} + P_{n+1}^{\cdot}]$$

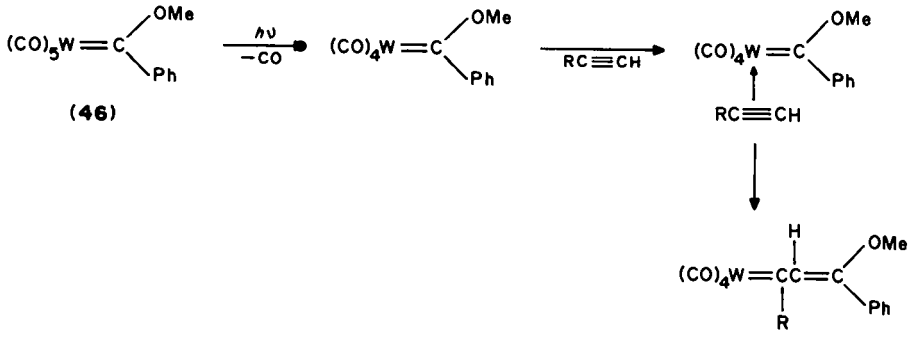
P_n = polymer; M = monomer

SCHEME 16

$$[(Neo)_3TiP_n] + P_m^{\cdot} \rightarrow [(Neo)_3Ti] + P_n(+H) + P_m(-H)$$

or

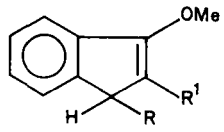
$$[(Neo)_3Ti] + (P_n + P_m) \qquad (18)$$



(46)

SCHEME 17

Polyalkynes were produced following photolysis of **46** in the presence of *n*-BuC≡CH or PhC≡CH[140]. The proposed mechanism involves the initial photodecarbonylation of **46** producing a vacant site to which the alkyne can bind (Scheme 17). The alkyne can then insert into the carbene, regenerating the coordinative unsaturation on the metal. When either diphenylacetylene or methylphenylacetylene is utilized the organic product is not polymeric in nature, but is the appropriate indene compound (**47**).



(47)

R=Ph; R^1=Ph or Me

There are many examples of photoinitiation of polymerization by free-radical processes involving metal carbonyl compounds. In many instances the mechanism involves a co-initiator, usually an alkyl halide (RX), which undergoes a reduction with the photogenerated metal carbonyl radical to produce MX and the free organic radical R·[141]. In a few cases, such as with $[Re_2(CO)_{10}]$ and $[Os_3(CO)_{12}]$, polymerization can be affected in the absence of an alkyl halide[142]. In these cases polymerization is initiated by abstraction of hydrogen from the monomer by the metal carbonyl photoproducts. $[Mn_2(CO)_{10}]$, $[Re_2(CO)_{10}]$, and $[Os_3(CO)_{12}]$ have been shown to induce polymerization of C_2F_4 at ambient temperature and at pressures close to atmospheric[143]. The initiation occurs via a direct interaction between the metal carbonyl radical, e.g. $Mn(CO)_5$·, with the monomer (**48**).

$$(CO)_5MnCF_2CF_2\cdot$$

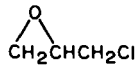
(48)

Bamford *et al.*[144] investigated the polymerization of methyl methacrylate following photolysis of $[(arene)Cr(CO)_3]$ in the presence of CCl_4. The primary photochemical reaction for $[(arene)Cr(CO)_3]$ is the loss of one carbonyl group, but these workers propose the formation of an exciplex $[M\cdots(arene)Cr(CO)_3]^*$ (M = methyl methacrylate) as the initiating species.

Many photoinitiators can provide a facile means of controlling the rate of polymerization, and also the molecular weight distribution of the end polymer. For instance, in the polymerization of isobutene, photoinitiation can be used in the preparation of butyl rubbers with widely differing physical properties[145]. Marek and coworkers investigated the photoinduced polymerization of isobutene[146,147] and the copolymerization of isobutene and isoprene[148] in the presence of Group 5 halides. They concluded that the polymerization was induced by the formation of a radical cation, formed as an intermediate following the photolysis of the monomer–MCl_4 charge-transfer complexes (reaction 19). However, a study utilizing the bulky 2,4,4-trimethylpent-1-ene (a non-polymerizable model for isobutene) indicated that its dimerization, induced by photolysis in the presence of $TiCl_4$, yields the conventional head-to-tail C_{16} olefins[149]. This observation is incompatible with a radical chain mechanism and can be explained by the photodecomposition of $TiCl_4$ to give $TiCl_3$ and Cl·. The chlorine atom then abstracts a

proton from the protic solvent, producing HCl, which is known to act as a co-initiator with $TiCl_4$[150,151]. Ferrocene is also known to act as a co-initiator with either aluminium or titanium chloride in the polymerization of epichlorohydrin (**49**)[152]. The polymer yield was found to increase dramatically on irradiation. The nature of the polymerization process is thought to be cationic.

$$[\text{monomer}—MCl_4] \rightarrow MCl_4^{-\cdot} + [\text{monomer}^+] \tag{19}$$



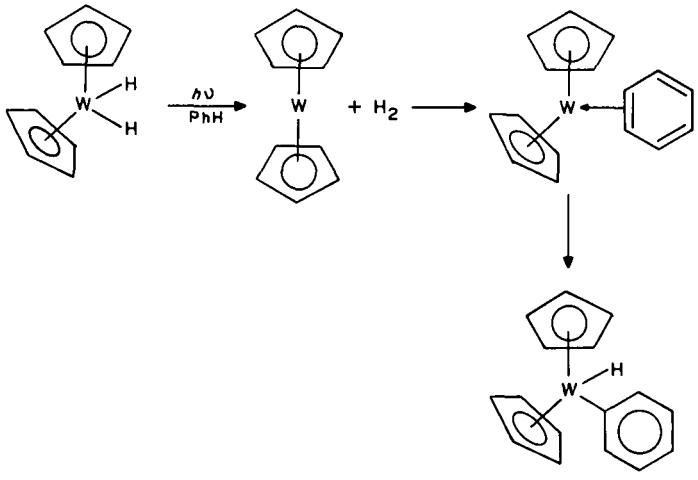
(49)

A mixture of ferrocene and CCl_4 is an efficient initiator for the polymerization of methyl methacrylate[153,154]. The efficiency of the process can be further enhanced if the FeH^+ produced is removed into the aqueous layer in a bilayer system[154].

F. Oxidative Addition Reactions

1. C—H bond activation

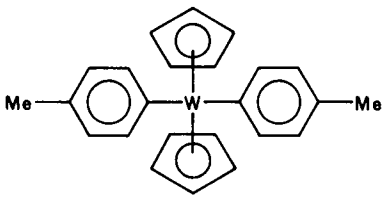
Many photoproduced organometallic fragments are sufficiently reactive to activate C—H bonds in hydrocarbon compounds, and in some cases the C—H bond to be activated is that which has the highest bond dissociation energy. The deposition of aluminium atoms in a methane matrix at 12 K followed by photolysis at wavelengths below 400 nm resulted in the formation of MeAlH[155]. This was confirmed by ultraviolet–visible, infrared, and electron spin resonance spectroscopy. No evidence was found for a ground-state reaction. Similar experiments with copper atoms also indicated activation of the C—H bond in methane, in this case forming [CMeCuH][156].



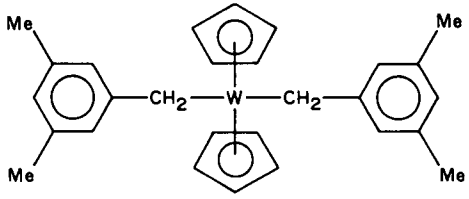
(50)

SCHEME 18

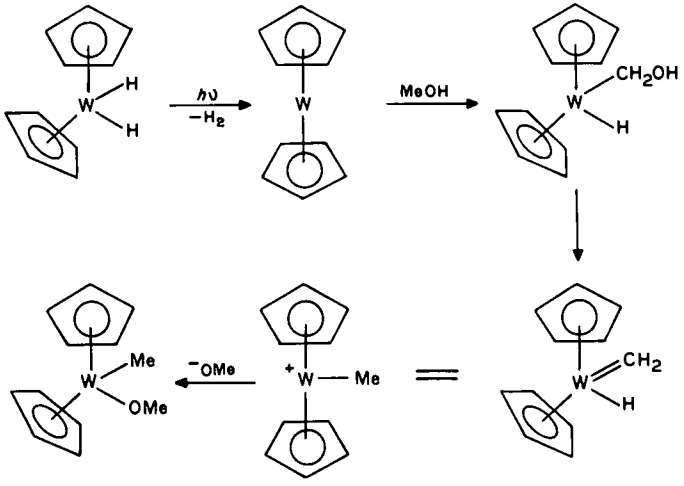
Activation of C—H bonds can also be achieved following photolysis of $[Cp_2WH_2]$ in neat substrate. Thus, photolysis of the dihydride in benzene lead to the formation of the phenyl hydride derivative (**50**) in good yield (up to 60%)[157]. The mechanism proposed is outlined in Scheme 18. The initial photochemical step involves the loss of molecular hydrogen to produce the very reactive tungstenocene, a 16-electron intermediate which presumably binds to the benzene forming an η^2-complex. Irradiation of the dihydride in toluene gave the *p*-tolyl derivative as the principal product. Insertion into uncoordinated and saturated C—H bonds is also observed in these systems when *p*-xylene or mesitylene is utilized[158]. In these cases the insertion occurs at the methyl C—H bonds to yield compounds **51** and **52**, respectively. Photolysis of $[Cp_2WH_2]$ in the presence of *β*-methoxyanisole gave the analogous bisalkyl derivative, which indicated that the methoxy methyl group is inert to attack by the tungstenocene intermediate[159]. Photolysis of the dihydride in the presence of methanol produced two principal products, the methoxy hydride $[Cp_2WH(OMe)]$ and the methoxy methyl $[Cp_2W(CH_3)(OMe)]$ derivatives, in a ratio of 1:5[160]. The mechanism for the production of the latter compound is outlined in Scheme 19, involving the initial insertion into the C—H bond in methanol. The photoinduced insertion of a tungsten atom into a C—H bond in tetramethylsilane has also been observed[161]. The 16-electron intermediate tungstenocene can also be generated from the monocarbonyl derivative $[Cp_2W(CO)]$[162].



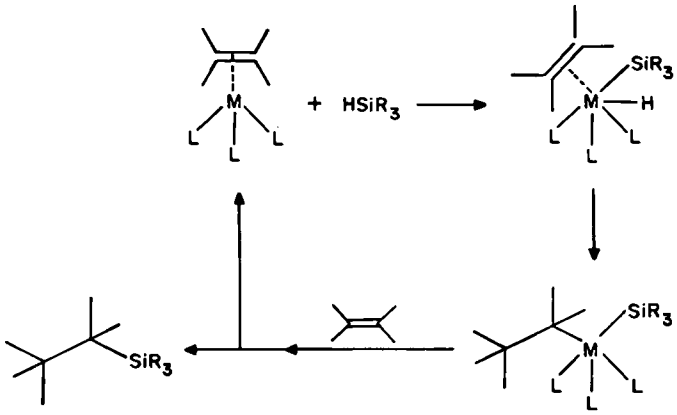
(51)



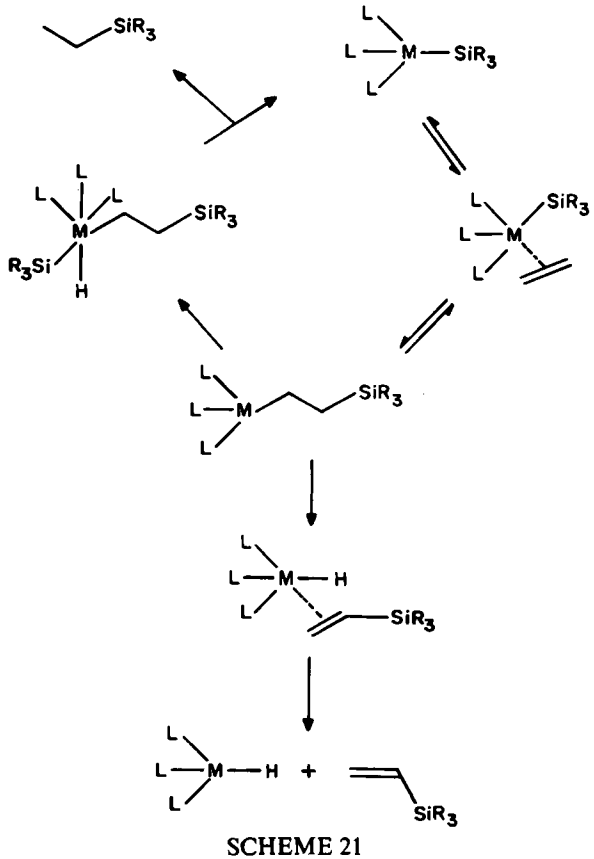
(52)



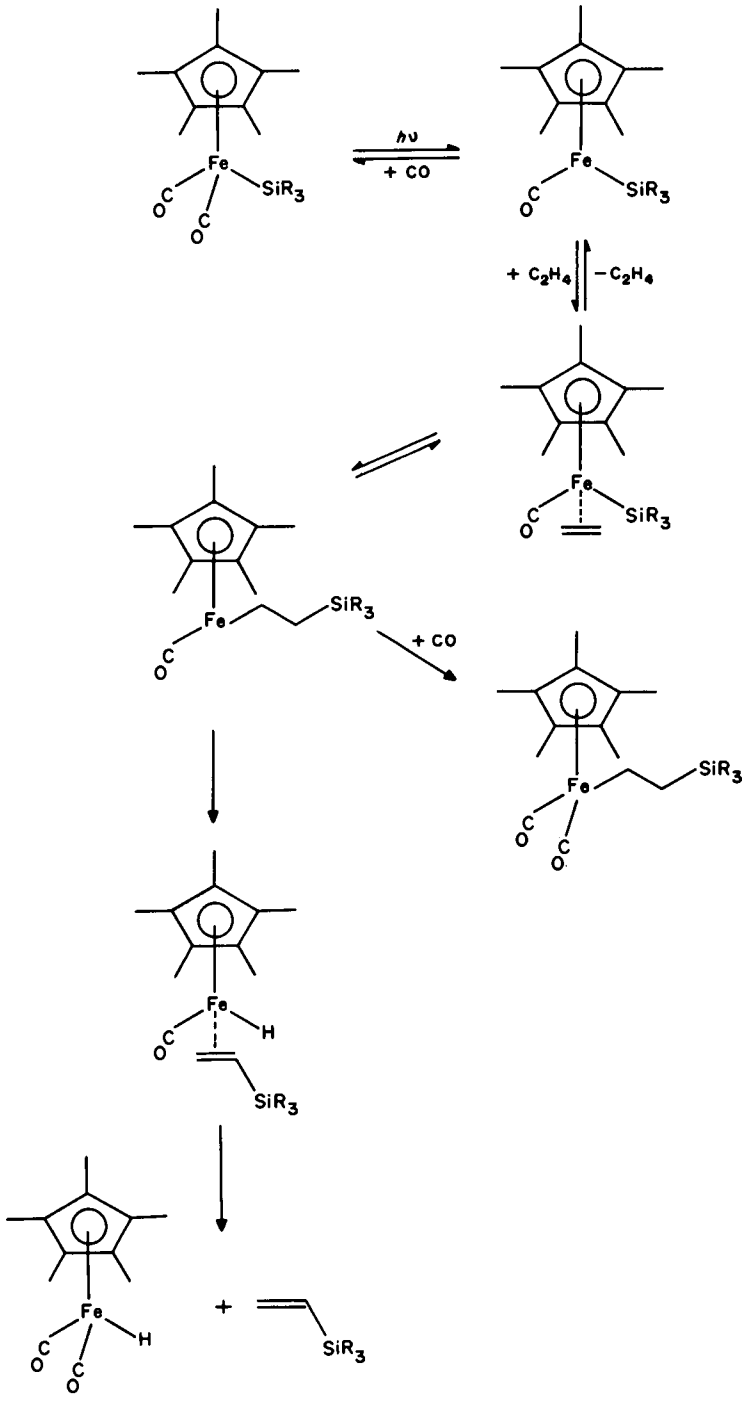
SCHEME 19



SCHEME 20



SCHEME 21



SCHEME 22

The $[Cp_2MH]$ compounds (M = Nb, Ta), which are isoelectronic to $[Cp_2W]$, are also known to activate C—H bonds[163]. These materials can be generated photochemically from the 18-electron trihydride or from the monocarbonyl hydride species[164]. $[CpRe(PMe)_3]$, $[CpIr\{C(p\text{-}ClC_6H_4)=NOC(=O)\}(CO)]$, and $[(\eta^5\text{-}C_5Me_5)Ir(CO)_2]$ have also been investigated for their ability to activate C—H bonds[165–167].

2. *Hydrosilation of alkenes*

Recent work by Randolph and Wrighton[168] has indicated that metal—silicon bonds are susceptible to olefin insertion reactions. The previously proposed mechanism for the transition metal-catalysed hydrosilation of olefins involves the reaction of the metal–olefin complex with silane, followed by the reductive elimination to produce the alkylsilane (Scheme 20)[169]. However, an alternative mechanism is possible, involving the insertion of the olefin into the metal—Si bond followed by a reductive elimination yielding the silylated derivative (Scheme 21). This mechanism accounts for the significant production of vinylsilane in these reacions. The plausibility of Scheme 21 is supported by the observation of the insertion of an olefin into the Fe—Si bond in Scheme 22.

IV. REFERENCES

1. G. L. Geoffroy and M. S. Wrighton, *Organometallic Photochemistry*, Academic Press, New York, 1979.
2. L. Mond and C. Langer, *J. Chem. Soc.*, 1090 (1891).
3. M. S. Wringhton, *Chem. Rev.*, **74**, 401 (1974).
4. J. Nasielski and A. Colas, *J. Organomet. Chem.*, **101**, 215 (1975).
5. J. D. Simon and X. Xie, *J. Phys. Chem.*, **91**, 5538 (1987).
6. J. Nasielski, P. Kirsch, and L. Wilputte, *J. Organomet. Chem.*, **29**, 269 (1971).
7. J. M. Kelly, H. Hermann, and E. Koerner von Gustorf, *J. Chem. Soc., Chem. Commun.*, 105 (1973).
8. J. M. Kelly, D. V. Dent, H. Hermann, D. Schulte-Frohlinde, and E. Koerner von Gustorf, *J. Organomet. Chem.*, **69**, 259 (1974).
9. R. Bonneau and J. M. Kelly, *J. Am. Chem. Soc.*, **102**, 1220 (1980).
10. J. M. Kelly, C. Long, and R. Bonneau, *J. Phys. Chem.*, **87**, 3344 (1983).
11. W. B. Maier, M. Poliakoff, M. B. Simpson, and J. J. Turner, *J. Chem. Soc., Chem. Commun.*, 587 (1980).
12. J. K. Burdett, M. A. Graham, R. N. Perutz, M. Poliakoff, A. J. Rest, J. J. Turner, and R. F. Turner, *J. Am. Chem. Soc.*, **97**, 4805 (1975).
13. R. N. Perutz and J. J. Turner, *Inorg. Chem.*, **14**, 262 (1975).
14. R. N. Perutz and J. J. Turner *J. Am. Chem. Soc.*, **97**, 4791 (1975).
15. M. Poliakoff, *J. Chem. Soc., Faraday Trans.* II, **73**, 569 (1977).
16. M. S. Wrighton, H. B. Abrahamson, and D. L. Morse, *J. Am. Chem. Soc.*, **98**, 4105 (1976).
17. E. Weitz and M. Poliakoff, *Acc. Chem. Res.*, **20**, 408 (1987).
18. M. Poliakoff and J. J. Turner, *J. Chem. Soc., Dalton Trans.*, 2276 (1974).
19. M. Poliakoff and J. J. Turner, *J. Chem. Soc., Dalton Trans.*, 1351 (1973).
20. A. B. Callear *Proc. R. Soc. London, Ser. A*, **71**, 265 (1961).
21. A. P. Garratt and H. W. Thompson, *J. Chem. Soc.*, 1817 (1934).
22. A. J. Rest, J. J. Turner, *J. Chem. Soc., Chem. Commun.*, 1026 (1969).
23. M. Poliakoff and J. J. Turner, *J. Chem. Soc., Dalton Trans.*, 2276 (1974).
24. D. B. Pourreau and G. L. Geoffroy, *Adv. Organomet. Chem.*, **24**, 249 (1985).
25. H. G. Alt and M. D. Rausch, *J. Am. Chem. Soc.*, **96**, 5936 (1974).
26. M. D. Rausch, W. H. Boon, and H. G. Alt, *J. Organomet. Chem.*, **141**, 299 (1977).
27. E. Samuel, H. G. Alt, D. C. Hrncir, and M. D. Rausch, *J. Organomet. Chem.*, **113**, 331 (1976).
28. C. H. Bamford, R. J. Puddephatt, and M. D. Slater, *J. Organomet. Chem.*, **159**, C31 (1978).
29. G. M. Whitesides, D. E. Bergbreiter, and P. E. Kendall, *J. Am. Chem. Soc.*, **96**, 2806 (1974).
30. M. D. Rausch, T. E. Gismondi, H. G. Alt, and J. A. Schwarzle, *Z. Naturforsch., Teil B*, **32**, 998 (1977).

31. R. G. Severson and A. Wujcicki, *J. Organomet. Chem.*, **157**, 173 (1978).
32. B. S. Creaven, A. J. Dixon, J. M. Kelly, C. Long, and M. Poliakoff, *Organometallics*, **6**, 2600 (1987).
33. J. Evans, S. J. Okrasinski, A. J. Pribula, and J. R. Norton, *J. Am. Chem. Soc.*, **99**, 5835 (1977).
34. M. Y. Darensbourg and O. J. Darensbourg, *Inorg. Chem.*, **9**, 32 (1970).
35. C. P. Casey and T. J. Burkhardt, *J. Am. Chem. Soc.*, **95**, 5833 (1973).
36. H. C. Foley, L. M. Strubinger, T. S. Targos, and G. L. Geoffroy, *J. Am. Chem. Soc.*, **105**, 3064 (1983).
37. L. K. Fong and N. J. Cooper, *J. Am. Chem. Soc.*, **106**, 2595 (1984).
38. S. M. Neuman, *PhD Dissertation*, University of Wisconsin (1978).
39. M. A. McGuire and L. S. Hegedus, *J. Am. Chem. Soc.*, **104**, 5538 (1982).
40. A. B. Bocarsly, R. E. Cameron, H.-D. Rubin, G. A. McDermott, C. R. Wolff, and A. Mayr, *Inorg. Chem.*, **24**, 3976 (1985).
41. A. Vogler, J. Kisslinger, and W. R. Roper, *Z. Naturforsch., Teil B*, **38**, 1506 (1983).
42. R. G. Beevor, M. J. Freeman, M. Green, C. E. Morton, and A. G. Orpen, *J. Chem. Soc., Chem. Commun.*, 68 (1985).
43. J. B. Sheridan, G. L. Geoffroy, and A. L. Rheingold, *Organometallics*, **5**, 1514 (1986).
44. J. B. Sheridan, D. B. Pourreau, G. L. Geoffroy, and A. L. Rheingold, *Organometallics*, **7**, 289 (1988).
45. E. O. Fischer and P. Friedrich, *Angew. Chem., Int. Ed. Engl.*, **18**, 327 (1979).
46. T. Akiyama, Y. Hoshi, S. Goto, and A. Sugimoni, *Bull. Chem. Soc. Jpn.*, **46**, 1851 (1973).
47. T. Akiyama, A. Sugimori, and H. Hermann, *Bull. Chem. Soc. Jpn.*, **46**, 1855 (1973).
48. T. Akiyama, P. Kitamura, T. Kato, W. Watanabe, J. Serizawa, and A. Sugimori, *Bull. Chem. Soc. Jpn.*, **50**, 1137 (1977).
49. L. H. Ali, A. Cox, and T. J. Kemp, *J. Chem. Soc.*, Dalton Trans., 1468 (1973).
50. R. A. Levenson and H. B. Gray, *J. Am. Chem. Soc.*, **97**, 6042 (1975).
51. R. A. Levenson, H. B. Gray, and G. P. Caesar, *J. Am. Chem. Soc.*, **92**, 3653 (1970).
52. D. R. Kidd and T. L. Brown, *J. Am. Chem. Soc.*, **100**, 4095 (1978).
53. A. E. Stiegman and D. R. Tyler, *Inorg. Chem.*, **23**, 527 (1984).
54. A. E. Stiegman and D. R. Tyler, *Coord. Chem. Rev.*, **63**, 217 (1985).
55. P. J. Davidson, M. F. Lappert, and R. Pearce, *Chem. Rev.*, **76**, 219 (1976).
56. D. Seyferth, *Acc. Chem. Res.*, **5**, 65 (1972).
57. K. A. Mahmoud, A. J. Rest, and H. G. Alt, *J. Chem. Soc., Chem. Commun.*, 1011 (1983).
58. S. M. B. Costa, A. R. Dias, and F. J. S. Pina, *J. Chem. Soc., Dalton Trans.*, 314 (1981).
59. M. D. Fryzuk, P. A. MacNeil, and S. J. Rettig, *J. Am. Chem. Soc.*, **107**, 6708 (1985).
60. M. D. Fryzuk, P. A. MacNeil, and S. J. Rettig, *J. Am. Chem. Soc.*, **109**, 2803 (1987).
61. M. D. Fryzuk and P. A. MacNeil, *J. Am. Chem. Soc.*, **108**, 6414 (1986).
62. J. W. Bruno, D. G. Kalina, E. A. Mintz, and T. J. Marks, *J. Am. Chem. Soc.*, **104**, 1860 (1982).
63. D. G. Kalina, T. J. Marks, and W. A. Wachter, *J. Am. Chem. Soc.*, **99**, 3877 (1977).
64. R. J. Kazlauskas and M. S. Wrighton, *J. Am. Chem. Soc.*, **102**, 1729 (1980).
65. R. J. Kazlauskas and M. S. Wrighton, *J. Am. Chem. Soc.*, **104**, 6005 (1982).
66. R. J. Kazluaskas and M. S. Wrighton, *Organometallics*, **1**, 602 (1982).
67. H. G. Alt and M. E. Eichner, *Angew. Chem., Int. Ed. Engl.*, **21**, 78 (1982).
68. M. Emphritikhine and M. L. H. Green, *J. Chem. Soc., Chem. Commun.*, 926 (1976).
69. G. J. A. Adams, S. G. Davies, K. A. Ford, M. Emphritikhine, P. F. Todd, and M. L. H. Green, *J. Mol. Catal.*, **8**, 15 (1980).
70. R. Srinivasin, *J. Am. Chem. Soc.*, **86**, 3318 (1964).
71. I. Haller and R. Srinivasin, *J. Am. Chem. Soc.*, **88**, 5084 (1966).
72. R. G. Saloman and N. El Sandi, *J. Am. Chem. Soc.*, **97**, 6214 (1975).
73. D. J. Trecker, R. S. Foote, J. P. Henry, and J. E. McKeon, *J. Am. Chem. Soc.*, **88**, 3021 (1966).
74. D. P. Schwendiman and C. Kutal, *Inorg. Chem.*, **16**, 719 (1977).
75. D. P. Schwendiman and C. Kutal, *J. Am. Chem. Soc.*, **99**, 5677 (1977).
76. P. A. Grutsch and C. Kutal, *J. Am. Chem. Soc.*, **99**, 6460 (1977).
77. G. M. Whitesides, G. L. Goe, and A. C. Cope, *J. Am. Chem. Soc.*, **97**, 2608 (1969).
78. J. A. Deyrup and M. Betkouski, *J. Org. Chem.*, **37**, 3561 (1972).
79. R. G. Saloman and M. F. Saloman, *J. Am. Chem. Soc.*, **98**, 7454 (1976).
80. R. G. Saloman and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 1137 (1974).
81. R. G. Saloman and J. K. Kochi, *Tetrahedron Lett.*, 2529 (1973).

82. R. G. Saloman, A. Sinha, and M. F. Saloman, *J. Am. Chem. Soc.*, **100**, 520 (1978).
83. W. Strohmeier, *Z. Naturforsch., Teil B*, **29**, 282 (1974).
84. G. N. Schrauzer, *Adv. Catal.*, **18**, 373 (1968).
85. C. W. Bird, R. C. Cookson, and J. Hudec, *Chem. Ind. (London)*, 20 (1960).
86. D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, **87**, 2596 (1965).
87. P. W. Jolly, F. G. A. Stone, and K. MacKenzie, *J. Am. Chem. Soc.*, **87**, 6416 (1965).
88. D. M. Lemal and K. S. Shim, *Tetrahedron Lett.*, 368 (1961).
89. R. Pettit, *J. Am. Chem. Soc.*, **81**, 1266 (1959).
90. W. Jennings and B. Hill, *J. Am. Chem. Soc.*, **92**, 3199 (1970).
91. J. M. Landesberg and J. Sieczkowski, *J. Am. Chem. Soc.*, **90**, 1655 (1968).
92. J. E. Baldwin, *Can. J. Chem.*, **44**, 2051 (1966).
93. G. N. Schrauzer, *J. Am. Chem. Soc.*, **81**, 5307 (1959).
94. H. W. Sternberg, R. Markby, and I. Wender, *J. Am. Chem. Soc.*, **80**, 1009 (1958).
95. M. Wrighton, G. S. Hammond, and H. B. Gray, *J. Am. Chem. Soc.*, **92**, 6068 (1970).
96. E. K. von Gustorf and F.-W. Grevels, *Fortschr. Chem. Forsch.*, **13**, 366 (1969).
97. M. Wrighton, G. S. Hammond, and H. B. Gray, *J. Organomet. Chem.*, **70**, 283 (1974).
98. H. Flechner, F.-W. Grevels, and D. Hess, *J. Am. Chem. Soc.*, **106**, 2027 (1984).
99. R. L. Whetten, K.-J. Fu, and E. R. Grant, *J. Am. Chem. Soc.*, **104**, 4270 (1982).
100. M. A. Schroeder and M. S. Wrighton, *J. Am. Chem. Soc.*, **98**, 551 (1976).
101. M. H. Chisholm, in *Reactivity of Metal–Metal Bonds* (Ed. M. H. Chisholm), American Chemical Society, Washington, DC, 1981, p. 17.
102. R. R. Burch, E. L. Meutteries, R. G. Teller, and J. M. Williams, *J. Am. Chem. Soc.*, **104**, 4257 (1982).
103. P. O. Nubel and T. L. Brown, *J. Am. Chem. Soc.*, **106**, 3474 (1984).
104. L. Pdungsap and M. S. Wrighton, *J. Organomet. Chem.*, **127**, 337 (1977).
105. M. S. Wrighton, D. L. Morse, and L. Pdungsap, *J. Am. Chem. Soc.*, **97**, 2073 (1975).
106. W. Strohmeier, *Chem. Tech. (Leipzig)*, **4**, 433 (1975).
107. W. Strohmeier and L. Weigelt, *J. Organomet. Chem.*, **125**, C40 (1977).
108. W. Strohmeier and L. Weigelt, *J. Organomet. Chem.*, **133**, C43 (1977).
109. W. Strohmeier and L. Weigelt, *J. Organomet. Chem.*, **129**, C47 (1977).
110. W. Strohmeier and K. Grunter, *J. Organomet. Chem.*, **90**, C48 (1975).
111. W. Strohmeier and L. Weigelt, *J. Organomet. Chem.*, **82**, 417 (1974).
112. W. Strohmeier and G. Csontos, *J. Organomet. Chem.*, **67**, C27 (1974).
113. W. Strohmeier and G. Csontos, *J. Organomet. Chem.*, **72**, 277 (1974).
114. W. Strohmeier, *J. Organomet. Chem.*, **94**, 273 (1975).
115. W. Strohmeier, H. Steigerwald, and L. Weigelt, *J. Organomet. Chem.*, **129**, 243 (1977).
116. W. Strohmeier and H. Steigerwald, *J. Organomet. Chem.*, **125**, C37 (1977).
117. G. L. Geoffroy, D. A. Denton, M. E. Keeney, and R. R. Bucks, *Inorg. Chem.*, **15**, 2382 (1976).
118. J. Nasielski, P. Kirsch, and L. Wilputte-Steinert, *J. Organomet. Chem.*, **27**, C13 (1971).
119. G. Platbrood and L. Wilputte-Steinert, *J. Organomet. Chem.*, **70**, 407 (1974).
120. G. Platbrood and L. Wilputte-Steinert, *Tetrahedron Lett.*, 2507 (1974).
121. M. Wrighton and M. A. Schroeder, *J. Am. Chem. Soc.*, **95**, 5764 (1973).
122. W. Gerhartz, F.-W. Grevels, W. E. Klotzbucher, E. A. Koerner von Gustorf, and R. N. Perutz, *Z. Naturforsch.*, **406**, 518 (1985).
123. M. A. Schroeder and M. S. Wrighton, *J. Organomet. Chem.*, **74**, C29 (1974).
124. M. Cais, E. N. Frenkel, and R. A. Rejoin, *Tetrahedron Lett.*, 1919 (1968).
125. D. Rietvelde and L. Wilputte-Stenert, *J. Organomet. Chem.*, **118**, 191 (1976).
126. M. D. Rausch, W. H. Boon, and E. A. Mintz, *J. Organomet. Chem.*, **160**, 81 (1978).
127. M. Peng and C. H. Brubaker, *Inorg. Chim. Acta*, **26**, 231 (1978).
128. H. Alt and M. D. Rausch, *J. Am. Chem. Soc.*, **96**, 5936 (1974).
129. D. J. Sikora, M. D. Rausch, R. D. Rogers, and J. L. Atwood, *J. Am. Chem. Soc.*, **101**, 5079 (1979).
130. J. L. Davison, M. Green, F. G. A. Stone, and A. J. Welch, *J. Chem. Soc., Dalton Trans.*, 2044 (1976).
131. A. Bond, M. Bottril, M. Green, and A. J. Welch, *J. Chem. Soc., Dalton Trans.*, 2372 (1977).
132. P. L. Pruitt, E. R. Beihl, and P. C. Reeves, *J. Organomet. Chem.*, **134**, 37 (1977).
133. W.-S. Lee and H. H. Brintzinger, *J. Organomet. Chem.*, **127**, 93 (1977).
134. H. G. Alt, *Chem. Ber.*, **110**, 2862 (1977).
135. H. G. Alt, *J. Organomet. Chem.*, **127**, 349 (1977).

136. H. G. Alt and W. Stadler, *Z. Naturforsch., Teil B*, **32**, 144 (1977).
137. H. G. Alt, *Angew. Chem.*, **88**, 800 (1976).
138. M. Ishikawa, K.-I. Nakagawa, and M. Kumana, *J. Organomet. Chem.*, **131**, C15 (1977).
139. J. C. W. Chien, J.-C. Wu, and M. D. Rausch, *J. Am. Chem. Soc.*, **103**, 1180 (1981).
140. H. C. Foley, L. M. Strubinger, T. S. Targos, and G. L. Geoffroy, *J. Am. Chem. Soc.*, **105**, 3064 (1983).
141. C. H. Bamford and S. U. Mullik, *J. Chem. Soc., Faraday Trans.* I, **69**, 1127 (1973).
142. C. H. Bamford and M. U. Mahmud, *J. Chem. Soc., Chem. Commun.*, 762 (1972).
143. C. H. Bamford and S. U. Mullik, *Polymer*, **17**, 225 (1976).
144. C. H. Bamford, K. G. Al-Lamee, and C. J. Konstantinov, *J. Chem. Soc., Faraday Trans.* I, **73**, 1406 (1977).
145. W. H. T. Davison, S. H. Pinner, and R. Warrall, *Chem. Ind. (London)*, **38**, 1274 (1957).
146. M. Marek, L. Toman, and J. Pilar, *J. Polym. Sci., Polym. Chem. Ed.*, **17**, 1565 (1975).
147. M. Marek and L. Toman, *Macromol. Chem., Rapid Commun.*, **184**, 343 (1980).
148. L. Toman, J. Pilar, J. Spevacak, and M. Marek, *J. Polym. Sci., Polym. Chem. Ed.*, **16**, 2759 (1978).
149. T. Diem and J. P. Kennedy, *J. Macromol. Sci., Chem.*, **A12**, 1359 (1978).
150. R. Bourne-Branchu, H. Cheradame, and P. Sigwalt, *C. R. Acad. Sci., Ser. C*, **268** 1292 (1969).
151. R. H. Biddulph, P. H. Plesch, and P. P. Rutherford, *J. Chem. Soc.*, 275 (1965).
152. K. Kaeriyama, *J. Polym. Sci., Polym. Chem. Ed.*, **14**, 1547 (1976).
153. K. Tsubakiyama and S. Fujisaki, *J. Polym. Sci., Polym. Lett. Ed.*, **10**, 341 (1972).
154. M. Tsunooka and M. Tanaka, *J. Polym. Sci., Polym. Lett. Ed.*, **16**, 119 (1978).
155. J. M. Parnis and G. A. Ozin, *J. Am. Chem. Soc.*, **108**, 1699 (1986).
156. J. M. Parnis, S. A. Mitchell, J. Garcia-Prieto, and G. A. Ozin, *J. Am. Chem. Soc.*, **107**, 8169 (1985).
157. C. Giannotti and M. L. H. Green, *J. Chem. Soc., Chem. Commun.*, 1114 (1972).
158. K. Elmitt, M. L. H. Green, R. A. Forder, I. Jefferson, and C. K. Prout, *J. Chem. Soc., Chem. Commun.*, 747 (1974).
159. M. Beryy, K. Elmitt, and M. L. H. Green, *J. Chem. Soc., Dalton Trans.*, 1950 (1979).
160. L. Farrugia and M. L. H. Green, *J. Chem. Soc., Chem. Commun.*, 416 (1975).
161. M. L. H. Green, M. Berry, C. Cauldwell, and K. Prout, *Nouv. J. Chim.*, **1**, 187 (1977).
162. K. L. Tang Wong, J. L. Thomas, and H. H. Brintzinger, *J. Am. Chem. Soc.*, **96**, 3694 (1974).
163. U. Klabunde and G. W. Parshall, *J. Am. Chem. Soc.*, **94**, 9081 (1972).
164. R. F. Baynham, J. Chetwynd-Talbot, P. Grabenik, R. N. Perutz, and M. H. A. Powell, *J. Organomet. Chem.*, **284**, 229 (1985).
165. T. T. Wenzel and R. G. Bergman, *J. Am. Chem. Soc.*, **108**, 4856 (1986).
166. P. A. Chetcuti and M. F. Hawthorne, *J. Am. Chem. Soc.*, **109**, 942 (1987).
167. J. K. Hoyano, A. D. McMaster, and W. A. G. Graham, *J. Am. Chem. Soc.*, **105**, 7190 (1983).
168. C. L. Randolf and M. S. Wrighton, *J. Am. Chem. Soc.*, **108**, 3366 (1986).
169. A. J. Chalk and J. F. Harrod, *J. Am. Chem. Soc.*, **87**, 16 (1965).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 3

Phase-transfer catalysis in organometallic chemistry

JEAN-FRANÇOIS PETRIGNANI

IPSOI, CNRS UA 126, Faculté des Sciences de Saint Jérôme, Université d'Aix Marseille, Av. de p'escadrille Normandie Niemen, 13397 Marseille, France

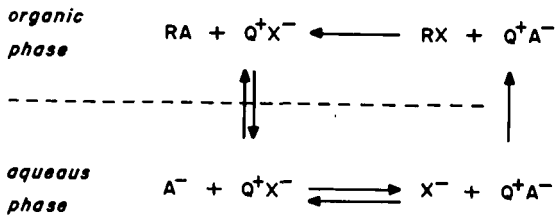
I. INTRODUCTION

The application of two-phase systems to catalysis, known as 'phase-transfer catalysis' (PTC) since the 1970s, is one of the most important new techniques to become widely accepted in organic chemistry both in the laboratory and in industry. This catalytic method has been intensively applied because it often provides many advantages, such as milder reaction conditions, facile work-up, higher yields, modification of selectivities, use of cheaper and less dangerous reactants or solvents, and in some cases, a means of performing new reactions.

PTC is firstly of great importance in chemical synthesis, but also in chemical analysis and biological studies; extensive information on the scope of the technique can be found in books[1-4] and reviews covering special fields such as triphase catalysis[5], the preparation and chemical modification of polymers[6], PTC in heterocyclic chemistry[7], industrial applications[8], drug synthesis[9], and applications in organometallic chemistry[10-14]. Before covering the recent developments in the application of PTC to organometallic compounds, general principles and different types of catalysts will be briefly summarized.

A. General Principles

The phase-transfer process involves a charged species, which is normally an anionic (A^-) and is based on the catalytic formation of lipophilic ion pairs (Q^+A^-), soluble in non-polar organic solvents, with lipophilic cations (Q^+). This occurs especially when reactions are carried out in systems where two immiscible phases are presents, with an aqueous (or anhydrous solid) inorganic phase as the source of anions and an organic phase where the chemical reaction takes place (Scheme 1). In a solid–liquid system, anhydrous solid salts form the inorganic medium and the phase-transfer catalyst brings the anion into the organic solvent. The catalysts can be classified in different groups.



SCHEME 1

B. Catalysts

The catalyst must supply the system with lipophilic species to form ion pairs with the desired anions, in order to solubilize them in an organic medium. The most common catalysts are tetraalkyl onium salts, mainly ammonium ($R_4N^+X^-$) but also phosphonium ($R_4P^+X^-$); their lipophilic properties depend on the length of the alkyl groups. Those most commonly used are tetra-*n*-butylammonium bromide (tbab), triethylbenzylammonium chloride (teba), cetyltrimethylammonium bromide (ctab), and methyltrioctylammonium chloride (Aliquat 336).

A variety of neutral organic ligands coordinate to cations or anions and can also act as phase-transfer catalysts. From a topological point of view, they are divided into three principal groups[15] (Scheme 2):

1. Open-chain compounds, called 'podands' (**1**), including glymes (**1a**)[16], polyethylene glycols (PEG) (**1b**)[17] and tris(dioxa-3,6 heptyl) amine (TDA-1) (**1c**)[18].
2. Simple cyclic ethers, named 'coronands', including the three most common crown ethers (**2a**, **2b**, and **2c**) and ca 4000 compounds of this type[19].
3. Oligocyclic spherical compounds or 'cryptands'[20] (**3**), showing a three-dimensionally surrounded cavity of varying sizes corresponding to the bridge length.

The principal function of all these compounds in phase-transfer catalysis is to complex the cation of a salt, thereby solubilizing it in organic solvents; the corresponding anion, which is not complexed, is weakly solvated in the organic phase. This 'naked' anion is in a very active state, enhancing its nucleophilicity and ability to initiate unusual reactions.

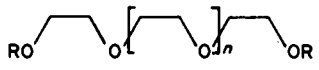
Complexation of neutral species has also been achieved. Cyclodextrins are cyclic oligomers of D-glucose classified on the basis of the number of glucose units where α-, β- and γ-cyclodextrins correspond six, seven, and eight monomers, respectively. These compounds form host–guest complexes with suitable organic substrates via the distinct cavity of variable dimensions for each class of cyclodextrins[21]. The presumed function of these reagents is to complex the organic molecules and transfer them into the aqueous phase.

Considerations of costs and toxicity are of prime importance with these types of compounds, and the use of these sequestering reagents in both organic and organometallic chemistry has often been limited to cases in which oniums were unsuitable[22], with some exceptions (e.g. PEG).

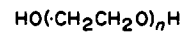
C. Organometallic Phase-transfer Catalysis

The formation of organometallic anions and the generation, *in situ*, of active homogeneous catalysts from inorganic anions has been of considerable significance; it was only in 1975–76, however, that the first examples of the application of phase-transfer catalysis to organometallic compounds were reported[23]. Since then, the number of publications in which phase-transfer and organometallic catalysis are combined (Figure 1) has increased considerably.

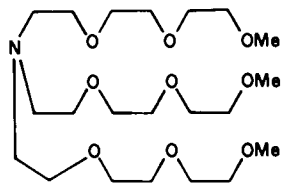
As mentioned already, several reviews have appeared on this subject[10–14] and the purpose of this chapter is to give to the reader an overview of the topic based on the most recent result. Consequently, it is subdivided into sections, depending on the role of the metal species in the system, reacting either as a homogeneous catalyst, as a reactant for organometallic synthesis, and finally as a phase-transfer reagent itself. Figure 2 shows how these studies are divided according to the nature of the reaction.



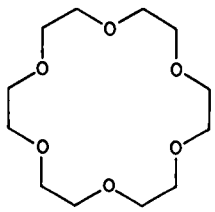
(1a)



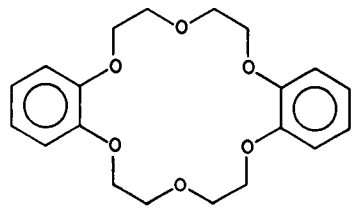
(1b)



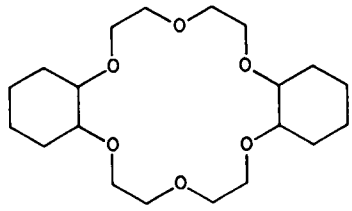
(1c)



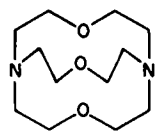
(2a)



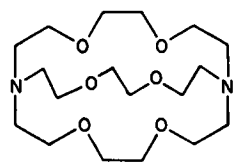
(2b)



(2c)



(3a)



(3b)

SCHEME 2

II. HOMOGENEOUS CATALYSIS

Homogeneous catalysis is the most important in terms of the number of publications and potential applications in industry. Among these reactions, the focus will be on carbonylations, oxidations, reductions, and alkylations.

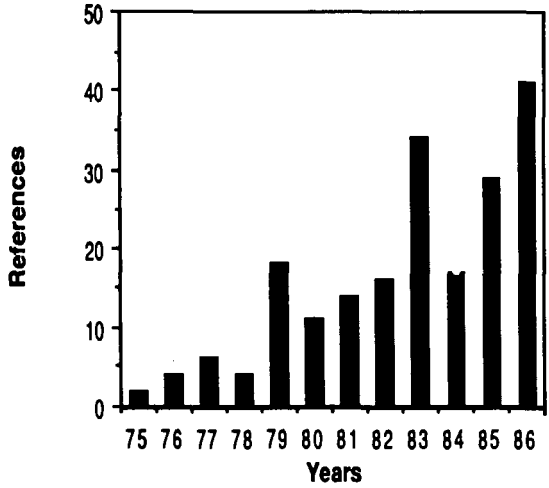


FIGURE 1. Increase in the number of publications on the application of phase-transfer catalysis to organometallic compounds (1975–86). From *Chemical Abstracts* file search statistics.

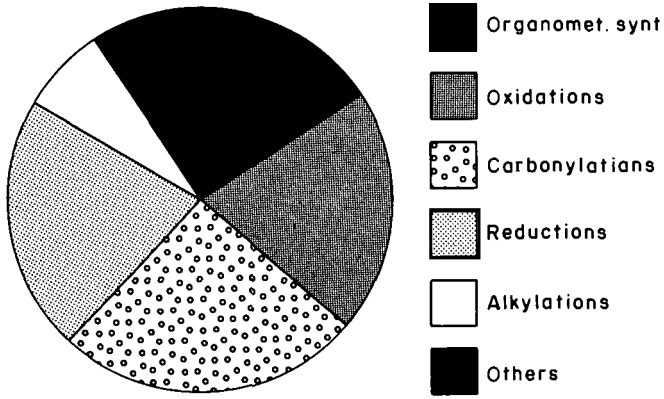


FIGURE 2. Relative numbers of publications on applications of phase-transfer catalysis to different reaction types.

A. Carbonylation Reactions

1. Organic halides

The carbonylation of organic halides to carboxylic acids has been the most studied application of PTC in organometallic catalysis. The two major reasons for that interest are the facile separation of the product (aqueous phase) from the starting halide and metal catalyst (organic phase) and the easy generation of the active catalytic species under mild conditions.

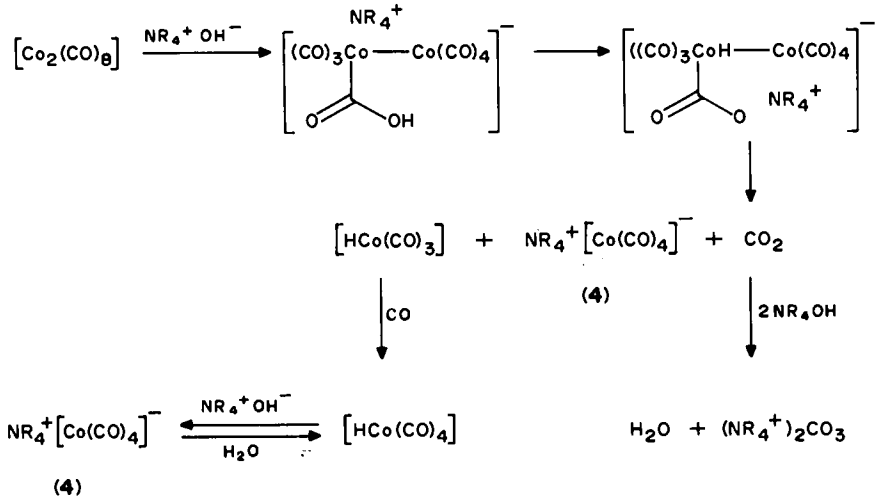
a. Benzylic halides. Benzylic chlorides or bromides react in the presence of dicobalt octacarbonyl under phase-transfer conditions [e.g. room temperature, atmospheric pressure, teba, sodium hydroxide (5 M), benzene] to give phenylacetic acid in reasonably good yield (85%)[24,25] compared with the same transformation effected under monophasic conditions (equation 1)[26].

$$ArCH_2X + CO \xrightarrow[\substack{\text{teba, 5 M NaOH,}\\ \text{RT, 1 atm}}]{[Co_2(CO)_8]} ArCH_2COOH \qquad (1)$$

The mechanism of this reaction[27,28] involves the 'classical' first step in PTC of formation of the required ion pair ($R_4N^+OH^-$) in the aqueous phase (equation 2).

$$R_4N^+X^- + Na^+OH^- \rightarrow R_4N^+OH^- + Na^+X^- \qquad (2)$$

In this case, the ion pair will react with the metal carbonyl complex at the interfacial area, according to Scheme 3.

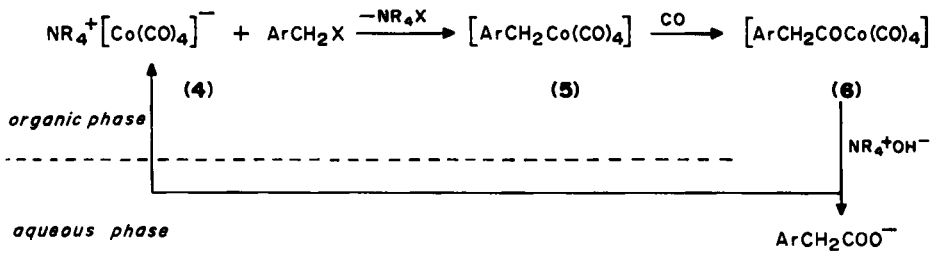


SCHEME 3

The organometallic ion pair (**4**) was shown to be located in the organic phase where the reaction with the halide occurs, via an alkyl (**5**) and then an acylcobalt tetracarbonyl complex (**6**); cleavage of **6** by $NR_4^+OH^-$ will then occur at the interface, regenerating the complex **4** and expelling the carboxylate in the aqueous phase (Scheme 4).

This phase-transfer process has been applied in polymer chemistry to the carbonylation of chloromethylated and partially quaternized chloromethylated polystyrene resins[29].

The reaction was extended to the less reactive aryl bromides in a photochemical phase-transfer process by using UV light (350 nm). This aromatic carboxylic acid synthesis occurs under mild conditions (65 °C, 1 atm carbon monoxide), probably through a single electron-transfer pathway[30,31]. Benzoic acid can also be obtained, albeit in modest yields,



SCHEME 4

by effecting the reaction in the presence of methyl iodide with acetophenone as a co-product (equation 3)[32].

$$2ArBr + MeI + 2CO \xrightarrow[\substack{1\text{ M NaOH, } Q^+X^-,\\ RT,\ 1\text{ atm}}]{[Co_2(CO)_8],\ C_6H_6} ArCOOH + ArCOMe \qquad (3)$$

Benzyl halides also react in PTC with iron pentacarbonyl to give ketones (7), hydrocarbons (8) and phenylacetic acid with a selectivity depending on the base concentration and the presence of carbon monoxide (equation 4)[33,34].

$$ArCH_2X + CO \xrightarrow[PTC]{[Fe(CO)_5],\ base} \underset{(7)}{ArCH_2COCH_2Ar} + \underset{(8)}{ArMe} + \underset{(9)}{ArCH_2COOH} \qquad (4)$$

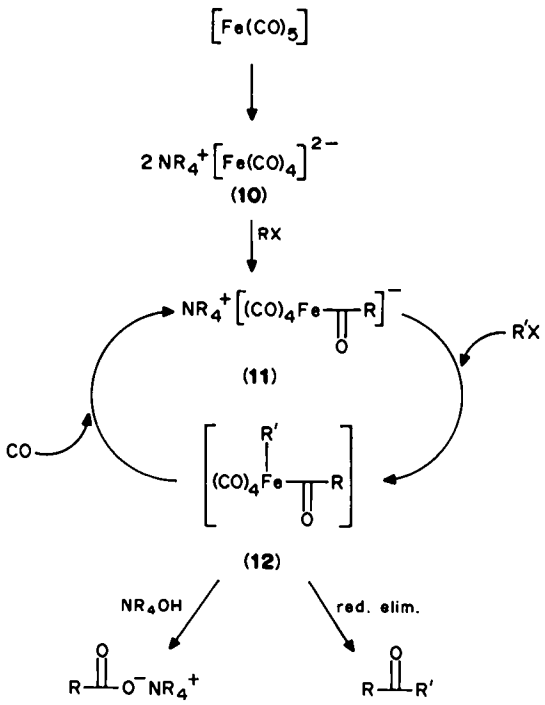
Poor selectivities and the formation of acid as the major product were reported when using a strongly alkaline aqueous solution (NaOH, pH14) under carbon monoxide, whereas an inert atmosphere and a less basic medium [$Ca(OH)_2$, pH 12.6] provided mostly ketones. In all cases the reaction remains stoichiometric with respect to iron pentacarbonyl. This reaction, however, was shown to be catalytic[35–37] under specific phase-transfer conditions (e.g. CH_2Cl_2 or PhMe, $Fe(CO)_5$, 1 M NaOH, CO, $(Bu_4N)_2SO_4$].

It was demonstrated that in such a system, the iron tetracarbonyl dianion (10) may be the active catalyst[38]. More recently Des Abbayes *et al.*[39] proposed an acyltetracarbonyl-iron anion (11) as the true catalyst for both ketone and acid formation (Scheme 5).

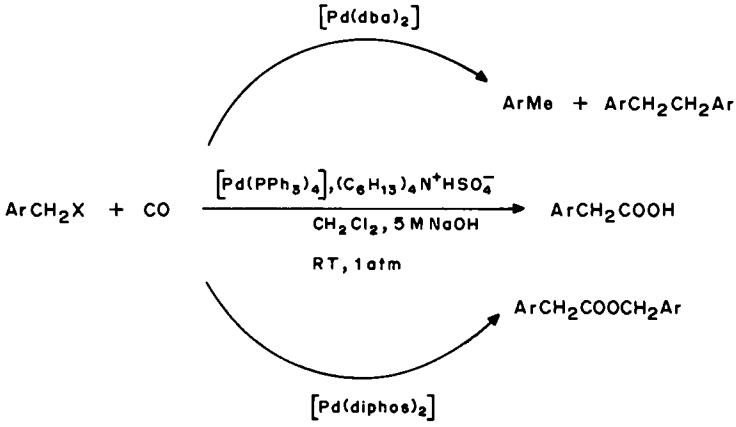
In the case of benzyl halides (R = R′), base cleavage (at the interface) would produce the carboxylate anion, whereas ketone could arise from reductive elimination of the complex **12**. This reaction was extended to other activated halides in combination with benzyl chloride (R ≠ R′).

Metal carbonyls are not the only catalyst precursors available for effecting this carbonylation reaction, and investigations with zero-valent palladium complexes have given interesting results[40,41]: first, the fact that a phase-transfer agent is not required (the presence of a quaternary ammonium salt only slightly increases the yields of carboxylic acids) implies an interfacial mechanism for such a biphasic system; second, the selectivity is closely related to the nature of the ligand coordinated to the palladium (Scheme 6).

If dibenzylideneacetone (dba) is used as a bidentate acceptor ligand, coupling and dehalogenation occur instead of carbonylation. In the presence of a bidentate donor ligand such as 1,2-diphenylphosphine (diphos), a carbalkoxylation reaction leading to an ester takes place. These transformations are true phase-transfer process since in the absence of tetraalkylammonium hydrogensulphate no reaction occurs with dba and carboxylic acid is formed (instead of ester) with diphos.

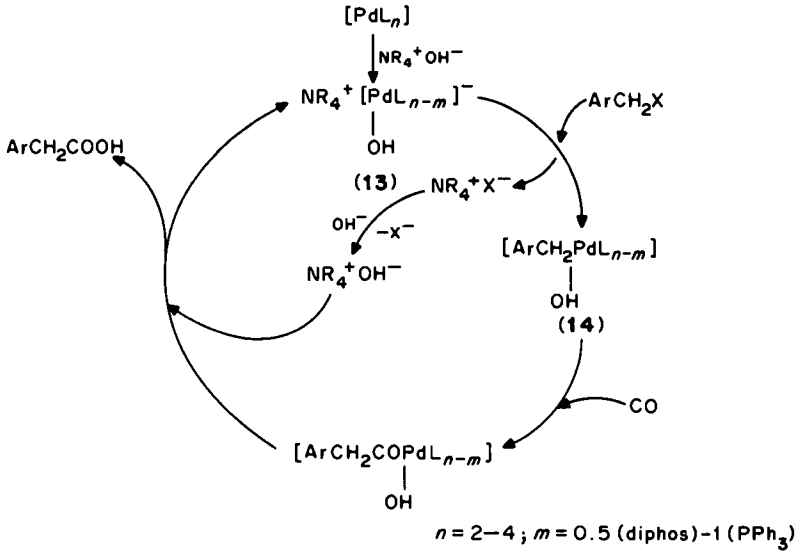


SCHEME 5



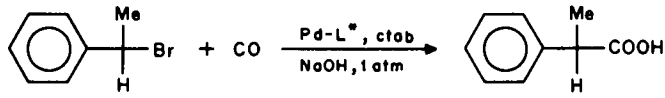
SCHEME 6

In order to rationalize these results, Alper *et al.*[41] proposed a mechanism involving an anionic palladium hydroxide (**13**) generated from the palladium precursor with the quaternary ammonium hydroxide. Successive reactions of this anion (oxidative addition, CO insertion and base cleavage or reductive elimination) give the acid (Scheme 7).

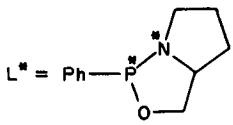


SCHEME 7

The ester formation is probably based on the potential reductive elimination of **14**, depending on the nature of L, to give the benzylic alcohol required for the carbalkoxylation. Although somewhat speculative, such a zero-valent palladium anion as the active species in this reaction has recently been supported by a study of the effect of a new kind of chiral phosphine ligands on that process, in order to effect the enantioselective carbonylation of 1-bromo-1-phenylethane under phase-transfer conditions[42]. Simple aminophosphine or 2-substituted-3, 1, 2-oxazaphospholanes (**15**) give significant enantiomeric excesses whereas the classical mono- or bidentate optically active phosphines[43] are inefficient (equation 5).

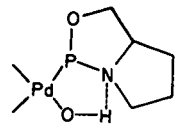


(5)



(**15**)

The reaction was shown to be a kinetic resolution process with a discriminative slow oxidative addition step, but the more interesting feature is that the presence of the phase-transfer agent is necessary to achieve enantiomeric discrimination, even though it is known that the acid is formed in an interfacial process. This was rationalized in terms of a second-order interaction involving the formation of a hydrogen bond between the nitrogen atom of the oxazaphospholane and the hydroxo group bound to palladium prior (**16**) to the addition of the substrate.



(**16**)

Under specific solid–liquid phase-transfer conditions, palladium-catalysed carbonylation of benzyl halides was extended to aryl, phenacyl, and aliphatic halides, affording esters in the presence of alcohol (equation 6)[44].

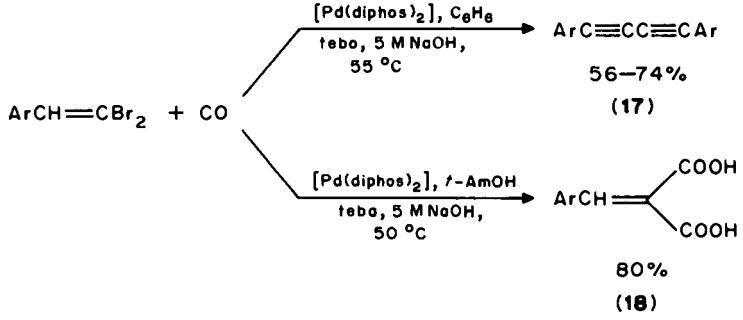
$$RX + CO + EtOH \xrightarrow[Bu_4N^+X^-,\ NaHCO_3,\ 70\,^\circ C,\ 2\,atm]{[Pd(PPh_3)_2Cl_2]} RCOOEt \qquad (6)$$

56–95%

Tetra-*n*-butylammonium iodide was shown to be more efficient than the bromide and chloride analogues and the presence of the phase-transfer agent increases the yield of the reaction; the most striking example was the carbonylation of ethyl chloroacetate, which afforded 70% of diethyl malonate when the onium salt was present, whereas no reaction occurred without it.

b. Vinylic halides. The palladium complex-catalysed carbonylation of vinylic dibromides has been investigated and it appears that, in contrast to benzylic bromides, the effect of the ligand does not affect the selectivity of the reaction whereas the natures of the solvent and the substrate do[45].

For example (Scheme 8), when the polar solvent *tert*-amyl alcohol is used as the organic phase, no coupling reaction affording diynes (**17**) occurs but the halide is carbonylated to a



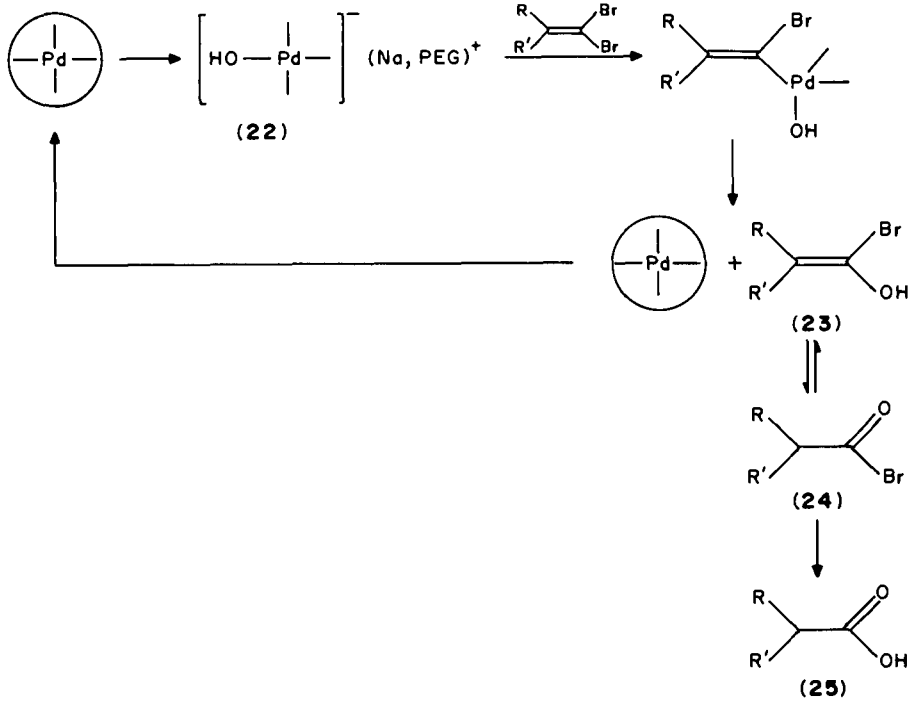
SCHEME 8

diacid (**18**) in good yield. Starting from a vinyl dibromide bearing an alkyl group (**19**), the major product is the mono acid **20** (with some diacid **21** as a by-product) (equation 7).

$$RCH{=}CBr_2 + CO \xrightarrow[5\,M\ NaOH,\ teba]{[Pd(diphos)_2],\ C_6H_6} RCH{=}CHCOOH + RCH{=}C(COOH)_2 \quad (7)$$

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

It is interesting that under an inert atmosphere, in the presence of a polyethylene glycol ('podand' phase-transfer agent), vinylic dibromides can be converted into monoacids[46]. This reaction is catalysed by $[Pd(diphos)_2]$ through a possible hydroxopalladium anion (**22**), which could induce an oxidative addition–reductive elimination sequence affording the enol form **23** of the acid bromide **24**, followed by a subsequent hydrolysis to give the acid **25** (Scheme 9).



SCHEME 9

The same systems have been extended to vinylic bromides (equation 8)[47].

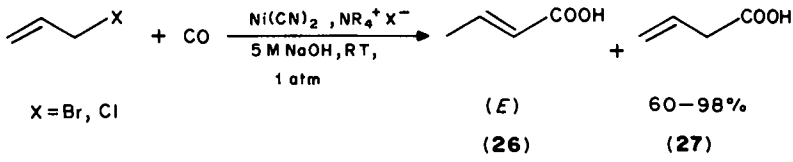
$$(E)\text{-}PhCH{=}CHBr + CO \xrightarrow[5\,M\ NaOH,\ teba,\ 50\,^{\circ}C]{[Pd(PPh_3)_4],C_6H_6} (E)\text{-}PhCH{=}CHCOOH \quad (8)$$

91%

The reaction can be stereospecific, since (*E*)-bromostyrene reacts with CO in the presence of $[Pd(PPh_3)_4]$ to give only (*E*)-cinnamic acid, but the nature of the phase-

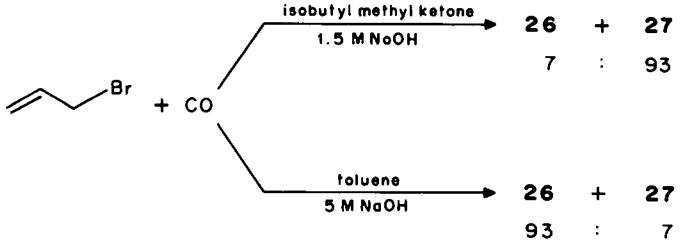
transfer reagent and the solvent modify the stereoselectivity. It should be noted that alkynes are never formed in these reactions and this different behaviour compared with the dibromides is explained in terms of the relative acidities of the benzylic protons in the two substrates[46].

c. Allylic halides. The carbonylation of allyl chlorides under phase-transfer conditions (e.g. 1 atm, Co, 25–45 °C, Aliquat 336), using nickel tetracarbonyl as the catalyst leads to a mixture of unsaturated acids[48]. More recently, Joo and Alper[49] reported the carbonylation reaction of allylic halides with cyanonickel complexes as catalysts (equation 9). While a



(9)

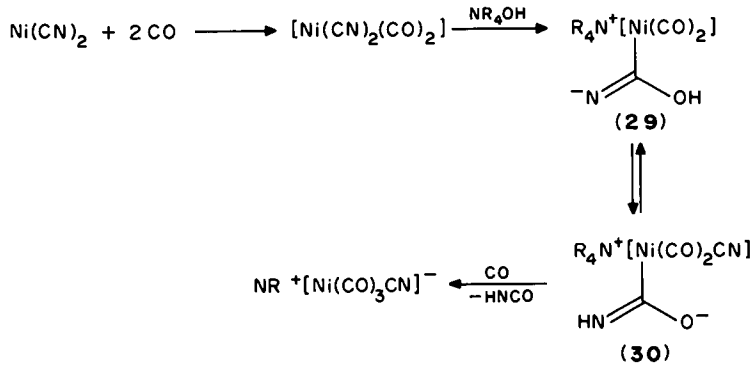
quaternary ammonium salt is beneficial to carbonylation, the reaction can occur in the absence of any phase-transfer agent (interfacial process). Different solvents have been used, isobutyl methyl ketone being the best. The base concentration influences both the yield and selectivity and under specific conditions a remarkable stereospecificity with respect to both **26** and **27** can be achieved (Scheme 10).



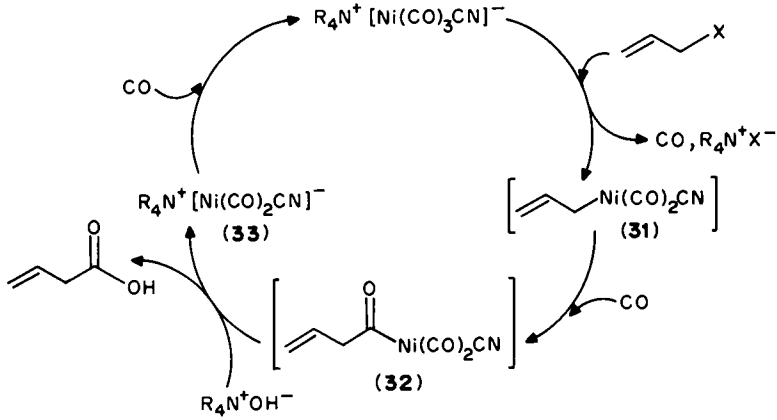
SCHEME 10

High yields of acids were obtained using a substituent at the 1- or 3- but not the 2-position of the allyl unit. The active nickel catalytic species has been characterized as $[Ni(CO)_3CN]^-$ and isolated as a bis(triphenylphosphine)iminium (PPN) salt. A possible mechanism for formation of this complex is outlined in Scheme 11. The key steps could be the addition of 2 mol of carbon monoxide on the nickel cyanide followed by the nucleophilic addition of hydroxide ion on the dicyanodicarbonylnickel (**28**) to obtain **29**, leading to **30** by hydrogen transfer. The final active species may result from the elimination of HNCO under a carbon monoxide atmosphere.

The mechanism of the carbonylation process (Scheme 12) can be rationalized as a displacement of the halide ion by the cyanotricarbonylnickel anion giving the η^1-allyl complex **31** (η^3-allyl species can also be involved, especially in the formation of isomeric acid products in some cases); a CO migration insertion sequence would transform **31** and **32** and the acid is then obtained by hydroxide cleavage of the acylnickel complex **33**. Regeneration of the catalyst occurs by carbonylation of **33**.



SCHEME 11



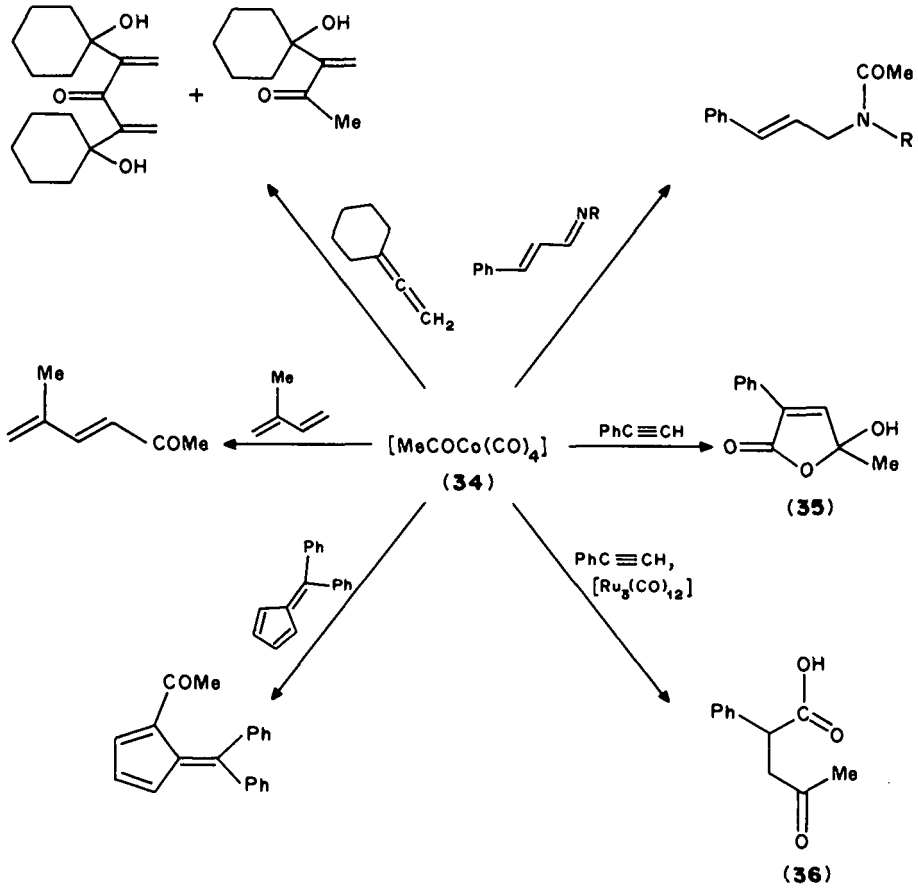
SCHEME 12

2. *Unsaturated organic compounds*

Different mechanisms for the carbonylation reactions described above show the importance of acyl complexes $[RCOM(L)_n]$ as key intermediates. Such transient species can react with suitable unsaturated organic compounds and the results are outlined in Scheme 13. These interesting mild, 'one-pot' syntheses are usually run with dicobalt octacarbonyl as the catalyst precursor and methyl iodide as the halide according to equation 10. High selectivities are usually obtained even in the bimetallic phase-transfer carbonylation where addition of $[Ru_3(CO)_{12}]$ gives the saturated γ-keto acid (**36**) rather than the hydroxybut-2-enolide **35**.

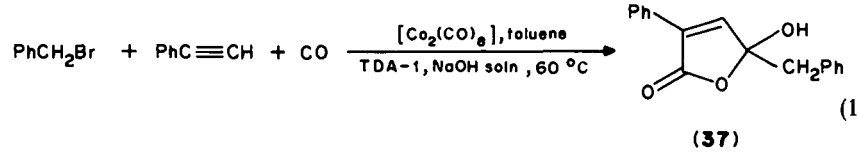
$$[Co_2(CO)_8] \xrightarrow{NR_4{}^+OH^-} [Co(CO)_4]^- \xrightarrow{MeI} [CH_3Co(CO)_4] \overset{CO}{\rightleftharpoons} [MeC(=O)—Co(CO)_4] \quad (10)$$

(**34**)



SCHEME 13

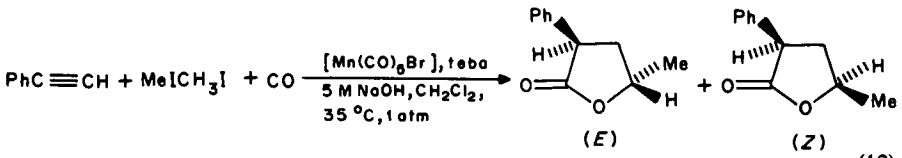
Reactions of the acylcobalt complex **34** with organic compounds are faster than the cleavage leading to the carboxylate anion. This is not the case when benzyl bromide is used instead of methyl iodide and phenylacetic acid is the only product. However, under specific solid–liquid phase-transfer conditions, the corresponding acylcobalt tetracarbonyl can be trapped by phenylacetylene to give the lactone **37** (equation 11)[56].



(11)

(37)

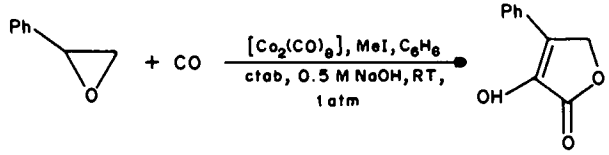
The carbonylation of alkynes with manganese carbonyl complexes has been reported[57]. The stoichiometric reaction of $[Mn_2(CO)_9Br]^-$, generated from bromopentacarbonyl-



(12)

manganese[58] and phenylacetylene, gives the γ-butyrolactone in 78% yield with a *E*/*Z* ratio of 57:31 (equation 12). A comparable yield and slightly higher selectivity with respect to the *E* isomer was observed when a polyethylene glycol (PEG 400) was used instead of the ammonium salt.

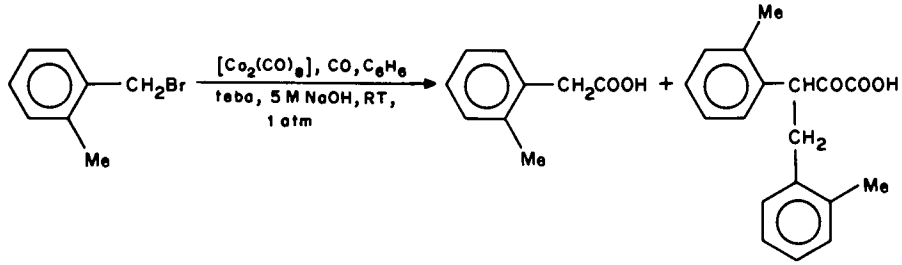
It is important to note that in all these reactions involving acyl–metal complexes, the halide precursor is used in a stoichiometric amount as a reactant. However, in some cases, these acyl species can be considered as the true catalyst of the carbonylation reaction. For example, the use of methyl iodide as the halide and styrene oxide as the organic receptor in a cobalt carbonyl-catalysed carbonylation under PTC results in the incorporation of two molecules of carbon monoxide in the strained ring to give the enol **38** of the α-keto lactone[59].



(38)

(13)

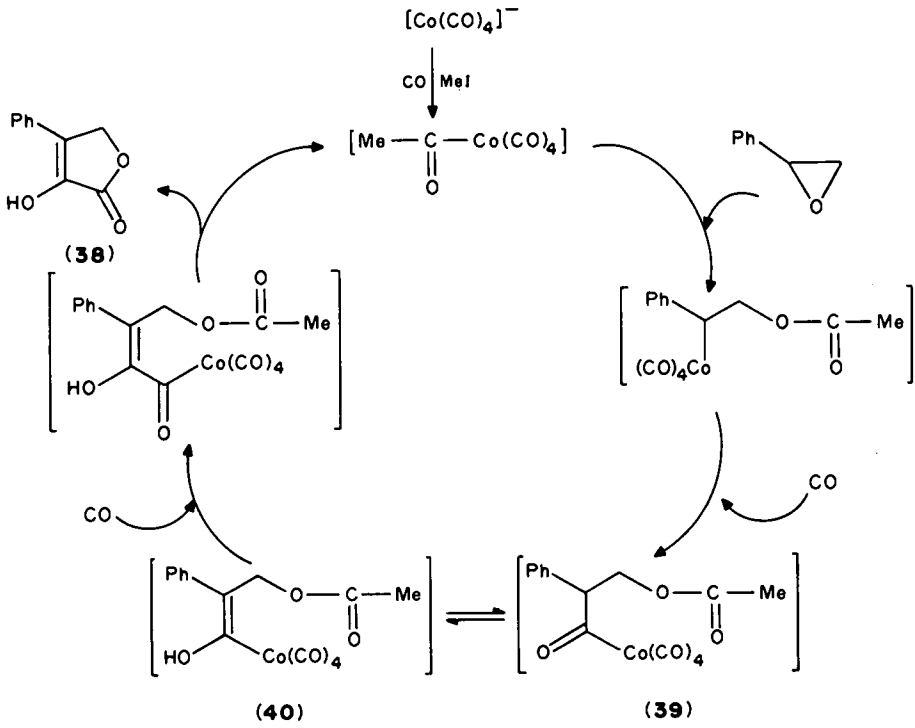
Such double carbonylation reactions have been extensively investigated in recent years[60] and syntheses of phenylpyruvic acid derivatives from substituted benzylic halides under PTC have been reported (equation 14)[24,25,61].



(14)

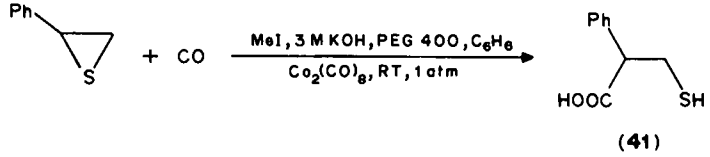
The enol structure of the lactone **38** largely supports the mechanism proposed for the double CO insertion through the ability of a transient phenacyl cobalt carbonyl complex (**39**) to undergo enolization, thereby promoting the second incorporation of CO in a vinylic cobalt—carbon bond (**40**) (Scheme 14).

The carbonylation of styrene oxide is a true phase-transfer process (no reaction without ammonium salt) and does not occur without methyl iodide or an aqueous phase (monophasic conditions). The base concentration is of prime importance. Whereas other types of oxiranes (aliphatic epoxides) do not react, carbonylation of the sulphur analogue



SCHEME 14

of styrene oxide (thiirane) does proceed to give a monocarbonylation product (equation 15)[62].



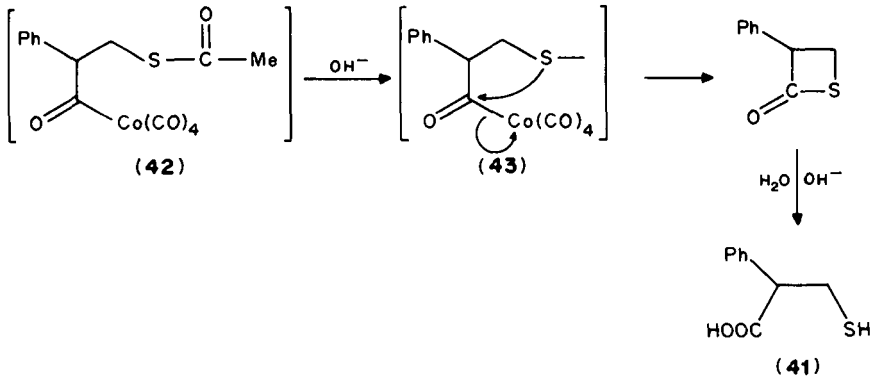
(15)

Thus, 2-phenylthiirane (styrene sulphide) was treated with carbon monoxide in the presence of the '*in situ*' generated acylcobalt tetracarbonyl to give the β-mercapto acid **38** in 75% yield. Polyethylene glycol (PEG) as the transfer agent was found to be superior to ammonium salts; sodium hydroxide is inferior to potassium hydroxide and the concentration effect is not as important as in the epoxide case. An interesting result is that the transformation of thiiranes to mercapto acids can be achieved by an acylcobalt catalyst formed from benzyl bromide (instead of methyl iodide) with lower yield; this is the first example of trapping such a complex in a liquid–liquid PTC[62].

Two contrasting features for oxiranes and thiiranes were observed. First, the reaction occurs for episulphides bearing either aromatic or aliphatic (linear or cyclic) substituent groups. Second, although the initial steps of both reactions may be analogous (generation

of acylcobalt, addition on the ring compound and CO insertion), the oxygen intermediate **39** can be enolized and promote a second CO insertion, whereas the thioester function of the sulphur analogue **42** undergoes rapid hydrolysis, affording the thiolactone which, in these specific conditions (base is present), is cleaved to give the mercapto acid **41** (Scheme 15).

It should be noted that under these phase-transfer conditions aziridines are only *N*-acylated without CO insertion[63].



SCHEME 15

B. Oxidation Reactions

1. Alkenes

Many inorganic oxidants can be transferred to an organic solvent by a phase-transfer catalyst, and the role of the latter can be to generate and stabilize active organometallic complexes for oxidation processes. For example, the industrially important palladium-catalysed conversion of ethylene to acetaldehyde (Wacker process) has been investigated under phase-transfer catalysis in order to allow the oxidation to occur under mild conditions[64]. Indeed, olefins are oxidized to ketones by oxygen, using palladium chloride as the catalyst, copper(II) chloride as a re-oxidant in a liquid–liquid system (80 °C, 1 atm), in the presence of a phase-transfer reagent. The nature of the latter is very important: when an ammonium salt is used, the reaction occurs only in the case of large lipophilic cations (e.g. at least one long alkyl chain with more than twelve carbon atoms). Further, only terminal olefins are converted into methyl ketones.

$$RCH{=}CH_2 + O_2 \xrightarrow[R_4N^+X^-,\ C_6H_6,\ 80\,^\circ C,\ 1\ atm]{PdCl_2,\ CuCl_2\cdot 2H_2O} RCOMe \qquad (16)$$

48–78%

Different palladium complexes can be used, including zero-valent species, and the catalyst can be recycled after reaction with only a slight reduction (5%) in activity.

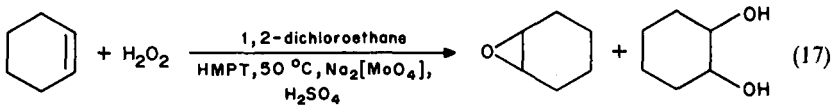
Complexes of rhodium, e.g. bis[(chloro)(hexa-1,5-diene)rhodium(I)], or ruthenium, including dichlorotris(triphenylphosphine)ruthenium(II) and ruthenium(III) chloride, catalyse the same reaction in lower yields, with both small or large quaternary ammonium

salts. When tetrabutylammonium sulphate was used, an isomerization reaction was reported and in the case of dienes the oxidation was not selective; these findings are in contrast with the results obtained in the presence of palladium species[65].

As mentioned previously, the nature of the phase-transfer catalyst is important and Alper *et al.*[66] reported the conversion of both internal and terminal olefins, simply by replacing the ammonium salt with a polyethylene glycol (PEG). It is interesting that 2- and 3- but not 4- and 5-ketones are generated by oxidation of *cis*-dec-2-ene or *trans*-non-2-ene and that the rate of oxidation of terminal olefins is greater than with the use of an onium salt as the phase-transfer agent.

When β-cyclodextrin was used as the phase-transfer reagent in palladium-catalysed oxidation, ketones from both internal and terminal olefins were formed in good yields. The reaction is applicable to a variety of olefins and, for instance, butanone is produced from either but-1-ene or both *cis*- and *trans*-but-2-ene. The use of such a cycloamylose (compared with an ammonium salt and PEG) is justified in the case of allylbenzene (no reaction with other types of phase-transfer reagents) and styrene, which affords benzaldehyde when oxidation is attempted using PEG or an ammonium salt but leads to acetophenone in 80% yield with the β-cyclodextrin system[67].

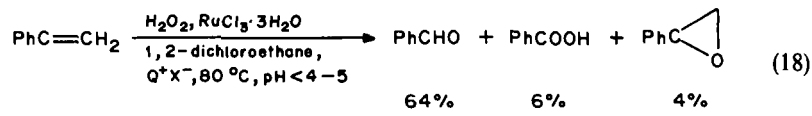
Selective epoxidation of olefins has been extensively studied[68,69] even under phase-transfer conditions, with or without a metal catalyst[4], where an ammonium salt or a crown ether extracts the HO_2^- ion (from hydrogen peroxide) in the organic medium. Hydrogen peroxide can also be used as the oxidant in a molybdenum- and tungsten-catalysed epoxidation reaction of olefins (and organic sulphides) in a biphasic system (equation 17). It was proposed that neutral lipophilic monodentate ligands (e.g. pyridine *N*-oxides, HMPT) play the role of phase-transfer catalysts[70].



(17)

The presence and the nature of the ligand affect the product yield and the decomposition of the oxidant. The acidity of the aqueous phase also has to be taken into account. Increasing the amount of sulphuric acid improves the reaction as a result of neutralization of anionic peroxo complexes in the aqueous phase followed by better ligand extraction of the catalytic species. On the other hand, the selectivity with respect to the epoxide tends to decrease owing to the acid-catalysed hydrolytic cleavage of the epoxide to the diol.

Hydrogen peroxide also promotes the oxidation of styrene to benzaldehyde in the presence of ruthenium chloride and a quaternary ammonium salt (dodecyldimethylammonium bromide) (equation 18).



(18)

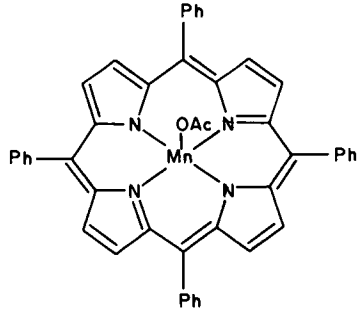
The true role of the phase-transfer agent was shown to be important for extracting both the peroxide and the metal into the organic medium[71]. Interestingly, when palladium chloride was used as the metal catalyst, a different selectivity was observed, since acetophenone was the main product (equation 19).

$$PhC{=}CH_2 \xrightarrow[\text{Aliquat 336}]{H_2O_2,\ PdCl_2,\ CH_2Cl_2} PhCOMe + PhCHO + PhCOOH \qquad (19)$$

56% 12% 14%

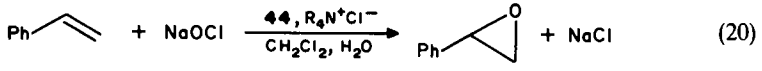
The use of hydrogen peroxide, especially at high concentrations, may be potentially hazardous[72] and other kinds of safer single-oxygen donors were investigated. Among these, sodium hypochlorite (NaOCl) appears to be a cheap, easy to handle, strong oxidant in basic media[73] able to oxidize (stoichiometrically) organic substrates[74].

Synthetic metalloporphyrins are efficient models of the cytochrome P-450 family of monooxygenase enzymes and have been widely used a catalysts in oxidations of organic substrates[75,76]. Thus, catalytic epoxidation of simple olefins by NaOCl under phase-transfer conditions occurs with [Mn(TPP)OAc] (**44**) as the metal catalyst[74,75]. The nature



(**44**)

of the metal is important and only the manganese(III) complex leads to significant amount of styrene oxide (36% after 3 h) (equation 20).



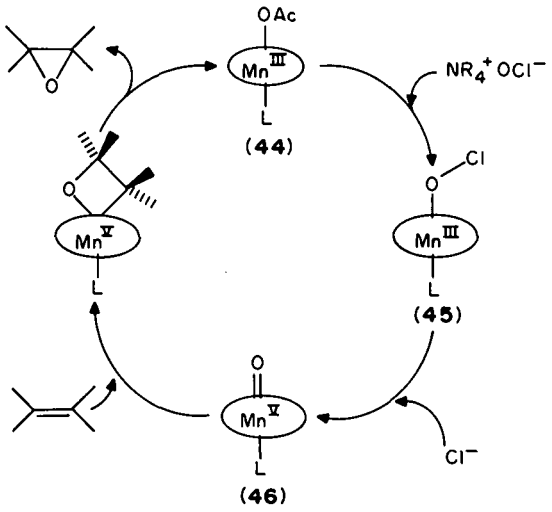
(20)

The reaction rates and selectivities are increased by addition of pyridines[77–81] or *N*-aryl-substituted imidazoles[79,80], which behave as axial ligands on the complexed metal. The phase-transfer agent is necessary in the reaction since less than 5% of styrene is converted without the ammonium salt, and only a small amount of the latter is needed to extract the hypochlorite anion into the organic phase.

A mechanism involving a high oxidation state oxomanganese complex (**46**) is outlined in Scheme 16. In the presence of the phase-transfer agent, the hypochlorite anion is extracted into the organic phase allowing a substitution reaction to occur with the axial ligand to give **45**. The electrophilic property of the oxygen atom in this transient complex is probably too weak to be transferred to the olefin, but the heterolytic cleavage of the oxygen—chlorine bond may occur to afford the oxomanganese(V) complex, which is potentially able to epoxidize the alkene[77].

2. *Alcohols*

The oxidation of alcohols under phase-transfer catalysis has been investigated using many transition metal compounds as catalysts. Using the same system as mentioned

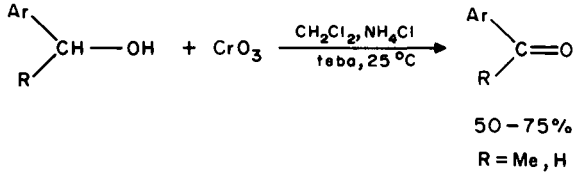


SCHEME 16

above involving manganese–porphyrin complexes and hypochlorite anion as the oxidant, benzyl alcohols were catalytically oxidized in benzaldehyde with good selectivity (equation 21)[82]. The presence of both the manganese complex and the trioctylmethylammonium salt considerably accelerates the reaction. Note that saturated hydrocarbons (e.g. adamantane) can be oxidized in this way, affording a mixture of chlorides, alcohols, and ketone[82]. The anionic iron complex $K_2[FeO_4]$ was shown to be able to achieve such an oxidation of benzyl alcohol to benzaldehyde under phase-transfer conditions[83].

$$PhCH_2OH + NaOCl \xrightarrow[(C_8H_{17})_3CNH_3{}^+Cl^-]{[Mn(tpp)],\ CH_2Cl_2} PhCHO \qquad (21)$$

The oxidation of alcohols by chromium(VI) compounds under PTC was also studied[84,85] and generally involved strongly acidic conditions incompatible with acid-sensitive substrates. More recently, a stoichiometric oxidation reaction with CrO_3 under mild conditions was reported[86] in which primary and secondary benzylic alcohols were converted into ketones or aldehydes, through an ammonium chlorochromate intermediate (equation 22).



(22)

Chromium is not the only transition metal able to perform this transformation. Thus, under PTC, dilute hydrogen peroxide oxidizes primary and secondary alcohols to the corresponding carbonyl compounds with a catalytic amount of molybdenum(VI) and tungsten(VI) oxides with high yields and selectivities[87] (equation 23). The efficiency of the

oxidant is closely related to the pH of the aqueous phase. High acid concentrations slow the reaction, whereas at low acidities the selectivity is reduced owing to the peroxide decomposition. It is important to note that in contrast to the similar catalytic system applied to olefins, described previously, the phase-transfer reaction is performed with a classical ammonium salt (Aliquat 336) instead of a neutral lipophilic compound (HMPT). The authors explained this in terms of anionic peroxo compounds as the extracted active catalysts, since such species have already been employed as effective oxidants for alcohols[88]. The other important differences is that in the case of alcohols, tungsten in much more efficient than molybdenum.

Analogous reaction can also be catalysed by palladium acetate [$Pd(OAc)_2$] in solid–liquid phase-transfer conditions (e.g. tetrabutylammonium chloride, DME, $NaHCO_3$, PhIO, RT, 48 h) with comparable yields (75–95%)[89], depending on the nature and concentration of the ammonium salt (tbac > tbab > tbai > tetraethylammonium chloride and tetramethylammonium bromide). Finally, ruthenium tetroxide generated *in situ* from ruthenium dioxide and periodate[90] or hypochlorite[91] can promote the oxidation of secondary alcohols to ketones[92].

$$RR'CHOH + H_2O_2 \xrightarrow[\substack{1,2\text{-dichloroethane,}\\ 75\,^\circ C,\ \text{Aliquat 336}}]{Na_2[MO_4],\ H_2O,\ H^+} RR'CO \qquad (23)$$

85–100%

M = Mo, W

3. *Aromatic hydrocarbons*

Oxidation of aromatic compounds is probably one of the most widely used processes on an industrial scale. The homogeneous transformation of alkyl aromatics to carboxylic acids is usually carried out in acetic acid solvent with cobalt or manganese complexes in the presence of bromide ions[68]. This reaction is effective for activated aromatic compounds and can be initiated by phase-transfer catalysis. Thus, in the presence of an ammonium salt, cobalt bromide catalyses the oxidation of *p*-xylene and maximum absorption rates of oxygen depend on the nature of the transfer agent[93]. The role of the latter could be to promote the formation of new active anionic cobalt(III) complexes and to stabilize them in the organic medium. Decomposition of the cobalt species could produce bromine radicals, initiating the oxidation process (equation 24).

$$(L—Co^{III}—Br)^-NR_4^+ \rightarrow (L—Co^{II}) + Br^\cdot \xrightarrow{RMe,\ O_2} RCH_2OO^\cdot + H^+Br^- \qquad (24)$$

However, these oxidation systems are inefficient for deactivated compounds such as nitrotoluene[94]. Note that in the presence of a phase-transfer agent (Bu_4NHSO_4), the mediated electro-oxidation of 4-nitrotoluene to 4-nitrobenzoic acid was achieved by hexavalent chromium complexes in a sulphuric acid medium a 80 °C[95].

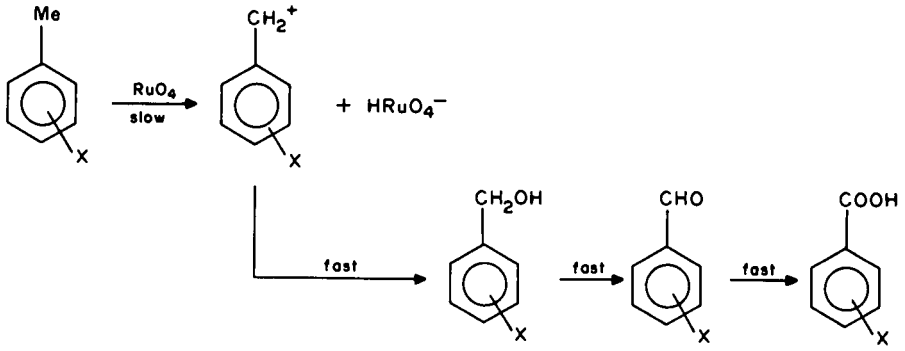
More important, from a catalytic point of view, is the oxidation of deactivated methylbenzenes by aqueous sodium hypochlorite, using ruthenium tetraoxide as the catalyst under PTC[96]. RuO_4 was introduced as a good oxidant in 1953 by Djerassi and Engle[97]; it is able to oxidize alcohols under PTC in combination with NaOCl (equation 25).

$$ArMe + 3NaOCl \xrightarrow[\substack{\text{tbab, RT, pH 9,}\\ 1,2\text{-dichloroethane}}]{RuCl_3\ 3H_2O} ArCOO^-Na^+ + 2NaCl + HOCl + H^+ \qquad (25)$$

92–99%

Ruthenium tetraoxide is formed *in situ* by the action of sodium hypochlorite on $RuCl_3$ and stays in the organic phase as long as NaOCl is present. When all the hypochlorite has been consumed, black RuO_2 precipitates, stopping the reaction. This is a true phase-transfer process since no reaction occurs without a quaternary ammonium salt. The pH of the aqueous phase has to be maintained between 8.0 and 10.5, corresponding to a range where NaOCl solutions are neither easily decomposed nor too stable.

Results of kinetic experiments show that the reaction is a overall first order in metal and phase-transfer catalyst, each being from zero to first order, depending on their relative concentrations. These kinetic results, the indirect detection of benzyl alcohol (trapped by the acid to form ester as a by-product), and the effect of various substituents led to the suggestion of a mechanism involving a carbonium intermediate, giving the alcohol, followed by fast oxidation to the isolated acid (Scheme 17).



SCHEME 17

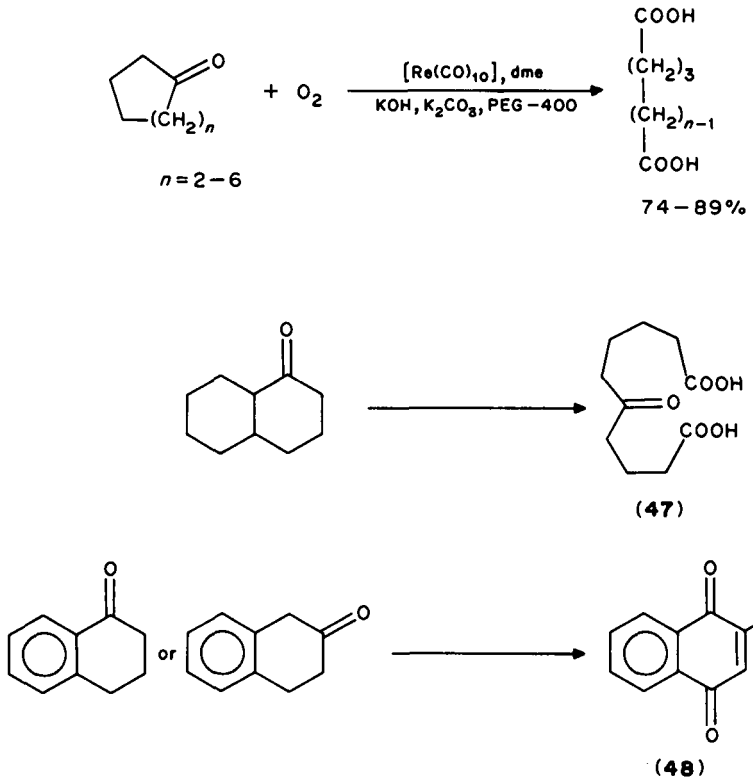
The oxidation of alcohols to aldehydes[98] and transformation of the latter to carboxylic acids[99] had been previously reported by Sasson and coworkers in a classical phase-transfer system (without metal catalyst) with sodium hypochlorite.

Aromatic dicarboxylic acids were prepared by oxidation of arenes (e.g. phenanthrene) with hydrogen peroxide under PTC at 80 °C in the presence of tungstic acid [H_2WO_4] and a quaternary ammonium salt[100].

4. Ketones

Oxidation of ketones to diacids is an important process of industrial value in which several transition metals, including rhenium[101], were shown to be active catalysts. The same transformation of cyclic ketones was studied by Osowska-Pacewicka and Alper[102] by means of phase-transfer and rhenium catalysis using oxygen as the oxidant under milder conditions (RT, 1 atm versus 98 °C, 300–500 psi), leading to diacids in good yields (Scheme 18). Oxidation of a bicyclic ketone (e.g. 1-decalone) affords the keto diacid (5-ketodecane-1, 10-dioic acid) (**47**), whereas hydroquinone (2-hydroxy-1,4-naphthoquinone) (**48**) was obtained starting either from 1- and 2-tetralone.

Low product yields were attained in the absence of the phase-transfer agent but quaternary ammonium salts or the podand TDA-1 (**1c**) can be used instead of PEG-400. The role of potassium hydroxide is believed to be promotion of the deprotonation of the ketone while potassium carbonate may be a dehydrating agent. These two salts, which are



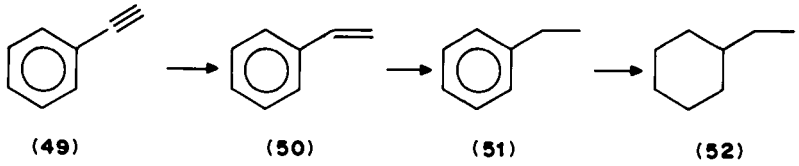
SCHEME 18

more efficient than their sodium analogues, are solubilized in dimethoxyethane (dme) by the phase-transfer catalyst. The effect of the rhenium complex is important ($ReCl_3$ is an inefficient catalyst for this process) and it could be involved in hydroperoxide decomposition. Although the mechanism is still unknown, this is the first example of a rhenium- and phase-transfer-catalysed reaction.

C. Reduction Reactions

1. Hydrogenation of unsaturated compounds

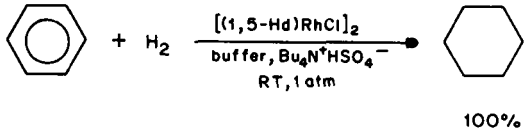
Hydrogenation of olefins in a biphasic system has been reported using rhodium catalysts located in the phase in which the organic substrate was not soluble[103]. More recently, Blum *et al.*[104] reported the hydrogenation of a variety of unsaturated compounds (olefins, alkynes, arenes) under mild conditions (room temperature and atmospheric pressure) using PTC and $RhCl_3$ as the catalyst. The presence of both water and an ammonium salt is essential and labelling experiments indicated that the hydrogen atoms of the water are not involved in the hydrogenation reaction. The different reaction rates between these various unsaturated compounds are well illustrated by the phenylacetylene case (equation 26).



(26)

Although olefins were shown to be reduced faster than alkynes, phenylacetylene (**49**) is not converted directly into ethylbenzene (**51**) or a cyclohexane derivative (**52**); instead, the first step of the reaction affords styrene (**50**), which is further reduced only when complete conversion of the acetylene has occured. As long as **50** was present, no ring hydrogenation was detected. This suggests that each reaction step could be achieved by a different transient transition metal complex.

The phase-transfer- and rhodium-catalysed reduction of arenes was also reported in the presence of the bis[chloro(hexa-1,5-diene)rhodium] complex[105] (equation 27).



(27)

Table 1 shows how this very mild process is efficient for a large variety of aromatic compounds and the specificity of the arene reduction was demonstrated when using benzamide, methyl benzoate, and phenyl acetate. Under homogeneous monophasic conditions (THF, cyclodextrin), the same rhodium catalyst promotes the reduction of acetophenone to ethylbenzene without any hydrogenation of the aromatic ring[106].

The stereoselectivity of the process is illustrated by the conversion of naphthalene into either tetralin or *cis*-decalin, depending on the reaction conditions, and for *p*-methylanisole, which gives *cis*-4-methylcyclohexyl methyl ether as the only product. Note that heterocyclic such as quinoline easily undergo exclusive hydrogenation of the heterocyclic ring. No reaction occurs without a phase-transfer agent, the pH of the buffer

TABLE 1. Hydrogenation of arenes by hydrogen catalysed by a [(1,5-Hd)RhCl]$_2$/PTC system[105]

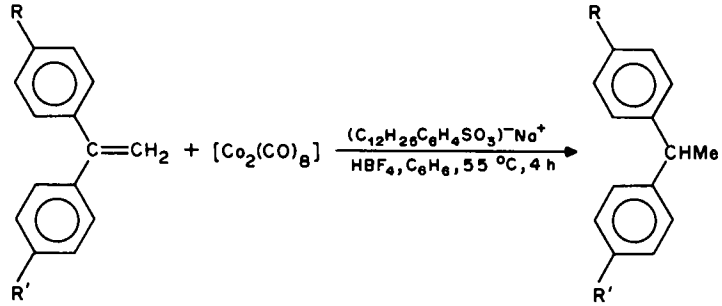
Reactant	Product	Yield (%)
$PhCONH_2$	$C_6H_{11}CONH_2$	79
PhCOOMe	$C_6H_{11}COOMe$	69
MeCOOPh	$MeCOOC_6H_{11}$	31
Naphthalene[a]	Tetralin	73
	Decalin	Trace
Naphthalene[b]	Tetralin	20
	Decalin	80
p-Methylanisole	*cis*-4-Methylcyclohexyl methyl ether	92
Quinoline	1,2,3,4-Tetrahydroquinoline	100[c]

[a]Benzene as the organic solvent.
[b]Hexane as the organic solvent.
[c]Yield for reaction effected at 75 °C (15% at RT).

(7.4–7.6) is critical, and under these conditions $RhCl_3 \cdot 3H_2O$ is inefficient, since $Rh(OH)_3 \cdot 3H_2O$ would be formed.

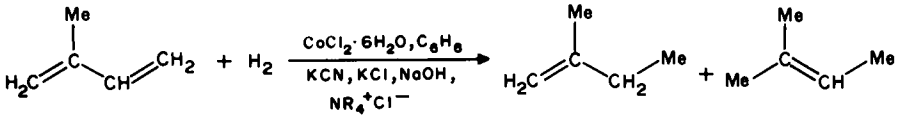
Rhodium is not the only transition metal that is potentially active in hydrogenation reactions under PTC. Thus, reduction of anthracene and nitrogen heterocyclics is catalysed by iron pentacarbonyl under drastic biphasic water gas shift conditions (KOH/H_2O, 300 °C, CO, NBu_4I or 18-crown-6)[107].

Cobalt carbonyl was shown to be a good reactant for hydrogenation of activated olefins under specific acidic phase transfer conditions[108], with sodium 4-dodecylbenzenesulphonate as the transfer agent (equation 28). Both cobalt and the phase-transfer catalyst are necessary to obtain high yields of ethane derivatives, and carbonium ion and hydridocobalt tetracarbonyl are involved as intermediates in this reduction process[109].



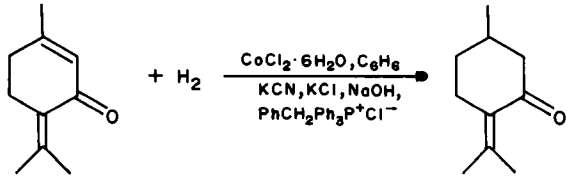
(28)

Conjugated dienes can be hydrogenated by phase-transfer catalysis with hydrated cobalt chloride as the catalyst precursor, using a mixture of potassium chloride, potassium cyanide, sodium hydroxide, benzene, hydrogen and a quaternary ammonium salt (micelles also work)[110–114] (equation 20). The active catalyst may be the hydridopentacyanocobaltate $[HCo(CN)_5]^{3-}$.



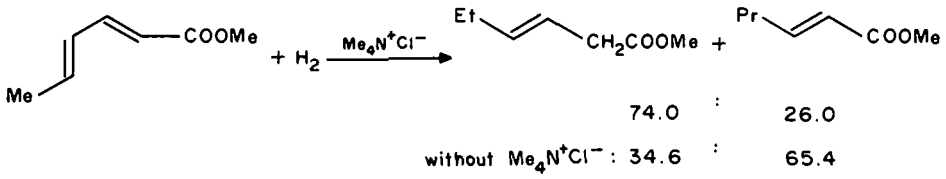
(29)

The reduction of α, β-unsaturated ketones can be achieved by the same cobalt-catalysed process involving $[HCo(CN)_5]^{3-}$ under biphasic conditions, where the role of the phase-transfer agent is to stabilize the anionic complex in the organic phase[115] (equation 30).



(30)

Methyl sorbate is also hydrogenated under such conditions and the results show that the presence of the phase-transfer catalyst changes the reaction pathway from a predominant 1,2-addition process to mostly 1,4-addition (Scheme 19).

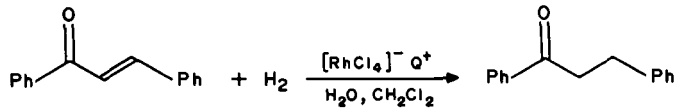


SCHEME 19

The reaction of α,β-unsaturated ketones and esters with sodium formate in PTC has been described as a dichlorotris(triphenylphosphine)ruthenium(II)- and phase-transfer (Aliquat 336)-catalysed process[116] (equation 31).

$$2PhCH{=}CHCOPh + 2HCOONa + H_2O \xrightarrow[\text{Aliquat 336, } o\text{-dichlorobenzene, } 109\,^\circ C]{[RuCl_2(PPh_3)_3]} 2PhCOCH_2CH_2Ph + CO_2 + Na_2CO_3 \quad (31)$$

A transient ruthenium hydride, generated by formate substitution of a chloro ligand of the ruthenium complex, is assumed to be the true catalyst in this reduction reaction. Considering the high temperature required (109 °C) in this method, another catalytic system circumventing this drawback was recently reported by Azran *et al.*[117], based on the powerful activity of the solvated ion pair $[(C_8H_{17})_3NCH_3]^+[RhCl_4]^-$; this hydrogenation reaction occurs under mild conditions (30 °C, 1 atm, PTC). The presence of water was found to be essential to the catalysis and replacement of the ammonium salt by a quaternary phosphonium salt accelerates the metal extraction and the reduction process (equation 32). It is interesting to note the selective olefinic reduction by this phase-transfer and rhodium catalysis which does not affect the C=O function at all.



(32)

The selective hydrogenation of olefinic double bonds in unsaturated nitro compounds using the rhodium trichloride and Aliquat 336 catalysts system was also reported[118]. No reduction of the nitro group leading to amino products was detected as long as complete hydrogenation of the double bond was not achieved. Under these conditions, nitrobenzene gives a mixture of aniline and nitrocyclohexane.

2. *Carbonyl compounds*

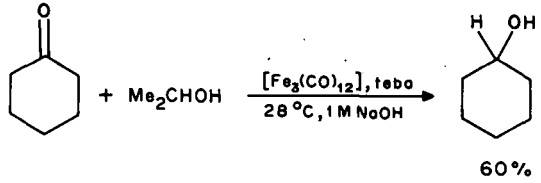
Hydrogenation of the carbonyl group on saturated aldehydes and ketones is possible under PTC with sodium formate and ruthenium or rhodium complexes[119] (equation 33).

$$RR'Co + HCOONa + H_2O \xrightarrow{90\,^\circ C} RR'CHOH + NaHCO_3 \quad (33)$$

R, R′ = H, alkyl, aryl

The reduction of aldehydes was shown to be more efficient when $[RuCl_2(PPh_3)_3]$ was used as the catalyst in the presence of Aliquat 336 as the phase-transfer agent. Complete conversions of the substrates usually resulted, whereas almost no transformation took place when the ammonium salt was absent. Further, the nature and concentration of the salt are also important[120]. This catalytic system was reported to proceed much more slowly when applied to ketones, and chlorotris(triphenylphosphine)rhodium was found to be more active than a ruthenium complex. A large excess of triphenylphosphine was required to prevent reduction of the rhodium catalyst to inactive free metal. Aromatic and alicyclic ketones may be converted to alcohols in good yields and the presence of the phase-transfer agent is beneficial but not so crucial as for the aldehyde reaction.

Iron carbonyl complexes were shown to be able to catalyse transfer hydrogenation of ketones under phase-transfer conditions[121] (equation 34). Triiron dodecacarbonyl



(34)

$[Fe_3(CO)_{12}]$ is more efficient than $[Fe_2(CO)_9]$ or $[Fe(CO)_5]$, and among the phase-transfer agents teba and 18-crown-6 are better than long-chain salts such as Aliquat 336. When the reaction is run without a phase-transfer agent, the yield of cyclohexanol drops from 60 to 20%. Finally, 1-phenylethanol is a better hydrogen donor than isopropanol.

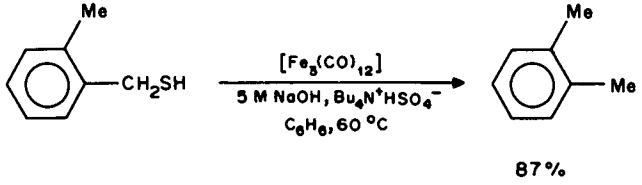
3. Organic halides

The property of primary or secondary carbinols such as benzyl alcohols of being excellent hydrogen donors has been used in a palladium- and phase transfer-catalysed reduction of aryl halides[122] (equation 35). Almost quantitative yields were obtained after 4 h, indicating a true intermolecular hydrogen transfer rather than a dehydrogenation–hydrogenation process. Non-polar solvents (benzene, *n*-alkanes) gave higher rates in the catalytic process and the best onium salts were the most lipophilic ones combined with the most hydrophilic counter anions.

$$ArBr + PhCH_2OH + NaOH \xrightarrow[C_6H_6,\ H_2O,\ 70\,^\circ C,\ \text{Aliquat 336}]{[PdCl_2(PPh_3)_2,\ PPh_3]} ArH + PhCHO + NaBr + H_2O \qquad (35)$$

4. Thiols

Desulphurization reactions have been effected stoichiometrically by phase-transfer catalysis with organometallic compounds[123]. Thus, treatment of *o*-methylphenylmethanethiol with triiron dodecarbonyl in benzene under PTC (NaOH, $Bu^n_4N^+HSO_4^-$, 16 h, 60 °C) afforded *o*-xylene in 87% yield (equation 36). No desulphurization reaction was observed in the absence of the ammonium salt and a variety of benzenediarylmethane- and triphenylmethanethiols were converted into hydrocarbons. The trinuclear iron hydride $[HFe_3(CO)_{11}]^-$ stabilized as an NR_4^+ salt could be a key intermediate in the mechanism of the reaction involving electron transfer pathways. The



(36)

same reaction was performed using dicobalt octacarbonyl instead of the iron cluster, giving better yields of hydrocarbons.

5. *Nitro compounds*

Stoichiometric reductions with triiron dodecarbonyl are not limited to ketones or thiols and one of the first reported organometallic and phase-transfer processes was reduction of nitro compounds to amines with iron complexes[124]. This transformation was obtained catalytically, shifting from iron to ruthenium as the metal catalyst under phase-transfer catalysis.

The first investigation was carried out on a zero-valent ruthenium cluster, $[Ru_3(CO)_{12}]$, giving excellent yields of amines, starting from aromatic or aliphatic nitro compounds[125], under milder conditions (RT, 1 atm) than those involved in the water gas shift reaction (100 °C, 500 psi)[126] (equation 37).

$$\underset{\textbf{(53)}}{RNO_2} \xrightarrow[5\text{M NaOH, RT, 1 atm}]{CO,\ [Ru_3(CO)_{12}],\ \text{teba}} \underset{\textbf{(54)}}{RNH_2} \qquad 85\text{–}100\% \tag{37}$$

It is assumed that the same type of hydridocarbonyl cluster $[HM_3(CO)_{11}]^-$ (M = Ru, Fe) is the active species, but the presence of a carbon monoxide atmosphere increases the product yields, whereas its influence was negative when iron carbonyl was used, suggesting the formation of different species as intermediates in the ruthenium and iron reduction processes.

When sodium methoxide was used instead of sodium hydroxide, formamides were obtained as the main products of this reaction, in which carbon monoxide was replaced by synthesis gas ($CO–H_2$)[127]. Note that substitution of $[Fe_3(CO)_{12}]$ for $[Ru_3(CO)_{12}]$ results in the preferential formation of carbamate esters. The same gas mixture was used in a catalytic reduction of nitro compounds by a ruthenium(II) complex, $[RuCl_2(PPh_3)_3]$, affording amines in reasonable yields[128].

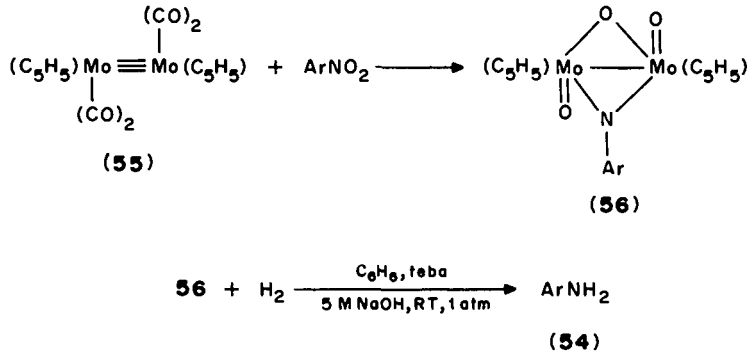
More recently, the use of bimetallic phase-transfer catalysis for the reduction of nitro compounds (**53**) under a carbon monoxide atmosphere has been described, assuming a synergistic effect of cobalt carbonyl and bis[(chloro)(hexa-1, 5-diene)rhodium] in the amine formation (50–91 yield) (equation 38); under the specific phase-transfer conditions employed, no reaction occurred when only one metal was present[129].

$$\textbf{53} \xrightarrow[\substack{[Co_2(CO)_8],\ [(1,5\text{-Hd})RhCl]_2,\\ \text{RT, 2.5 h}}]{5\text{M NaOH, } C_6H_6} \textbf{54} \tag{38}$$

It was then shown that rhodium carbonyl clusters are able to catalyse the reduction reaction in a biphasic system in the absence of a phase-transfer agent and cobalt carbonyl. The bimetallic effect was established to be a coincidence of inhibition and reactivation of

the true catalyst by the quaternary ammonium salt and cobalt carbonyl, respectively[130]. When rhodium was used alone, the true catalytic species, probably anionic polyrhodate clusters {such as $[Rh_6(CO)_4]^-$ or $[Rh_{10}(CO)_{30}]^{2-}$}, are soluble in water and the reduction occurs at the interface. The presence of a phase-transfer agent leads to ammonium polyrhodates $\{NR_4^+[Rh_6(CO)_{14}]^-\}$, which are insoluble in both phases and consequently inefficient for the reduction reaction. In the bimetallic system, the role of $[Co_2(CO)_8]$ was presumed to be to trap the phase-transfer cation as $NR_4^+[Co(CO)_4]^-$, leaving the rhodium catalyst free to perform the reaction.

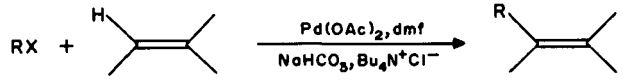
The mechanism for such reductions of nitro compounds has not been clarified, although nitroso compounds and nitrene complexes have been postulated[128]. However, it is noteworthy that hydrogenation of an isolated molybdenum–nitrene complex (**56**), generated from $[Mo_2(C_5H_5)_2(CO)_4]$ (**55**) and nitrotoluene, affords *p*-toluidine under phase-transfer conditions in a quantitative yield (Scheme 20)[131].



SCHEME 20

D. Vinylation Reactions

Vinylation reactions of organic halides catalysed by a palladium complex[132] have been achieved under solid–liquid phase transfer catalysis (equation 39). This process has been



(39)

well described in homogeneous monophasic systems by Heck[133] and the advantage of using the mild conditions of PTC was to control the stereospecificity of the reaction. Thus, highly stereoselective palladium-catalysed alkylation of vinylic halides[143] or acetylenic iodides[135] can be performed at room temperature in DMF in the presence of a quaternary ammonium salt (Table 2).

It has been observed that the vinylation reaction can be accelerated by using potassium carbonate instead of sodium hydrogencarbonate as the inorganic base. The stereospecificity is also improved by the enhancement of the reaction rate. The advantages of the synthesis of methyl (*E*)-enynoates and (*E*)-enynones by vinylation of acetylenic iodides are the availability of the starting materials, the simple work-up, and the extremely high stereoselectivity for such useful synthetic intermediates.

TABLE 2. Palladium catalysed vinylation of halides under solid–liquid PTC[134,135]

Halide	Vinylic substrate	Product	Yield (%)	Selectivity
(*E*)-$C_4H_9CH{=}CHI$	$CH_2{=}CHCOOMe$	$C_4H_3CH{=}CHCH{=}CHCOOMe$	90	94/6[a]
(*Z*)-$C_4H_9CH{=}CHI$	$CH_2CHCOOMe$	$C_4H_3OH{=}OHCH{=}CHCOOMe$	93	77/23[a]
(*E*)-$C_4H_9CH{=}CHI$	$CH_2{=}CHCOOMe$	$C_4H_9CH{=}CHCH{=}CHCOMe$	97[b]	99/7[a,b]
$C_4H_9C{\equiv}CI$	$CH_2{=}CHCOOMe$	$C_4H_9C{\equiv}CCH{=}CHCOOMe$	53[b]	100/0[b,c]
$C_6H_5C{\equiv}CI$	$CH_2{=}CHCOMe$	$C_6H_5C{\equiv}CCH{=}CHCOMe$	60[b]	100/0[b,c]

[a](*E*, *E*)/(*E*, *Z*) ratio.
[b]Using K_2CO_3 instead of $NaHCO_3$.
[c](*E*)/(*Z*) ratio.

TABLE 3. Ligand exchange in metal complexes under phase-transfer conditions

Metal	L	Product	Ref.
$[M(CO)_6]$[a]	bipy	$[M(CO)_4bipy]$[b]	137
$[M(CO)_6]$[a]	diphos	$[M(CO)_4diphos]$[b]	137
$[M(CO)_6]$[a]	$AsPh_3$	$[M(CO)_5AsPh_3]$	137
$[M(CO)_6]$[a]	Bu^tNC	$[M(CO)_5CNBu^t]$[b]	138
$[M(CO)_6]$[b]	OH^-	$[M(CO)_5OH]^-$[d]	139
$[M(CO)_6]$[b]	F^-	$[M(CO)_5F]^-$	140
$[M(CO)_6]$[a]	S^{2-}	$[M(CO)_5SH]^-$[d]	141
$[M(CO)_6]$[a]	SH^-	$[M(CO)_5SH]^-$[d]	142
$[Mn_2(CO)_{10}]$	Br^-	$[Mn_2(CO)_8Br]$[d]	143
$[M(CO)_5PPh_3]^+$[e]	OH^-	$[M(CO)_4HPPh_3]$[d]	144, 145

[a]M = Cr, Mo, W.
[b]Liquid–liquid PTC.
[c]M = Cr, W.
[d]Solid–liquid PTC.
[e]M = Mn, Re.

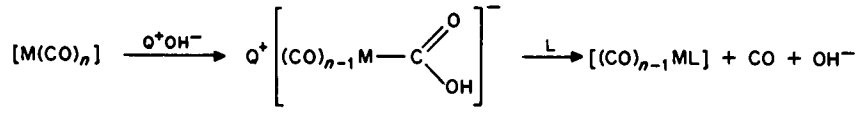
III. ORGANOMETALLIC SYNTHESIS

Phase-transfer catalysis is an excellent method for promoting the synthesis of new transition metal complexes in organometallic chemistry[10–12].

A. Ligand Exchange

A large number of ligand substitution reactions under PTC have been described. As shown in Table 3, this reaction has been applied to metal carbonyls in the presence of hydroxide anion, which could induce the formation of a transient hydroxycarbonyl complex (**57**) (equation 40). According to Brown and Bellus[136], the substitution by the entering ligand L occurs with the CO group in the labilized *cis* position in the hydroxycarbonyl species **57**.

Ligand substitution can be promoted by PTC on complexes other than metal carbonyls. Thus low-valent nickel cyanide $K_4[Ni(CN)_4]$ reacts with diphenylacetylene in a solid–liquid phase-transfer system in the presence of 18-crown-6 to give the first example of an anionic alkyne adduct of a cyano nickel complex[146] (equation 41). An unexpected reaction



(57) (40)

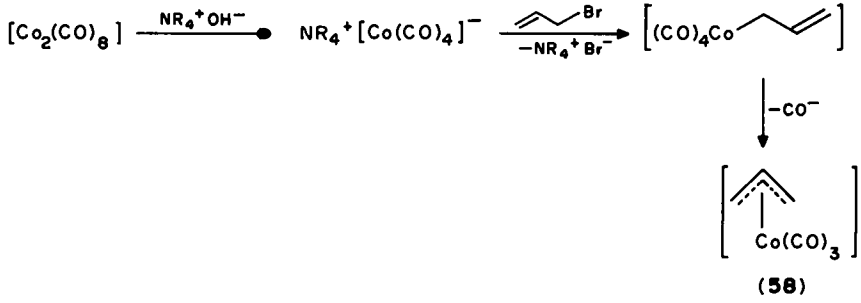
occurs when $K_4[Ni(CN)_4]$ is treated with benzaldehyde in acetonitrile under the same conditions. The same species can be obtained starting directly from (*E*)-cinnamonitrile using the same phase transfer method (equation 42).

$$[K_4Ni(CN)_4] + PhC{\equiv}CPh \xrightarrow[18\text{-crown-6}]{MeCN} 2(K\cdot crown)^+[Ni(CN)_2(PhC{\equiv}CPh)] \quad (41)$$

$$PhCHO + K_4[Ni(CN)_4] \rightarrow 2(K\cdot crown)^+[\eta^2\text{-}PhCH{=}CHCN)Ni(CN)_2]^- \quad (42)$$

B. Allyl Complexes

The first example of an η^3-allylcobalt complex synthesis in PTC was reported in 1976[147]. As discussed before, the tetracarbonylcobalt anion, $[Co(CO)_4]^-$, is easily generated from $[Co_2(CO)_8]$ and OH^- under phase-transfer conditions and extracted into the organic solvent as an ammonium salt, where reaction with the halide takes place, as outlined in Scheme 21. Good yields (72–80%) of η^3-allylcobalt complexes (e.g. **58**) were



(58)

SCHEME 21

obtained by using allyl halides with a substituent at the 2- or 3-position of the allyl unit. More recently, this organometallic synthesis was extended to other allyl complexes using metal carbonyl halides instead of metal carbonyl. Gibson and coworkers[148,149] showed that η^3-allyl complexes (Table 4) are the usual reaction products, although η^1-allyl species were isolated in some cases.

η^3-Allyl complexes could be synthesized through a metallocarboxylic acid intermediate (**59**) followed by the attack of the allyl halide on the *cis*-position of **59** to give **60**, as illustrated for $[BrMn(CO)_5]$ in Scheme 22[58].

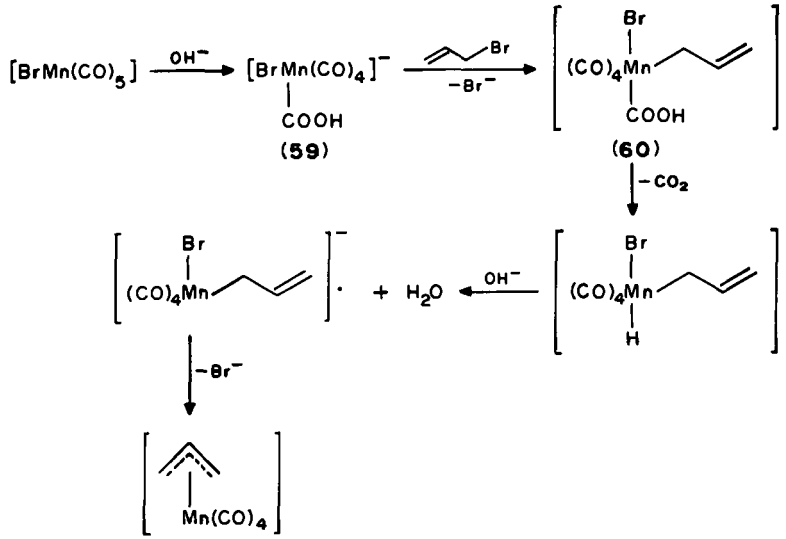
C. Metallation

Phase-transfer catalysis is a valuable method for the metallation of organic ligands. Ferrocenes are easily synthesized under solid–liquid PTC using a crown ether

TABLE 4. η^3-Allyl generation from metal carbonyl halides with allyl halides under PTC

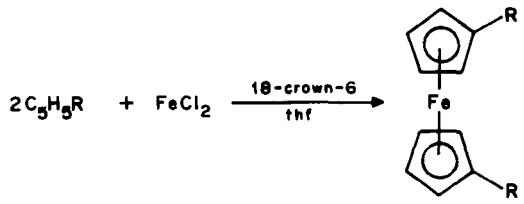
Metal carbonyl halide	Allyl halide	η^3-Allyl complex	Yield (%)	Ref.
$[Mn(CO)_5Br]$	C_3H_5Br	$[\eta^3\text{-}C_3H_5Mn(CO)_4]$	80	148
$[Mn(CO)_5Br]$	$2\text{-}MeC_3H_4Cl$	$[2\text{-}Me\text{-}\eta^3\text{-}C_3H_4Mn(CO)_4]$	48	148
$[Mn(CO)_4PPh_3Br]$	C_3H_5Br	$[\eta^3\text{-}C_3H_5Mn(CO)_3PPh_3]$	90	148
$[\eta^3\text{-}C_3H_5Fe(CO)_3Br]$	C_3H_5Br	$[(\eta^3\text{-}C_3H_5)_2Fe(CO)_2]$	76	148
$[CpMo(CO)_3Cl]$	C_3H_5Br	$[\eta^3\text{-}C_3H_5(Cp)Mo(CO)_2]$	95	148
$[CpFe(CO)_2Br]$	C_3H_5Br	$[\eta^3\text{-}C_3H_5(Cp)Fe(CO)_2]$	60	148
$[CpRU(CO)_2Cl]$	C_3H_5Cl	$[\eta^3\text{-}C_3H_5(Cp)Ru(CO)]$	80[a]	149

[a] 1.1 *exo–endo*.



SCHEME 22

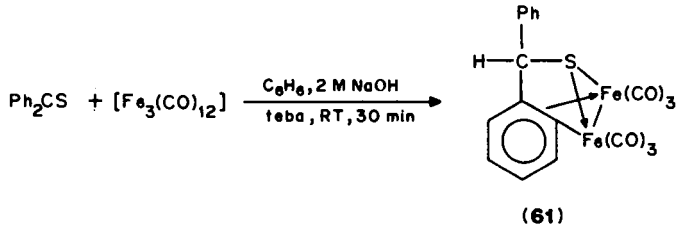
(equation 43). This mild and useful reaction (especially for 1, 1′-disubstituted ferrocenes) can be achieved without anhydrous conditions or alkali metals[150].



(43)

R = H, Me, $PhCH_2$, *n*-Pr, cyclohexyl

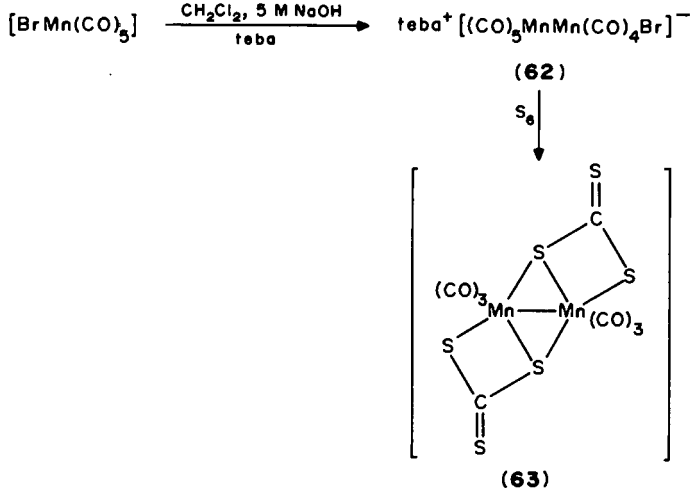
The synthesis of *ortho*-metallated complexes of sulphur-donor ligands (**61**) usually requires long reaction times, but PTC appears to be a facile route to these important products.



(44)

(**61**)

Elemental sulphur is also able to react with a metal carbonyl halide, $[Mn(CO)_5Br]$, to give a polysulphur–metal complex (**63**)[151] under phase-transfer conditions, probably via the binuclear anion **62**[144,146] (Scheme 23). The carbon atom of the SCS unit arises from a carbonyl carbon and not from CH_2Cl_2.



SCHEME 23

Phase-transfer catalysed metallation of *meso*-tetratolylporphyrin, by Zn^{24}, Cu^{27} and Mn^{27} in water–oil media was described[152]. The system offers a model for porphyrin metallation in geochemical sediments and biological environments. The metallation process is promoted by long-chain carboxylic acids as the phase-transfer reagents, which function as surfactants. Thus the metal species, initially present as inert, water-soluble salts ($ZnCl_2$, $CuCl_2$, $MnCl_2$), are extracted into the organic phase, where they become labile. Such a phase-transfer labilization has been reported in the synthesis of a very reactive oxopentacyanomolybdenum(IV) anion (**64**) (equation 45). The analogous hydrated salt was generated in a monophasic aqueous medium[153,154] and shown to be inert towards

molecular oxygen, whereas an unprecedented reaction occurred between **64** and oxygen, leading to an oxoperoxo molybdate (**65**)[155] (equation 46).

$$MoCl_5 + 5KCN \xrightarrow[Ph_4P^+Cl^-]{CH_2Cl_2,\ H_2O} 3(PPh_4)^+[Mo(O)(CN)_5]^{3-} \quad (45)$$

(**64**)

$$[Mo(O)(CN)_5]^{3-} \xrightarrow[-CN^-]{O_2} \left[\begin{array}{c} O \\ \diagup\diagdown \\ O \end{array} Mo(O)(CN)_4\right]^{2-} \quad (46)$$

(**64**) (**65**)

D. Ylid Complexes

Sulphur ylid–metal complexes can be prepared very easily under phase-transfer conditions[156]. Trimethyloxosulphonium iodide reacts with $[Pd(PPh_3)_2Cl_2]$ in the presence of a quaternary ammonium salt (tbai) to give the sulphur ylid compound **66** in 60% yield (equation 47). No ylid complex was detected in absence of the phase-transfer agent and the reaction rate was increased by using 18-crown-6 instead of tbai. The base concentration appears to be of prime importance since a different palladium sulphur ylid (67) was obtained at lower NaOH concentrations (0.2 M). The mild conditions, high yield, and use of NaOH instead of NaH favour the phase-transfer method to form this type of complex.

$$Me_3SO^+I^- + [Pd(PPh_3)_2Cl_2] \xrightarrow[RT,1\,h,\,tbai]{CHCl_3,\,2.5\ M\ NaOH} \left[\begin{array}{c} Ph_3P \quad CH_2 \quad O \\ \diagdown \diagup \diagup \\ Pd \quad S \\ \diagup \diagdown \diagdown \\ Ph_3P \quad CH_2 \quad Me \end{array}\right]^+ I^- \quad (47)$$

(**66**)

$$\left[\begin{array}{c} Ph_3P \quad CH_2 \quad O \\ \diagdown \diagup \diagup \\ Pd \quad S \\ \diagup \diagdown \diagdown \\ I \quad CH_2 \quad Me \end{array}\right] \cdot 1/2\,CHCl_3$$

(**67**)

$$[Fe(CO)_5] + 2PPh_3 \xrightarrow[1\ M\ NaOH,\ (Bu_4N)_2SO_4,\ 10\,^\circ C,\ 20\,min]{CH_2Cl_2} [(CO)_4FeCH_2PPh_3] + [(CO)_4FePPh_3] \quad (48)$$

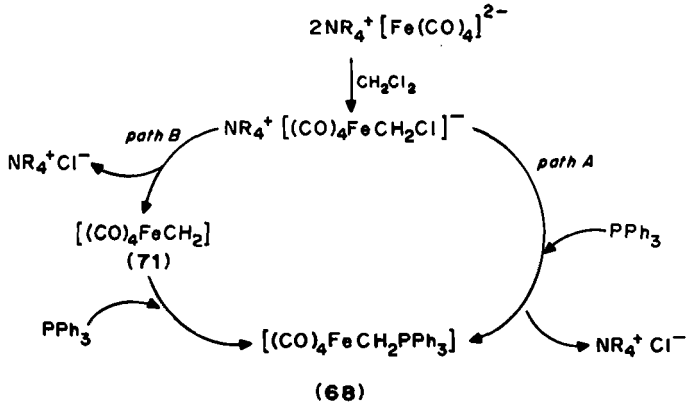
An iron ylid adduct synthesis was reported by Weinberger *et al.*[157] starting from iron pentacarbonyl and dichloromethane under PTC in the presence of triphenylphosphine (equation 48). Evidence for the formation of the tetracarbonylferrate anion $[Fe(CO)_4]^{2-}$ was established since the ylid adduct **68** was obtained starting from this preformed anion either under anhydrous monophasic conditions or in a liquid–liquid phase-transfer system; whereas the hydrido anion $[HFe(CO)_4]^-$ was unable to perform this reaction. These results support the generation of $[Fe(CO)_4]^2$ from $[Fe(CO)_5]$ under such conditions; the role of the phase-transfer agent is to stabilize the anion in the organic

phase, preventing protonation or coupling {leading to $[HFe(CO)_4]^-$ and $[Fe_2(CO)_8]^{2-}$, respectively}, but also promoting the formation of anionic hydroxycarbonyl species (**69**) (equation 49).

$$[Fe(CO)_5] \xrightarrow{NR_4^+OH^-} NR_4^+ [(CO)_4FeCOOH]^- \xrightarrow[H_2O]{NR_4^+OH^-}$$

$$(NR_4^+)_2[(CO)_4FeCOO]^{2-} \xrightarrow[-CO_2]{} (NR_4^+)_2[(CO)_4Fe]^{2-} \qquad (49)$$

The tetracarbonyl ferrate anion can react with CH_2Cl_2 to afford the ylid complex **66**. Two pathways have been proposed for the synthesis (Scheme 24), either a nucleophilic displacement on the anionic intermediate **70** (path A), or via the transient carbene **71** (path B). Although the carbene intermediate **71** is still unknown, binuclear transition metal methylene complexes (e.g. **78**) have already been isolated[158] and phase-transfer catalysis is an efficient method for obtaining such iron complexes[159]. The reaction is effected in good yield (76%) and the same intermediate as in the ylid adduct (**68**) formation can be invoked (equation 50).



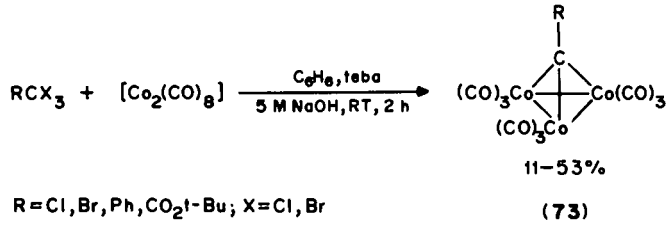
SCHEME 24

$$[Fe(CO)_5] + CH_2Br_2 \xrightarrow[1\,M\,NaOH,\,0\,^\circ C]{(Bu_4N^+)_2SO_4^{2-}} CO_4Fe\!\!<\!\!\overset{CH_2}{}\!\!>\!\!Fe(CO)_4 \qquad (50)$$

(72)

E. Polymetallic Compounds

Phase-transfer catalysis can be employed in a facile 'one-pot' cobalt cluster synthesis. Tri- or tetrahalogenoalkanes react with dicobalt octacarbonyl to give the trimetallic compound **73**[160] (equation 51). Although the mechanism is unknown, the reaction probably proceeds via the '*in situ*' generated tetracarbonyl cobalt anion $[Co(CO)_4]^-$, which then reacts with the halide.



(51)

There has been a steady development of interest in organometallic polymers and the synthesis of some polyarenyl platinum ethers was achieved by using a liquid–liquid biphasic system with dibenzo-24-crown-8 as the phase-transfer catalyst[161].

IV. ORGANOMETALLIC PHASE-TRANSFER AGENTS

In all the examples showing the advantages of phase-transfer catalysis with organometallic compounds, the synergism involved both the presence of a metal catalyst and a phase-transfer agent. However, a new concept has been developed in parallel, in which a unique active species could play, at the same time, the role of both the homogenous and the phase-transfer catalyst. Different approaches were investigated based on the crucial properties that a good phase-transfer catalyst should have, including either a salt structure, as we found in quaternary ammonium salts, a sequestering agent as in crown ethers, or hydrophilicity using water-soluble ligand complexes.

A. Salt Structure

In order to mimic an efficient onium salt, the catalyst must contain a relatively lipophilic cation associated with a hydrophilic anion. From that role, Goldberg *et al.*[162] developed an approach involving the use of cationic transition metal complexes bearing lipophilic ligands for biphasic processes. The cationic rhodium (**74**, **76**), iridium (**75**), and iron (**77**) complexes with 2,2'-bipyridyl (bipy) or 1,10-phenanthroline (phen) were shown to catalyse classical phase-transfer substitution reactions (Scheme 25).

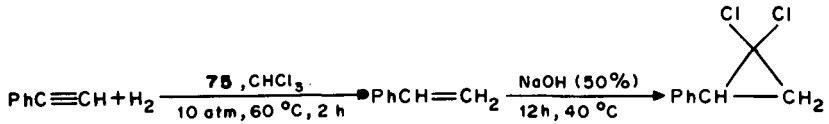
$[Rh(bipy)_2Cl_2]^+Cl^-$ (**74**) $[Ir(phen)_2Cl_2]^+Cl^-$ (**75**)

$[Rh(phen)_2Cl_2]^+Cl^-$ (**76**) $[Fe(phen)_2Cl_2]^+Cl^-$ (**77**)

$$C_4H_9Cl + KSCN \xrightarrow{74, 75, \text{ or } 76} C_4H_9SCN$$

SCHEME 25

In order to demonstrate that these new phase-transfer agents could also act as homogeneous catalysts, the iridium complex **75** was tested in the hydrogenation reaction of phenylacetylene to styrene followed by $:CCl_2$ addition under PTC (equation 52). The reduction of cinnamaldehyde to hydrocinnamaldehyde and subsequent transformation of the latter into the alcohol **78** has also been described (equation 53).



(52)

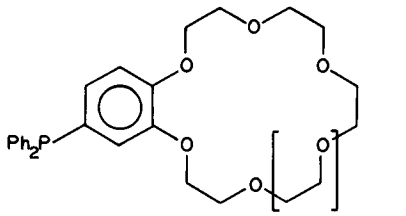
$$PhCH{=}CHCHO + H_2 \rightarrow PhCH_2CH_2CHO \xrightarrow{NaOH} PhCH_2CH_2CH(OH)CCl_3 \quad (53)$$

(78)

These catalysts present the advantage of being potentially recycled after the reactions without loss of activity, but are limited in catalysing only consecutive reactions such as hydrogenation followed by the phase-transfer transformation.

B. Sequestrating Agent

A second possibility of bifunctionalization of the catalyst was to synthesize transition metal complexes bearing phosphine ligands having polyether units (e.g. crown ethers). Such ligands are difficult to prepare[163,164] or unstable[164,165], decreasing the potential activity of the complex. Nevertheless, Okano *et al.*[166] described the synthesis and reactivity of palladium complexes having crown functionalized triarylphosphines (Scheme 26), this ligand being more efficient than phosphine-bearing linear polyethers[167]. These complexes were used in phase-transfer organometallic synthesis for ligand exchange, leading to dibromo complexes (equation 54). Complete conversion was observed after 1 h at 40 °C when 79 was used, and the yield of the dibromo compound was estimated to be 30% after 10h in the case of PPh_3. The catalytic properties of these species was tested in the reduction of 1-chloromethylnaphthalene by formate salts under, either solid–liquid or liquid–liquid biphasic conditions (equation 55).



(79)

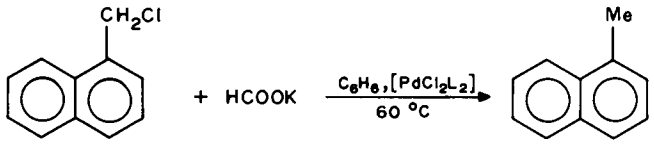
$$[PdCl_2(NCPh)_2] + 2\,L \xrightarrow[80\,^\circ C,\,5\,min]{C_6H_6} [PdCl_2L_2]$$

L = 79

SCHEME 26

$$trans\text{-}[PdCl_2L_2] \xrightarrow[40\,^\circ C]{NaBr,\,CHCl_3} trans\text{-}[PdBr_2L_2] \quad (54)$$

L = PPh_3, 79



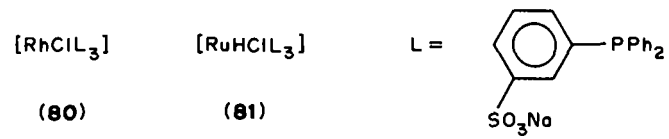
(55)

It is interesting to emphasize that $[PdCl_2(PPh_3)_2]$ had no significant activity under the specific two-phase conditions, and a mixture of this complex and 2 equivalents of benzo-18-crown-6 was reported to be less efficient than the preformed catalyst.

C. Hydrophilic Ligands

As noted earlier, an important asset of PTC is the easy separation of the product, especially in the case of acids present in the aqueous phase. However, most of the organic compounds obtained by organometallic phase-transfer catalysis are found in the organic medium and, from an industrial point of view, separation of both products and catalysts is of prime importance.

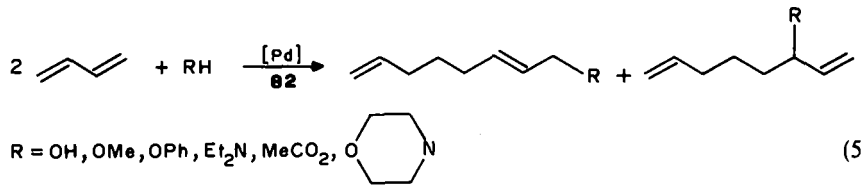
This can explain why homogeneous catalysis in aqueous or aqueous–organic media have been developed since 1973, when Chatt *et al.*[168] reported the first transition metal-catalysed reaction in aqueous solution in the presence of alkylphosphine. Improvement of the technique was then investigated by functionalization of the phosphine ligands. Water solubility of the latter was achieved by introducing highly polar substituents (OH NH_2, SO_3H, COOH) in the phosphine unit. Transition metal complexes bearing such ligands have been tested in catalysis and the results have been reviewed[169–171]. In this system, the aqueous phase contains the metal catalyst whereas the organic medium can be the starting substrate or the reaction product, either with or without an organic solvent. Thus, hydrogenation of alkenes can be effected in a biphasic system in the presence of water-soluble phosphine complexes of rhodium (**80**) or ruthenium (**81**).



(**80**) (**81**)

Rhodium was shown to be more active than ruthenium and terminal olefins are preferably reduced (with some isomerization). According to Borowski *et al.*[172], the reaction may occur without the organic solvent as an interfacial process, whereas Dror and Manassen[103] assumed that the important role of the solvent is to solubilize the olefin in the aqueous phase.

Hydroformylation of propene[173] or hex-1-ene is catalysed by $[RhH(CO)L_3]$, L being $P(4\text{-}NaSO_3C_6H_4)_3$ (**82**), with formation of less than 1% of hydrogenated products (e.g. propane). Excellent yields (99%) and high selectivities (9% of *n*-butanol and 4% of isobutanol) were observed in this process, which has been applied on industrial scale; the presence of alcohol enhances the reaction rate owing to better solubilization of the olefin in the aqueous phase and an immiscible solvent such as toluene allows an easy separation of the catalyst. The use of a quaternary ammonium salt increased the conversion to aldehydes in the case of hex-1-ene (41% versus 22%), but slightly decreased the *n*-to iso-ratio (95:5 versus 98:2)[174].



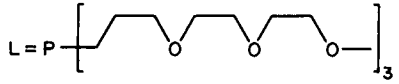
(56)

Telomerization of dienes (e.g. butadiene) with small molecules can be effected by a palladium–phosphine complex (**82**)[175] in a water–organic solvent mixture (miscible with water) (equation 56).

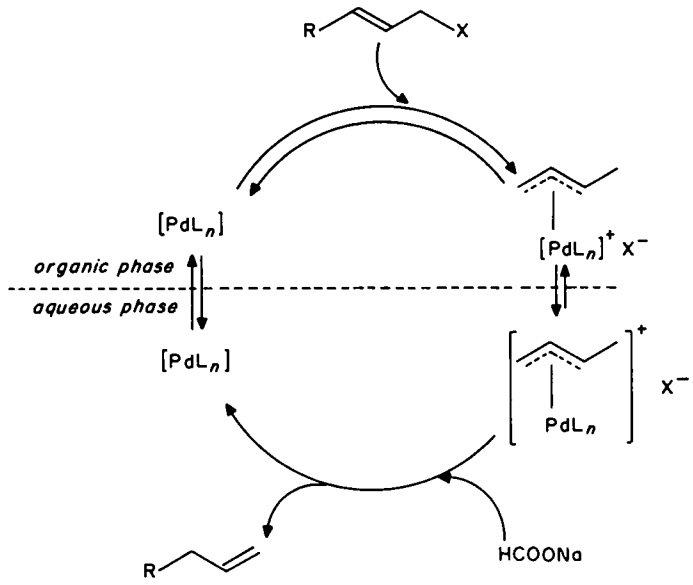
In all these processes, the role of the organic solvent is either to solubilize the substrate in water or to help in the separation and recycling of the catalyst. Therefore, they cannot be described as real 'phase-transfer' systems. Nevertheless, Okano *et al.*[176] reported the catalytic reduction of allyl chlorides and acetates with sodium formate in a two phase-system with water-soluble phosphine complexes (equation 57). They proposed that the metal complex reacts as a phase-transfer reagent to transport the substrate into the aqueous phase, in which reaction with sodium formate takes place (Scheme 27). Although ligand **83**, owing to its polyether chains, can act as a normal phase-transfer catalyst, it was demonstrated by trapping propene from the reduction of allyl acetate that the reaction occurred in the aqueous phase.

$$\mathrm{RCH{=}CHCH_2Cl + HCOONa} \xrightarrow[\text{heptane, } H_2O,\ 61]{[PdCl_2L_2]} \mathrm{RCH_2CH{=}CH_2 + RCH{=}CHCH_3} \qquad (57)$$

$R = C_6H_{13}$: 82% 17%
$R = C_6H_5$: 95% 4%

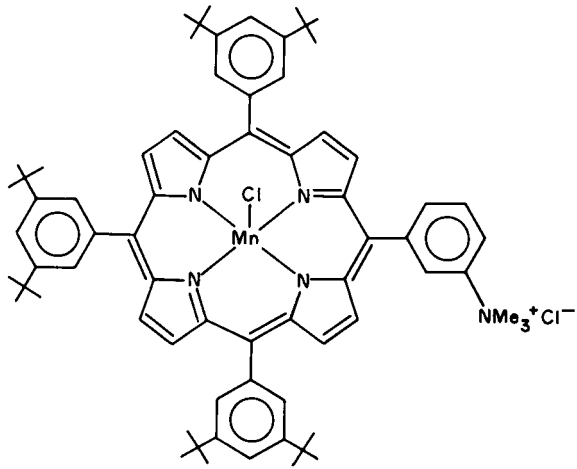


(**83**)



SCHEME 27

Phosphines are not the only hydrophilic ligands used in organometallic biphasic catalysis. The synthesis of an amphiphilic porphyrin manganese complex (**84**) reacting as a phase-transfer and epoxidation catalyst has been reported[177]. In addition to the simplification of the system (two functions in one reactant), the catalyst appeared to be more efficient than a system including a quaternary ammonium salt and a classical manganese–porphyrin complex. For example, styrene oxidation using **84** reached a turnover number of 1200 instead 240 for the normal system.



(84)

V. CONCLUSION

Phase-transfer catalysis is an excellent technique and, rather than providing a universal methodology, we have to consider it as a tool, especially in organometallic chemistry and homogeneous catalysis. The scope of this field is still wide open and, as good craftsmen, we have to understand how the tool can be best used by investigating the mechanisms involved in these processes and elaborating improvements to it in order to discover new concepts and applications.

VI. AKNOWLEDGEMENTS

The author is indebted to Dr H. Arzoumanian and Professor H. Alper for reviewing the manuscript.

VII. REFERENCES

1. A. Brändström, *Preparative Ion Pair Extraction. An Introduction to Theory and Practice*, Apotekarsocieten, Hässle Läkemendel, Stockholm, 1974.
2. W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer, Berlin 1977.
3. C. M. Starks and C. Liotta, *Phase Transfer Catalysis: Principles and Techniques*, Academic Press, New York, 1978.

4. E. V. Dehmlov and E. S. Dehmlov, *Phase Transfer Catalysis*, VCH, Weinheim, 1980 and 1983.
5. S. L. Regen, *Nouv. J. Chim.*, **6**, 629 (1982).
6. J. M. J. Frechet, *Polym. Sci. Technol.*, **24**, 1 (1984).
7. R. Gallo, M. Makosza, H. J. M, Dou, and P. Hassanaly, *Adv. Heterocycl. Chem.*, **36**, 175 (1984).
8. H. H. Freedman, *Pure Appl. Chem.*, **58**, 857 (1986).
9. P. Cocagne, R. Gallo, and J. Elguero, *Heterocycles*, **20**, 1379 (1983).
10. H. Des Abbayes, *Isr. J. Chem.*, **26**, 249 (1985); *Nouv. J. Chim.*, **11**, 535 (1987).
11. H. Alper, *Fundam. Res. Homog. Catal.*, **4**, 79 (1984).
12. H. Alper, *Adv. Organomet. Chem.*, **19**, 183 (1981).
13. L. Cassar, *Ann. N.Y. Acad. Sci.*, **333**, 208 (1980).
14. L. Cassar, *Fundam. Res. Homog. Catal.*, [Proc. Int. Workshop], 1st Meeting, Date 1276 Plnum Press, New York, 1977, p. 115–127.
15. E. Weber and F. Vögtle, *Top. Curr. Chem.*, **98**, 1 (1981).
16. K. Yoshikagu and S. L. Regen, *J. Org. Chem.*, **47**, 2493 (1982).
17. G. Soula, *J. Org. Chem.*, **50**, 3717 (1985).
18. G. W. Gökel, D. M. Goli, and R. A. Schultz, *J. Org. Chem.*, **48**, 2837 (1983).
19. C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 2495 (1967); G. W. Gökel and S. H. Korzeniowski, *Macrocyclic Polyether Syntheses*, Springer, Berlin, 1982.
20. J. M. Lehn, *Pure Appl. Chem.*, **52**, 2303 (1980).
21. J. Szejtli, *Cyclodextrins and Their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.
22. C. M. Starks, Chemtech, 110 (1980).
23. M. A. Boudeville and H. Des Abbayes, *Tetrahedron Lett.*, **32**, 2727 (1975); H. Alper and D. Des Roches, *J. Organomet. Chem.*, **117**, C44 (1976).
24. H. Alper and H. Des Abbayes, *J. Organomet. Chem.*, **134**, C11 (1977).
25. L. Cassar and M. Foa, *J. Organomet. Chem.*, **139**, C11 (1977).
26. R. Perron, *Fr. Pat.*, 29459-00533 (1975).
27. H. Des Abbayes, A. Buloup, and G. Tanguy, *Organometallics*, **2**, 1730 (1983).
28. H. Des Abbayes and A. Buloup, *Tetrahedron Lett.*, **21**, 4343 (1980).
29. C. Ungurenasu and C. Cotzur, *Polym. Bull.*, **14**, 411 (1985).
30. J. J. Brunet, C. Sidot, and P. Caubere, *Tetrahedron Lett.*, **22**, 1013 (1981).
31. J. J. Brunet, C. Sidot, and P. Caubere, *J. Org. Chem.*, **48**, 1156 (1983).
32. M. Miara, F. Akase, and M. Nomura, *J. Chem. Soc., Chem. Commun.*, 241 (1986).
33. G. Tanguy, B. Weinberger and H. Des Abbayes, *Tetrahedron Lett.*, **25**, 5529 (1984).
34. Y. Kimura, Y. Tomita, S. Nakanishi, and Y. Otsuji, *Chem. Lett.*, 321 (1979).
35. C. B. Ou and L. K. Liu, *J. Chin. Chem. Soc.*, **32**, 23 (1985).
36. G. Tanguy, B. Weinberger, and H. Des Abbayes, *Tetrahedron Lett.*, **24**, 4005 (1983).
37. G. C. Tustin and R. T. Hembre, *J. Org. Chem.*, **49**, 1761 (1984).
38. B. Weinberger, G. Tanguy, and H. Des Abbayes, *J. Organomet. Chem.*, **280**, C31(1985).
39. P. Laurent, G. Tanguy, and H. Des Abbayes, *J. Chem. Soc., Chem. Commun.*, 1754 (1986).
40. L. Cassar, M. Foa, and A. Gardano, *J. Organomet. Chem.*, **121**, C55 (1976).
41. H. Alper, K. Hashem, and J. Heveling, *Organometallics*, **1**, 775 (1982).
42. H. Arzoumanian, G. Buono, M. Choukrad, and J. F. Petrignani, *Organometallics*, **7**, 59 (1988).
43. H. B. Kagan, *Asymmetric Synthesis* (Ed. J. D. Morrison) Vol. 5, Academic Press, New York. 1985, p. 17.
44. B. M. Choudary, N. P. Reddy, and B. A. Shok, *Appl. Catal.*, **32**, 357 (1987).
45. V. Galamb, M. Gopal, and H. Alper, *Organometallics*, **2**, 801 (1983).
46. P. Li and H. Alper, *J. Org. Chem.*, **51**, 4354 (1986).
47. V. Galamb and H. Alper, *Transition Met. Chem.*, **8**, 271 (1983).
48. M. Foa and L. Cassar, *Gazz. Chim. Ital.*, **109**, 619 (1979).
49. F. Joo and H. Alper, *Organometallics*, **4**, 1775 (1985).
50. H. Alper, J. K. Currie, and H. Des Abbayes, *J. Chem. Soc., Chem. Commun.*, 311 (1978).
51. H. Alper and J. K. Currie, *Tetrahedron Lett.*, **29**, 2665 (1979).
52. H. Alper and J. F. Petrignani, *J. Chem. Soc., Chem. Commun.*, 1154 (1983).
53. H. Alper and D. E. Laycock, *Tetrahedron Lett.*, **22**, 33 (1981).
54. S. Gambarotta and H. Alper, *J. Org. Chem.*, **46**, 2142 (1981).
55. H. Alper and S. Amaratunga, *Can. J. Chem.*, **61**, 1309 (1983).
56. H. Arzoumanian and J. F. Petrignani, *Tetrahedron Lett.*, **27**, 5979 (1986).
57. J. X. Wang and H. Alper, *J. Org. Chem.*, **51**, 275 (1986).

58. D. H. Gibson, W. L. Hsu, and F. U. Ahmed, *J. Organomet. Chem.*, **215**, 379 (1981).
59. H. Alper, H. Arzoumanian, M. Saldana-Maldonado, and J. F. Petrignani, *J. Chem. Soc., Chem. Commun.*, 340 (1985).
60. F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto, and A. Yamamoto, *J. Am. Chem. Soc.*, **107**, 3235 (1985), and references cited therein.
61. F. Francalanci and M. Foa, *J. Organomet. Chem.*, **232**, 59 (1982).
62. S. Calet, H. Alper, J. F. Petrignani, and H. Arzoumanian, *Organometallics*, **6**, 1625 (1987).
63. M. Saldana-Maldonado, *Thesis*, Marseille (1987).
64. K. Januszkiewicz and H. Alper, *Tetrahedron Lett.*, **24**, 5159 (1983).
65. K. Januszkiewicz and H. Alper, *Tetrahedron Lett.*, **24**, 5163 (1983).
66. H. Alper, K. Januszkiewicz, and D. J. H. Smith, *Tetrahedron Lett.*, **26**, 2263 (1985).
67. H. A. Zahalka, K. Januszkiewicz, and H. Alper, *J. Mol. Catal.*, **35**, 249 (1986).
68. R. A. Sheldon and J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981.
69. H. Mimoun, in *The Chemistry of Functional Groups, Peroxides* (Ed. S. Patai), Wiley, Chichester 1982, pp. 463–482.
70. O. Bortolini, F. Di Furia, G. Modena, and R. Seraglia, *J. Org. Chem.*, **50**, 2688 (1985).
71. G. Barak and Y. Sasson, *J. Chem. Soc., Chem. Commun.*, 1266 (1987).
72. K. B. Sharpless and J. R. Verhoeven, *Aldrichim. Acta*, **12**, 63 (1979).
73. S. C. Chakrabartty, in *Oxidation in Organic Chemistry, Part C*, (Ed. W. S. Trahanovski) Academic Press, New York, 1978, pp. 343–370.
74. S. Rishnam, D. G. Kuhn, and G. A. Hamilton, *J. Am. Chem. Soc.*, **99**, 8121 (1977).
75. J. E. Baldwin and P. Perlmutter, *Top. Curr. Chem.*, **121**, 181 (1984).
76. B. Meunier, *Bull. Soc. Chim. Fr.*, 345 (1983).
77. B. Meunier, E. Guilmet, M. E. De Carvalho, and R. J. Poilblanc, *J. Am. Chem. Soc.*, **106**, 6668 (1984), and references cited therein.
78. J. P. Collman, J. I. Brauman, B. Meunier, T. Hayashi, T. Kodalek, and S. A. Raybuck, *J. Am. Chem. Soc.*, **107**, 2000 (1985), and references cited therein.
79. J. A. S. J. Razenberg, A. W. Van Der Made, J. W. H. Smeets, and R. J. M. Nolte, *J. Mol. Catal.*, **31**, 271 (1985).
80. J. P. Collmann, T. Kodalek, S. A. Raybuch, and B. Meunier, *Proc. Natl. Acad. Sci. USA*, **80**, 7039 (1983).
81. F. Montanari, M. Penso, S. Quici, and P. Vigano, *J. Org. Chem.*, **50**, 4888 (1985).
82. I. Tabushi and N. Koya, *Tetrahedron Lett.*, 3681 (1979).
83. Y. Tsuda and S. Nakajidi, *Chem. Lett.*, 1397 (1978).
84. D. Pletcher and J. D. Tait, *J. Chem. Soc., Perkin Trans. 2*, 788 (1979).
85. D. Landini, F. Montanari, and F. Rolla, *Synthesis*, 134 (1979).
86. C. Someswara Rao, A. A. Deshmukh, M. R. Thakor, and P. S. Srinivasan, *Indian J. Chem., Sect. B*, **25**, 324 (1986).
87. O. Bortolini, V. Conte, F. Di Furia, and G. Modena, *J. Org. Chem.*, **51**, 2661 (1986).
88. S. E. Jacobson, D. A. Mussigrosso, and F. Mares, *J. Org. Chem.*, **44**, 921 (1979).
89. B. M. Choudary, N. P. Reddy, M. L. Kantam, and Z. Jamil, *Tetrahedron Lett.*, **26**, 6257 (1985).
90. D. C. Baker, D. Horton, and C. G. Tindall, Jr, *Methods Carbohydr. Chem.*, 7, 3 (1976).
91. C. L. Stevens and C. P. Bryant, *Methods Carbohydr. Chem.*, **6**, 337 (1972).
92. P. E. Morris and D. E. Kiely, *J. Org. Chem.*, **52**, 1149 (1987).
93. M. Hronec, M. Harustiak, and J. Havsky, *React. Kinet, Catal. Lett.*, **27**, 231 (1985).
94. Dynamit Nobel, *Br. Pat.*, 1 464 569 (1977).
95. F. Lapicque and A. Stork, *Electrochim. Acta*, **30**, 1247 (1985).
96. Y. Sasson, G. D. Zappi, and R. Neumann, *J. Org. Chem.*, **51**, 2880 (1986).
97. C. Djerassi and R. R. Engle, *J. Am. Chem. Soc.*, **75**, 3838 (1953).
98. S. Abramovici, R. Neumann, and Y. Sasson, *J. Mol. Catal.*, **29**, 295 (1985).
99. S. Abramovici, R. Neumann, and Y. Sasson, *J. Mol. Catal.*, **29**, 291 (1985).
100. Y. Salto, S. Araki, Y. Sugita, and N. Kurata, *Eur. Pat. Appl.*, EP 193368 AI, 1986.
101. D. M. Roundhill, M. K. Dickson, N. A. Dixit, and B. P. Sudha-Dixit, *J. Am. Chem. Soc.*, **102**, 5538 (1980).
102. K. Osowska-Pacewicka and H. Alper, *J. Org. Chem.*, **53**, 808 (1988).
103. Y. Dror and J. Manassen, *J. Mol. Catal.*, **2**, 219 (1977).
104. J. Blum, I. Amer, A. Zoran, and Y. Sasson, *Tetrahedron Lett.*, **24**, 4139 (1983).

105. K. R. Januszkiewicz and H. Alper, *Organometallics*, **2**, 1055 (1983).
106. H. A. Zahalka and H. Alper, *Organometallics*, **5**, 1909 (1985).
107. T. J. Lynch, M. Banah, H. D. Kaesz, and C. R. Porter, *J. Org. Chem.*, **49**, 1266 (1984).
108. H. Alper and J. Heveling, *J. Chem. Soc., Chem. Commun.*, 365 (1983).
109. V. Galamb, S. C. Shim, F. Sibtain, and H. Alper, *Isr. J. Chem.*, **26**, 216 (1985).
110. D. L. Reger and M. M. Habib, *Adv. Chem. Ser.*, No. **173**, 43 (1979).
111. D. L. Reger, M. M. Habib, and D. J. Fauth, *Tetrahedron Lett.*, 115 (1979).
112. D. L. Reger, M. M. Habib, and D. J. Fauth, *J. Org. Chem.*, **45**, 3860 (1980).
113. D. L. Reger and M. M. Habib, *J. Mol. Catal.*, **4**, 315 (1978).
114. D. L. Reger and A. Gabrielli, *J. Mol. Catal.*, **12**, 173 (1981).
115. D. L. Reger and M. M. Habib, *J. Mol. Catal.*, 7, 365 (1980).
116. R. Bar and Y. Sasson, *Tetrahedron Lett.*, **22**, 1709 (1981).
117. J. Azran, O. Buchman, I. Amer, and J. Blum, *J. Mol. Catal.*, **34**, 225 (1986).
118. I. Amer, T. Bravdo, J. Blum, and K. P. Vollhardt, *Tetrahedron Lett.*, **22**, 1321 (1987).
119. R. Bar, Y. Sasson, and J. Blum. *J. Mol. Catal.*, **26**, 327 (1984).
120. R. Bar, L. K. Bar, Y. Sasson, and J. Blum, *J. Mol. Catal.*, **33**, 161 (1985).
121. K. Jothimony, S. Vancheesan, and J. C. Kuriacose, *J. Mol. Catal.*, **32**, 11 (1985).
122. A. Zoran, Y. Sasson, and J. Blum, *J. Mol. Catal.*, **27**, 349 (1984).
123. H. Alper, F. Sibtain, and J. Heveling, *Tetrahedron Lett.*, **24**, 5329 (1983).
124. H. Des Abbayes and H. Alper, *J. Am. Chem. Soc.*, **99**, 98 (1977).
125. H. Alper and S. Amaratunga, *Tetrahedron Lett.*, **21**, 2603 (1980).
126. K. Cann, T. Cole, W. Slegeir, and R. Pettit, *J. Am. Chem. Soc.*, **100**, 3969 (1978).
127. H. Alper and K. Hashem, *J. Am. Chem. Soc.*, **103**, 6514 (1981).
128. K. Januszkiewicz and H. Alper, *J. Mol. Catal.*, **19**, 139 (1983).
129. K. Hashem, J. F. Petrignani, and H. Alper, *J. Mol. Catal.*, **26**, 285 (1984).
130. F. Joo and H. Alper, *Can. J. Chem.*, **63**, 1157 (1985).
131. H. Alper, J. F. Petrignani, F. W. B. Einstein, and A. C. Willis, *J. Am. Chem. Soc.*, **105**, 1701 (1983).
132. T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1287 (1984).
133. R. Heck, *Org. React.*, **27**, 345 (1982).
134. T. Jeffery, *Tetrahedron Lett.*, **26**, 2667 (1985).
135. T. Jeffery, *Synthesis*, **1**, 70 (1987).
136. T. L. Brown and P. A. Bellus, *Inorg. Chem.*, 17, 3726 (1978).
137. K. Y. Hui and B. L. Shaw, *J. Organomet. Chem.*, **124**, 262 (1977).
138. S. A. Al-Jibori and B. L. Shaw, *J. Organomet. Chem.*, **192**, 83 (1980).
139. J. L. Cihonski and R. A. Levenson, *Inorg. Chem.*, **14**, 1717 (1975).
140. L. Cassar and M. Foa, *Inorg. Nucl. Chem. Lett.*, **6**, 291 (1970).
141. M. K. Cooper, P. A. Duckworth, K. Henrick, and M. McPartlin, *J. Organomet. Chem.*, **212**, C10 (1981).
142. D. J. Darensbourg, A. Rockicki, and R. Kudaroski, *Organometallics*, **1**, 1161 (1982).
143. J. L. Cihonski and R. A. Levenson, *Inorg. Chim. Acta*, **18**, 215 (1976).
144. J. A. Froelich and D. J. Darensbourg, *Inorg. Chem.*, **16**, 960 (1977).
145. D. J. Darensbourg, *Isr. J. Chem.*, **15**, 247 (1976–77).
146. R. Del Rosario and L. S. Stuhl, *J. Am. Chem. Soc.*, **106**, 1160 (1984).
147. H. Alper, H. Des Abbayes, and D. Des Roches, *J. Organomet. Chem.*, **121**, C31 (1976).
148. D. H. Gibson, W. L. Hsu, and D. S. Lin, *J. Organomet. Chem.*, **172**, C7 (1979).
149. D. H. Gibson, W. L. Hsu, A. L. Steinmetz, and B. V. Johnson, *J. Organomet. Chem.*, **208**, 89 (1981).
150. M. Salisova and H. Alper, *Angew. Chem., Int. Ed. Engl.*, **18**, 792 (1979).
151. H. Alper, F. Sibtain, F. W. B. Einstein, and A. C. Willis, *Organometallics*, **3**, 604 (1985).
152. G. Lipiner, I. Willner, and Z. Aizenshat, *Nouv. J. Chim.*, **10**, 91 (1986).
153. K. Wieghardt, G. Backes-Dahmann, and W. Haltzbach, *Z. Anorg. Allg. Chem.*, **499**, 44 (1983).
154. M. Dudekard and A. Samotus, *Transition Met. Chem.*, **10**, 271 (1985).
155. J. Sanchez-Marcano, *Thesis*, Marseille (1987).
156. Y. J. B. Lin, H. Y. C. Lai, S. C. Wu, and L. Hwan, *J. Organomet. Chem.*, **304**, C24 (1986).
157. B. Weinberger, G. Tanguy, and H. Des Abbayes, *J. Organomet. Chem.*, **280**, C31 (1985).
158. C. E. Summer, Jr, J. A. Collier, and R. Pettit, *Organometallics*, **1**, 1350 (1982).
159. G. Tanguy, J. C. Clement, and H. Des Abbayes, *J. Organomet. Chem.*, **314**, C43 (1986).
160. H. Alper, H. Des Abbayes, and D. Des Roches, *J. Organomet. Chem.*, **121**, C31 (1976).

161. I. K. Ahmed, J. K. Jawad, and M. A. M. Rashied, *Eur. Polym. J.*, **23**, 163 (1987).
162. Y. S. Goldberg, I. G. Lovel, and M. V. Shymanska, *J. Chem. Soc., Chem. Commun.*, 286 (1986).
163. S. J. Mclain, *J. Am. Chem. Soc.*, **105**, 6355 (1983).
164. B. A. Boyce, A. Carroy, J. M. Lehn, and D. Parker, *J. Chem. Soc., Chem. Commun.*, 1546 (1984).
165. E. M. Hyde, B. L. Shaw, and I. Shepherd, *J. Chem. Soc., Dalton Trans.*, 1696 (1978).
166. T. Okano, M. Iwahara, T. Suzuki, H. Konishi, and J. Kiji, *Chem. Lett.*, 1467 (1986).
167. T. Okano, M. Yamamoto, T. Noguchi, H. Konishi, and J. Kiji, *Chem. Lett.*, 977 (1982).
168. J. Chatt, G. J. Leigh, and R. M. Slade, *J. Chem. Soc. Dalton Trans.*, 2021 (1973).
169. F. Joo and Z. Toth, *J. Mol. Catal.*, **8**, 369 (1980), and references cited therein.
170. F. Joo, *Kem, Kozl.*, **61**, 33 (1984).
171. D. Sinou, *Bull. Soc. Chim. Fr.*, 480 (1987).
172. A. F. Borowski, D. J. Cole-Hamilton, and G. Wilkinson, *Nouv. J. Chim.*, **2**, 137 (1978).
173. E. G. Kuntz, Chem. Tech., 570 (1987).
174. H. Bahrmann, B. Cornils, W. Konkol, and W. Lipps (Ruhr-Chemie), *Ger. Offen.*, 3 412 335 (1985).
175. E. G. Kuntz, *Ger. Offen.*, 2 733 516 (1978).
176. T. Okano, Y. Moriyama, H. Konishi, and J. Kiji, *Chem. Lett.*, 1463 (1986).
177. J. Takagi, T. K. Miyamoto, and Y. Sasaki, *Bull. Chem. Soc. Jpn.*, **59**, 2371 (1986).

Part 2
Synthetic Reactions

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited By F. R. Hartley

CHAPTER **4**

Enantioselective syntheses with optically active transition metal catalysts

H. BRUNNER

Institut für Anorganische Chemie, Universität Regensburg, Universitätsstrasse 31, D-8400 Regensburg, FRG

I. INTRODUCTION

A. Significance of Optically Active Compounds

L-Asparagine, one of the 20 natural amino acids which build up the proteins, has a bitter taste whereas D-asparagine tastes sweet; (+)-estrone is a female sex hormone whereas (−)-estrone has no hormone activity; the metabolites of (+)-benzopyrene are carcinogens whereas those of (−)-benzopyrene are not; there are barbiturates one enantiomer of which is a narcotic whereas its mirror image is inactive. In these and similar cases, a given amount of a racemic mixture has the same biological effect as half of the amount of the pure enantiomer, the inactive enantiomer being only ballast.

The *R*-isomer of thalidomide is a sleeping aid whereas the *S*-isomer is teratogenic. The commercial application of the racemic mixture in the 1960s caused the Contergan scandal, which established a new 'enantiomer consciousness' as far as drugs are concerned. For thalidomide, the enantiomer that is not active as a sleeping aid is a formidable hazard, not only ballast.

In the class of barbiturates there are compounds one enantiomer of which stimulates whereas the other deactivates the central nervous system. In such cases the effects of the two enantiomers compensate each other and there is no overall effect of the racemic mixture, the biological activity being due to the separate enantiomers.

The examples enumerated above demonstrate that the enantiomers of chiral compounds behave differently in biological systems. The reason for this is that metabolism in all living beings uses optically active compounds and not racemic mixtures, e.g. L-amino acids in the proteins. Therefore, biological systems should not be approached with racemic mixtures but with optically pure compounds to avoid side-effects such as those in the Contergan case and to guarantee that minimum amounts give maximum effects. This is the present strategy for the development of additives to human food, supplements to animal food and the application of drugs and agrochemicals. Thus, L-phenylalanine is part of the new sweetener aspartame used in cola-mix beverages. Food for pigs and poultry based on corn is supplemented with about 20 000 tons per annum of L-lysine. About 60% of all the drugs in the market contain chiral molecules. However, only about 60% of these chiral drugs are available in optically active form, which means that 40% of them are still used as racemic mixtures, irrespective of the fact that the pharmaceutical activity may be due to only one of the two enantiomers. The same situation holds for agrochemicals, e.g. insecticides based on chrysanthemic acid. Compared with the racemic mixture, the application of the biologically active enantiomer of an insecticide reduces the amount needed to achieve a certain effect in agriculture and diminishes environmental pollution. These examples demonstrate the growing importance of optically active substances.

B. Synthesis of Optically Active Compounds by Enantioselective Catalysis with Transition Metal Complexes

Optically active compounds can be prepared by transformation of other optically active compounds provided in the natural pool or obtained by resolution. If a new element of

chirality, e.g. an asymmetric carbon atom, is to be generated from a prochiral precursor, an optically active auxiliary is required for optical induction. There are many reactions in which stoichiometric amounts of a chiral auxiliary are used; superior are syntheses which require substoichiometric amounts, e.g. an enantioselective catalysis using an optically active catalyst. The enzymes which produce all the optically active substances needed for life in man, animals and plants, are perfect enantioselective catalysts, combining stereospecificity with high catalytic activity and working under mild conditions. However, they are confined to their natural substrates or closely related compounds. Nevertheless, the use of enzymes is becoming increasingly popular in organic synthesis.

For a long time there have been efforts to mimic the enzymes by chemical catalysts, e.g. alkaloids[1]. A relatively new and promising approach is the use of optically active transition metal compounds as synthetic enantioselective catalysts, with the help of which not only natural optically active substances but also optically active products not available in nature can be prepared.

Enantioselective catalysis is an elegant and economical concept because it results in a multiplication of the chirality contained in the optically active catalyst. As the catalyst introduces its chiral information into each new catalytic cycle, large amounts of optically active products are accessible using small amounts of optically active catalysts. This aspect demonstrates the superiority of systems working with sub-stoichiometric amounts of an optically active auxiliary compared with systems which require stoichiometric or overstoichiometric amounts. With simple, durable, and efficient catalysts, e.g. the transition metal systems to be discussed here, synthetic enantioselective catalysts enter into competition with enzymes.

C. Scope and Subdivision of the Review

This review deals with the synthesis of organic compounds in which new chiral centres are built up starting from prochiral precursors. The discussion is limited to catalytic reactions with optically active transition metal compounds applied in sub-stoichiometric amounts. There are no examples requiring stoichiometric amounts of optically active catalysts.

In this chapter emphasis is placed on practical organic synthesis. Therefore, only procedures for established reaction types and only effective systems giving high chemical and optical yields have been selected. In the first, shorter, part a general discussion of the catalysts is given. In the second, larger, part specific reactions are presented, including the specific catalysts necessary to achieve high enantioselectivities. The chapter ends with a mechanistic discussion examplified with two prominent enantioselective catalyses.

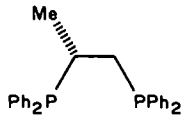
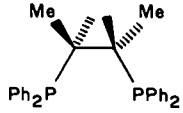
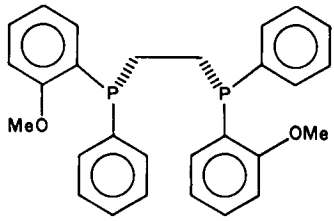
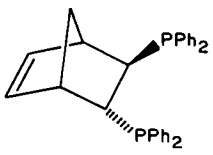
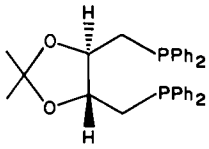
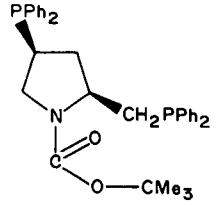
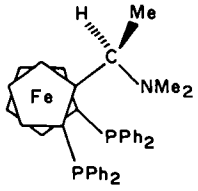
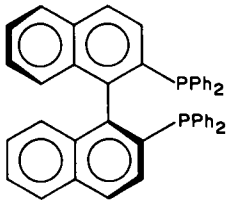
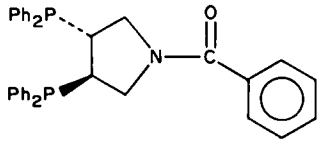
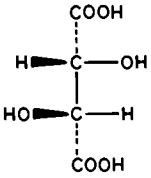
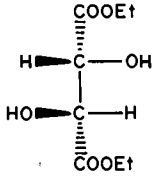
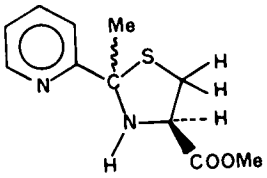
Recent comprehensive reviews are available in refs 2–9 covering the whole field.

II. CATALYSTS

A. Optically Active Ligands

In enantioselective catalysis with transition metal compounds, the optical activity in the organic products to be synthesized derives from the ligands used. Bound to the transition metal, the optically active ligands transfer their chiral information to the metal coordination sites where the prochiral precursors are converted into the optically active products. In the first heterogeneous enantioselective catalysis, the palladium-catalysed hydrogenation of prochiral keto groups[10], the protein of silk fibroin was used as the chiral matrix. The first example of homogeneous enantioselective catalysis was the cyclopropanation of olefins with ethyl diazoacetate using soluble copper complexes of salicylaldimine ligands, prepared from optically active primary amines[11]. Subsequently the optically

TABLE 1. Frequently employed optically active ligands, with abbreviations and references to their synthesis

		
(*R*)-(+)-prophos Ref. 15	(2*S*,3*S*)-(−)-chiraphos Ref. 16	(*R*,*R*)-(−)-dipamp Refs 17, 18
		
(*R*,*R*)-(−)-norphos Refs 19, 20	(*R*,*R*)-(−)-diop Refs 21, 22	(2*S*,4*S*)-(−)-bppm Ref. 23
		
(R_C,S_{Fc})-(−)-bppfa Refs 24, 25	(*S*)-(−)-binap Refs 26, 27	(*R*,*R*)-(+)-pyrphos Refs 28, 29
		
(*R*,*R*)-(+)-tartaric acid	(*R*,*R*)-(+)-diethyl tartrate	(4*R*)-(+)-pythia Refs 30, 31

active phosphines with their steric and electronic variability became the ligands of choice and have dominated the field of enantioselective catalysis with transition metal compounds in the last two decades. In pioneering studies, the monodentate Horner phosphines PPhPrMe, containing a chiral P atom, were introduced as ligands into the rhodium-catalysed enantioselective hydrogenation of C=C bonds[12,13]. Soon, however, bidentate phosphine ligands took over. Owing to the bidentate binding, a chelated ligand can adopt only a limited number of conformations compared with two unidentate ligands, this reduction being advantageous for the optical induction on product formation[8,14].

The nine most frequently used bisphosphines are shown at the top of Table 1, arranged according to increasing C, H content. In all of them, two PPh_2 groups are attached to chiral backbones by P—C bonds, except dipamp, which contains chiral P atoms attached to an achiral skeleton. Most of these bisphosphines are air-stable solids which are commercially available. Literature references to the best syntheses are given below the formulae. The prototype is diop, routinely applied in most studies dealing with enantioselective catalysis.

In addition to the phosphines, tartaric acid, used to modify heterogeneous catalysts[32–35], diethyl tartrate, used in Sharpless and coworkers' epoxidation of allyl alcohols[36–41] and Kagan and coworkers' oxidation of sulphides[42,43], and the pyridine-thiazolidine ligand pythia, used for the hydrosilylation of ketones[14,30,31,44], are included in Table 1. These ligands are also commercially available. In contrast to most of the phosphines, pythia is readily accessible in a one-step condensation of 2-acetylpyridine and (*S*)-methyl cysteinate[31]. Therefore, pythia is a cheap ligand in comparison with the optically active phosphines, which are expensive because their syntheses usually involve many steps.

In recent years, hundreds of optically active ligands have been prepared and used in enantioselective catalysis. Many of them are bisphosphines similar to those shown in Table 1. Usually they are classified with respect to their elements of chirality[45]. They can be chiral at the phosphorus atom, in the P substituents or in the chelate backbone, including combinations. Another important classification criterion is the size of the chelate ring formed with a metal atom. Depending on the number of carbon atoms separating the PR_2 groups, chelate ligands may be able to form five-, six-, or seven-membered chelate rings with a transition metal. The bisphosphines prophos, chiraphos, dipamp, norphos, and pyrphos in Table 1 form five-membered chelate rings, whereas diop, bppm, and binap form seven-membered chelate rings.

In addition to ligands having exclusively P—C bonds, a variety of phosphorus ligands has been reported containing P—N and P—O bonds. They are usually prepared by phosphinylation of optically active NH and OH compounds, such as amino alcohols or carbohydrates. Unfortunately, these compounds easily undergo P—N and P—O bond cleavage, rendering them optically inactive, especially in the alcoholic solvents frequently required, e.g. for hydrogenation reactions. Although the ligands which bind to the metal by P atoms still dominate the field, there are promising developments of ligands which bind to the metal atom by N atoms, such as pythia, and to a lesser extent also by S or O atoms. A compilation of ligands useful for enantioselective catalysis is given in ref. 45, and ref. 3 contains the formulae of 330 optically active ligands recently used in asymmetric catalysts.

B. Homogeneous Catalysts—*In Situ* Catalysts

For some of the enantioselective catalyses it is well known which compounds are the true catalysts or their immediate precursors entering the catalytic cycle. Sometimes these compounds can be isolated, stored, and used directly in catalytic enantioselective syntheses. If commercially available, these catalysts undoubtedly will be accepted by the preparative organic chemist. However, if these catalysts have to be synthesized in extra

steps prior to the actual catalysis, their routine application will be limited. For the typical organic chemist, the handling of organometallic compounds with exclusion of air and moisture will be impossible owing to a lack of the necessary laboratory facilities or undesirable owing to the extra work with unfamiliar compounds.

Fortunately, there is an alternative, viz. the *in situ* preparation of the catalyst for an enantioselective synthesis by combining a procatalyst and a cocatalyst. The procatalyst usually is a stable transition metal compound, such as $Cu(OAc)_2$, $NiCl_2$, $[Rh(cod)Cl]_2$, $[Rh(nbd)_2]BF_4$, $[Pd(dba)_2]$, or $[Co(dmg)_2]$, present in most laboratories, commercially available, or readily accessible. The cocatalyst is an optically active ligand which, most conveniently, should also be commercially available or easy to prepare. In solution the procatalyst and cocatalyst combine to give the active catalyst—a simple procedure for routine application. The preparation of such *in situ* catalysts is straightforward and takes only a few minutes before the actual reaction is carried out. Henceforth *in situ* catalysts are represented by the formulae of a procatalyst and a cocatalyst joined with a solidus; thus, $[Rh(cod)Cl]_2$/diop is the *in situ* catalyst consisting of the procatalyst $[Rh(cod)Cl]_2$ and the cocatalyst diop.

Another argument in favor of *in situ* catalysts is the possibility of varying the ligand to metal ratio, which may have an impact on the optical induction, e.g. an increase in the ligand to metal ratio may suppress an achiral reaction path. However, as outlined in Section IV, for kinetic and mechanistic studies isolated compounds of known composition are superior to *in situ* catalysts.

C. Heterogeneous Catalysts—Heterogenized Homogeneous Catalysts

Compared with homogeneous catalysts, heterogeneous catalysts are less selective, particularly with regard to optical induction. Ideally, an enantioselective homogeneous catalyst should be present in solution exclusively as one definite species, which could be adapted to a specific substrate by tailoring the optically active ligand. A heterogeneous catalyst, on the other hand, inevitably contains different catalytically active sites on its surface, each of which has its own selectivity, resulting in a low overall selectivity. The advantage of a heterogeneous catalyst is its easy separation from the reaction products and its potential reusability, whereas the recycling of a homogeneous catalyst with respect to the metal and especially with respect to the ligand is difficult.

For a heterogeneous enantioselective catalyst, the optically active modification of the surface introduces the optically active ligand into the coordination sphere of a homogeneous enantioselective catalyst. The chiral surface modification is carried out by treating the solid catalyst with a solution of an optically active compound, e.g. an amino acid or a hydroxy acid. (*R*,*R*)-(+)-Tartaric acid is the most frequently used optically active modifier, e.g. in tartaric acid–NaBr–modified Raney nickel, an advanced heterogeneous asymmetric catalyst[46-48]. The pH and the temperature of the modification and also pre- and post-treatment of the heterogeneous catalyst distinctly influence its enantioselectivity[32-35].

There are other ways of preparing asymmetric heterogeneous catalysts. Optically active transition metal compounds can be impregnated on surface-rich supports, e.g. charcoal[49] or silica gel[50], so that they do not dissolve during the catalysis. Frequently, these immobilized catalysts give an optical induction similar to their soluble counterparts. Also, transition metal salts with optically active anions, such as copper tartrate[51] and zinc tartrate[52], are heterogeneous catalysts, provided that they are insoluble in the reaction medium.

Heterogenized homogeneous catalysts combine the properties of heterogeneous and homogeneous catalysts. A heterogenized homogeneous catalysts contains a ligand covalently bonded to a surface to which a metal fragment can coordinate. A spacer

between surface and the catalytically active metal complex makes such a heterogeneous catalyst closely resemble its homogeneous counterpart. Although combining the advantages of a homogeneous and a heterogeneous catalyst, a heterogenized homogeneous catalyst may lose its activity and enantioselectivity owing to metal leaching[53–56] (see also Chapter 14 in Volume 4 of this series).

III. REACTION TYPES

A. Reduction

In most optically active compounds one of the substituents at the asymmetric carbon atom is a hydrogen atom. This hydrogen atom can be delivered to a prochiral carbon atom by hydrogenation of C=C bonds. Therefore, this reaction is of fundamental importance in the synthesis of optically active compounds.

1. Dehydroamino acid derivatives

Dehydroamino acids were introduced as substrates into enantioselective catalysis in 1971[57,58]. They could be hydrogenated to amino acids in high enantiomeric excess (ee). The field has been reviewed frequently; some recent and comprehensive references are refs 2–5, 8, 9 and 59–67.

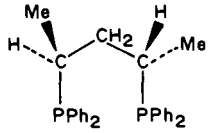
The model reaction is the hydrogenation of (*Z*)-α-acetamidocinnamic acid giving *N*-acetylphenylalanine according to equation 1. As a rule, this reaction is chosen to test the efficiency of a newly developed ligand or catalyst.

$$\begin{array}{l} (Z)\text{-PhCH}{=}\text{CCOOH} + \text{H}_2 \rightarrow \text{PhCH}_2\text{CHCOOH} \\ \qquad\quad | \qquad\qquad\qquad\quad | \\ \qquad\quad \text{NHCOMe} \qquad\qquad \text{NHCOMe} \end{array} \tag{1}$$

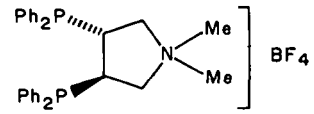
Table 2 lists a series of catalysts which have been applied in the hydrogenation according to equation 1. The first nine entries in Table 2 represent catalysts containing the nine optically active chelate phosphines lig* shown in Table 1. Some of them are isolated catalysts of the type [Rh(olefin)$_2$lig*]X and some are *in situ* catalysts of the type [Rh(olefin)$_2$Cl]$_2$/lig*. Most are rhodium compounds, but ruthenium compounds are also good hydrogenation catalysts. Entry 8 in Table 2 shows an example where a Ru–binap complex is superior to the corresponding Rh–binap complex[26,69,74]. In addition to the optically active phosphines, the catalysts usually contain olefin ligands, such as cod, nbd, 1,5-Hd, coct or ethylene. These olefin ligands are removed on hydrogenation, generating the vacant coordination sites necessary for catalytic activity.

The hydrogenations are carried out under mild reaction conditions. In alcoholic solvents, room temperature and 1 bar of hydrogen are sufficient for rapid quantitative hydrogenation, although an increase in temperature or hydrogen pressure usually does not harm the optical yields. In the hydrogenation in equation 1 the ligand diop gives the lowest optical induction, with 81% ee. The enantiomeric excess obtained with the other ligands is above 90% or even 95% ee. Whereas prophos, chiraphos, dipamp, norphos, and pyrphos form five-membered chelate rings, diop, bppm, and binap form seven-membered rings. Chelate ligands which form six-membered rings have been considered unsuitable to induce high optical inductions[75]; bdpp forms six-membered chelate rings but still gives high optical inductions[70]. The rhodium catalyst in entry 11, containing the cationic ligand A, is water soluble and allows the hydrogenation of *N*-α-acetamidocinnamic acid in aqueous suspension[71]. Ligand B in entry 12 is a new organometallic molecule, the chirality of which is due only to an asymmetric Re atom[72]. It extends the series of organometallic ligands for which the ferrocene derivatives of the type bppfa are well known examples[76].

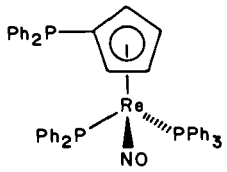
TABLE 2. Hydrogenation of (Z)-α-acetamidocinnamic acid according to equation 1



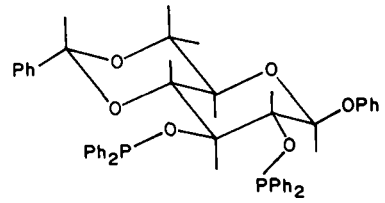
bdpp



A



B



Ph-β-glup

Entry	Catalyst	%ee	Reaction conditions	Ref.
1	[Rh(nbd)prophos]ClO_4	91 *S*	thf, 25 °C, 1 bar H_2	15
2	[Rh(nbd)chiraphos]ClO_4	89 *R*	EtOH, 25 °C, 1 bar H_2	16
3	[Rh(cod)dipamp]BF_4	96 *S*	MeOH–NaOH, 25 °C, 4 bar H_2	17, 18
4	[Rh(cod)norphos]BF_4	97 *S*	MeOH, 20 °C, 1.1 bar H_2	19,20
5	$[Rh(coct)_2Cl]_2$/diop	81 *R*	EtOH–C_6H_6, 20 °C, 1.1 bar H_2	21,68
6	$[Rh(1,5\text{-Hd})Cl]_2$/bppm/NEt_3	91 *R*	EtOH, 20 °C, 50 bar H_2	23
7	$[Rh(1,5\text{-Hd})Cl]_2$/bppfa	93 *S*	MeOH, 20 °C, 50 bar H_2	24
8	$[Ru_2Cl_4(binap)_2NEt_3]$	86 *S*	EtOH–thf, 35 °C, 2 bar H_2	69
9	[Rh(cod)pyrphos]BF_4	99 *S*	MeOH, 20 °C, 40 bar H_2	28,29
10	[Rh(nbd)bdpp]ClO_4	96 *R*	MeOH, 30 °C, 1 bar H_2	70
11	[Rh(cod)A]$(BF_4)_2$	87 *S*	H_2O, 22 °C, 50 bar H_2	71
12	[Rh(nbd)B]PF_6	93 *R*	thf, 20 °C, 1 bar H_2	72
13	[Rh(cod)Ph-β-glup)]BF_4	97 *S*	MeOH, 25 °C, 1 bar H_2	73

The ligand Ph-β-glup (entry 13) is a carbohydrate-derived phosphinite ligand which is stable towards hydrolysis under hydrogenation conditions in alcoholic solvents[73]. When immobilized on an ion-exchange resin it gives an enantiomeric excess several per cent higher than its soluble counterpart[77]. With a rhodium catalyst containing a ligand of the pyrphos type (entries 9 and 11) heterogenized on silica, the same optical induction is achieved as with the homogeneous pyrphos catalyst[78].

Most of the optically active phosphines used in asymmetric hydrogenation are bisphosphines containing a chiral backbone and two diphenylphosphino groups attached to it[45,79]. It is well established that the puckering of the chelate ring and the arrangement of the phenyl rings at the phosphorus atoms transmit the chiral information from the chiral centres in the ligand skeleton to the catalytically active sites of the catalyst, allowing a correlation of the product configuration with the inducing chirality of the ligand[2,5,8,16,65,80,81].

In addition to (Z)-α-acetamidocinnamic acid, other amino acid precursors are frequently used as substrates. Table 3 provides a selection of catalysts based on the conventional optically active phosphine ligands which give a high enantiomeric excess in

TABLE 3. Hydrogenation of dehydroamino acid derivatives[a]

Entry	Reaction	Catalyst	%ee	Ref.
1	$PhCH{=}C(NHCOPh)COOH + H_2 \rightarrow PhCH_2CH(NHCOPh)COOH$	$[Rh(binap)]ClO_4$	100 *S*	29
		$[Rh(cod)pyrphos]BF_4$	92 *S*	29
		$[Ru_2Cl_4(binap)_2NEt_3]$	95 *S*	69
2	$PhCH{=}C(NHCOMe)COOMe + H_2 \rightarrow PhCH_2CH(NHCOMe)COOMe$	$[Rh(cod)Cl]_2$/prophos	95 *S*	82
		$[Rh(cod)pyrphos]BF_4$	94 *S*	29
		$[Rh(cod)Cl]_2$/norphos	88 *S*	82
3	$CH_2{=}C(NHCOMe)COOH + H_2 \rightarrow MeCH(NHCOMe)COOH$	$[Rh(nbd)prophos]ClO_4$	90 *S*	15
		$[Rh(nbd)bdpp]ClO_4$	90 *R*	70
		$[Rh(cod)pyrphos]BF_4$	86 *S*	29
4	$CH_2{=}C(NHCOMe)COOMe + H_2 \rightarrow MeCH(NHCOMe)COOMe$	$[Rh(cod)Cl]_2$/prophos	77 *S*	82
		$[Co(dmg)_2]/PPh_3$/base[b]	43 *R*	83

[a] For the formulae of the ligands in entries 1–4 see Table 1; for the formula of bdpp see Table 2.

[b] base =

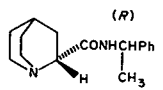
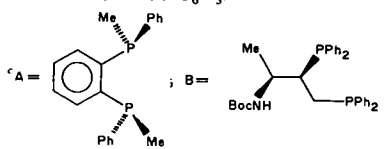
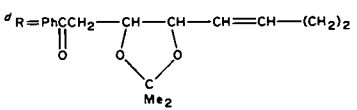


TABLE 4. Hydrogenation of α-acetamidoacrylic acid derivatives with additional β-substituents[a]

Entry	Reaction	Catalyst	%ee	Ref.
1[b]	$ArCH{=}C(NHCOMe)COOH + H_2 \rightarrow ArCH_2CH(NHCOMe)COOH$	$[Rh(cod)(dipamp)]BF_4$	94 *S*	17
		$[Rh(nbd)pyrphos]BF_4$	98 *S*	29
		$[Rh(cod)Cl]_2$/norphos	94 *S*	82
2	(indolyl)$CH{=}C(NHCOMe)COOH + H_2$ $\rightarrow$(indolyl)$CH_2CH(NHCOMe)COOH$	$[Rh(cod)pyrphos]BF_4$	99.5 *S*	29
		$[Rh(cod)Cl]_2$/diop	86 *R*	84
3[c]	$Pr^iCH{=}C(NHCOMe)COOH + H_2 \rightarrow Pr^iCH_2CH(NHCOMe)COOH$	$[Rh(nbd)A]PF_6/NEt_3$	94 *S*	85
		$[Rh(nbd)_2]ClO_4$/B	89 *S*	86
4[d]	$RCH{=}C(NHCBz)COOMe + H_2 \rightarrow RCH_2CH(NHCBz)COOMe$	$[Rh(cod)dipamp]BF_4$	> 98 *S*	87

[a] For the formulae of the ligands in entries 1–4 see Table 1 and below.
[b] Ar = 3-MeO-4-AcO-C_6H_3.





the hydrogenation of (*Z*)-α-benzamidocinnamic acid (entry 1), methyl (*Z*)-α-acetamidocinnamate (entry 2), α-acetamidoacrylic acid (entry 3), and methyl α-acetamidoacrylate (entry 4). With a heterogenized Rh–pyrphos system instead of the corresponding homogeneous catalyst virtually complete optical induction was obtained in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate[78]. Entry 4 shows that the noble metal rhodium can be replaced in hydrogenation catalysts by 3d metals such as cobalt, and that the phosphine ligands used throughout Tables 2 and 3 can be replaced by nitrogen ligands.

Table 4 gives examples for the hydrogenation of α-acylamidoacrylic acid derivatives with additional β-substituents which can be in an *E*- or *Z*-orientation[8,59]. Provided that the α-acylamidoacrylic acid moiety is kept constant to ensure bidentate binding, high optical inductions are obtained. Entry 1 in Table 4 shows the hydrogenation of a precursor of the anti-Parkinson drug L-Dopa, needed in amounts of 200 tons per annum. This enantioselective hydrogenation with an Rh–dipamp complex was the first industrial process using the concept of enantioselective catalysis with transition metal compounds (Monsanto amino acid process)[17,88].

In entries 2 and 3 in Table 4 the β-substituents in the α-acetamidoacrylic acids are indolyl and isopropyl, the hydrogenation leading to the amino acids tryptophan and leucine[29,84–86]. In entry 4 an exotic β-substituent is used because the hydrogenation shown is part of the synthesis of the natural product chlamydocin[87]. This example is representative of the enantioselective steps in the synthesis of other biologically active molecules, such as the cyclopeptide alkaloid mucronin B[89] and the dopamine agonist PHNO[90]. Similarly, asymmetric hydrogenation of dehydroamino acids is a method to introduce ^{3}H or ^{14}C labels conveniently into optically active amino acids[91–93].

In dehydrodipeptides, a dehydroamino acid can be combined with an optically active amino acid, the dehydroamino acid being in the *N*- or *C*-terminal position (Table 5). In the hydrogenation with an enantioselective catalyst there is double stereoselection[97] consisting of a contribution from the optical activity of the catalyst and a contribution from the optically active amino acid in the substrate[98–100]. Sometimes, the asymmetric catalyst only slightly modifies the contribution of the amino acid chirality (substrate control)[101,102]. However, frequently the contribution of the catalyst dominates, allowing the introduction of a new *S* or *R* configuration in a dipeptide depending on the ligand enantiomer used in the catalyst (catalyst control)[94–96].

The dehydrodipeptide derivatives in entries 1 and 2 in Table 5 differ only in the configuration of the phenylalanine component. (*R*,*R*)-dipamp as the optically active ligand in the rhodium catalyst induces predominantly the *S* configuration in the ΔPhe component (catalyst control), resulting in a diastereomeric excess of 98.8 and 91.6%, respectively[94]. Another example of catalyst control in the asymmetric hydrogenation of a dehydrodipeptide is shown in entries 3 and 4. Hydrogenation of the ΔPhe moiety with *in situ* catalysts containing (−)- and (+)-bppm gives the dipeptide in 88% (*RS*) and 84% de (*S*,*S*), de = diastereomeric excess, the contribution of the (*S*)-Leu component present in the substrate being negligible[95]. Enantioselective hydrogenation has also been extended to dehydrooligopeptides[98,99]. Entry 5 in Table 5 shows an example of a pentapeptide which has been obtained in 93% de.

2. *Other olefins*

The more the substitution pattern of an olefin departs from that of the acylaminoacrylic acids or their esters, discussed in the preceding section, the more difficult it is to obtain high optical inductions in the catalytic hydrogenation[8,59]. The replacement of the COOH or COOR substituents with other electronegative groups such as cyano or benzoyl does not lead to a large decrease in enantiomeric excess on hydrogenation (entries 1 and 2,

TABLE 5. Hydrogenation of methyl esters of dehydrodipeptides to give dipeptides[a]

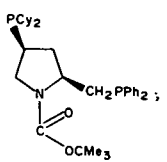
Entry	Reaction	Catalyst	%de[b]	Ref.
1	Ac-(*S*)-Phe-ΔPhe-OMe + H_2 → Ac-(*S*)-Phe-(*S*)-Phe-OMe	[Rh(dipamp)]X	98.8 *S*	94
2	Ac-(*R*)-Phe-ΔPhe-OMe + H_2 → Ac-(*R*)-Phe-(*S*)-Phe-OMe	[Rh(dipamp)]X	91.6 *S*	94
3	Boc-Gly-ΔPhe-(*S*)-Leu-OMe + H_2 → Boc-Gly-(*R*)-Phe-(*S*)-Leu-OMe	$[Rh(nbd)_2]ClO_4$/(−)-bppm	88 *R*	95
4	Boc-Gly-ΔPhe-(*S*)-Leu-OMe + H_2 → Boc-Gly-(*S*)-Phe-(*S*)-Leu-OMe	$[Rh(nbd)_2]ClO_4$/(+)-bppm	84 *S*	95
		$[Rh(nbd)_2]ClO_4$/dipamp	97.8 *S*	95
5	Cbz-(*O*)Ts-Tyr-Gly_2-ΔPhe-Leu-OMe + H_2 → Cbz-(*O*)Ts-Tyr-Gly_2-(*S*)-Phe-Leu-OMe	[Rh(cod)dipamp]BF_4	93 *S*	96

[a]For the formulae of the ligands in entries 1–5 see Table 1.
[b]de = diastereomeric excess.

TABLE 6. Hydrogenation of α-acylamino acrylic acid derivatives in which the carboxylic acid and α-acylamino substituents are varied systematically[a]

Entry	Reaction	Catalyst	%ee	Ref.
1	PhCH=C(NHCOPh)CN + H_2 → $PhCH_2CH$(NHCOPh)CN	[Rh(cod)dipamp]BF_4	89 *S*	103
2	PhCH=C(NHCOMe)C(O)Ph + H_2 → $PhCH_2CH$(NHCOMe)C(O)Ph	[Rd(cod)dipamp]BF_4	85 *S*	103
3	CH_2=C(NHCHO)$PO(OMe)_2$ + H_2 → MeCH(NHCHO)$PO(OMe)_2$	$[Rh(nbd)Cl]_2$/diop	76 D	104
4	CH_2=C(OCOMe)COOEt + H_2 → MeCH(OCOMe)COOEt	[Rh(cod)dipamp]BF_4	89 *S*	105
5[b]	CH_2=C(CH_2COOH)COOH + H_2 → MeCH(CH_2COOH)COOH	[Rh(cod)bppm]ClO_4	94 *S*	106
		$[Ru_2Cl_4(binap)_2NEt_3]$	88 *S*	107
		[Rh(cod)bcpm]ClO_4/NEt_3	92 *S*	108
		$[Rh(cod)Cl]_2$/capp	95 *R*	109

[a]For the formulae of the ligands see Table 1 and below.

[b]bcpm= 

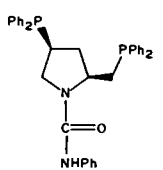
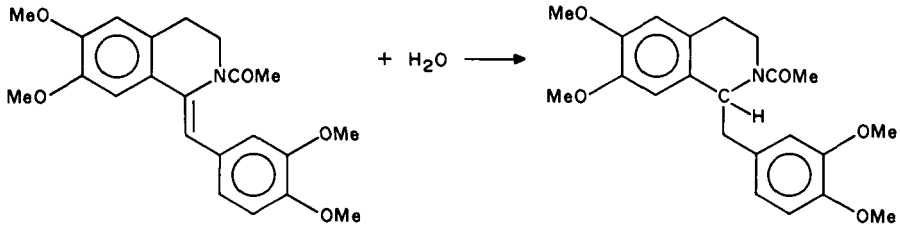
; capp= 

Table 6)[103]. Entry 3 shows that enantioselective hydrogenation also could be successfully transferred from dehydroamino acids to dehydrophosphonic acids[104].

An exchange of the acylamido substituent in the dehydroamino acid moiety is critical. High enantiomeric excesses on hydrogenation are obtained only when the substituent replacing the acetamido group is able to coordinate to the rhodium atom. Such substituents are OC(O)R and CH_2COOH having a β-carbonyl for chelation (entries 4 and 5 in Table 6). In particular, itaconic acid has been frequently used as a substrate in asymmetric hydrogenation and entry 5 gives a selection of results with various catalysts. The highest optical induction was achieved with an Rh–capp catalyst[109] and the highest reaction rates with an Rh–bcpm catalyst[108]. Both ligands are bppm derivatives, depicted at the bottom of Table 6.

Tetrahydroisoquinolines with an exocyclic double bond at ring carbon $C_{(1)}$ are enamides having the structural requirements for bidentate binding to a catalyst by the double bond of the olefin and the oxygen atom of the *N*-acyl substituent. Therefore, in their hydrogenation (equation 2) with an $Ru(OAc)_2$binap catalyst 1-substituted tetrahydroisoquinolines are obtained in optical yields close to 100%[110].



(2)

This reaction represents the stereospecific step in the newly established commercial production of tetrahydropapaverine, tretoquinol, laudanosine, norreticuline, and salsolidine. The same method was applied to the synthesis of morphine-based analgesics such as benzomorphans and dextrorphans[111]. Enamides similar to the starting material in equation 2 have been hydrogenated previously with Rh–diop and Rh–dipamp catalysts in optical yields of 82–92% ee[112].

Until recently, α,β-unsaturated carboxylic acids lacking the acylamino or a related substituent in the α-position could not be hydrogenated with high optical induction. A representative example is α-methylcinnamic acid (entry 1, Table 7). Its hydrogenation with conventional catalysts such as the Ru–diop catalyst in entry 1 gives optical inductions in the middle range. Only special approaches, e.g. transition metal catalysts modified by enzymes, lead to high enantiomeric excesses[116]. Similarly, the substrates atropic acid and tiglic acid (entries 2 and 3) have been difficult to hydrogenate with high optical yields. The situation changed with the recent development of the catalyst $Ru(OAc)_2$binap, which induces > 90% ee in the hydrogenation of atropic acid and tiglic acid (entries 2 and 3) in addition to similar substrates, including the precursor to the drug naproxen[114].

Hydroxyl substitution of the substrate may direct asymmetric hydrogenation[117–119]. A new success of this concept has been reported for the enantioselective hydrogenation of prochiral allyl alcohols, e.g. geraniol (entry 4, Table 7) and nerol. Citronellol is obtained in 96–99% ee using a Ru–binap catalyst[115]. In the same reaction, Rh–binap catalysts have achieved only 66% ee[120].

Enantioselective hydrogenation is most difficult for olefins containing nonfunctionalized double bonds such as α-ethylstyrene, which at best can be reduced with enantiomeric excesses in the middle range (entry 5). Only with heterogeneous catalysts at low conversion higher enantiomeric excesses have been achieved[121].

TABLE 7. Hydrogenation of olefins lacking the β-carbonyl substituent for additional coordination to the catalyst[a]

Entry	Reaction	Catalyst	%ee	Ref.
1	$PhCH{=}C(Me)COOH + H_2 \rightarrow PhCH_2CH(Me)COOH$	$[H_4Ru_4(CO)_8(diop)_2]$	68 *S*	113
2	$CH_2{=}C(Ph)COOH + H_2 \rightarrow MeCH(Ph)COOH$	$[Ru(OAc)_2binap]$	92 *S*	114
3	$MeCH{=}C(Me)COOH + H_2 \rightarrow MeCH_2CH(Me)COOH$	$[Ru(OAc)_2binap]$	91 *R*	114
4	$MeC(=CHCH_2OH)CH_2CH_2CH{=}CMe_2 + H_2$ $\rightarrow MeCH(CH_2CH_2OH)CH_2CH_2CH{=}CMe_2$	$[Ru(OAc)_2binap]$	87 *S*	115
5	$PhC(Et){=}CH_2 + H_2 \rightarrow PhCH(Et)Me$	$[Rh(nbd)Cl]_2$/bdpp	54 *S*	70

[a]For the formulae of the ligands see Table 1.

TABLE 8. Hydrogenation of prochiral ketones and imines[a]

Entry	Reaction	Catalyst	%ee	Ref.
1	$PhCOMe + H_2 \rightarrow PhCH(OH)Me$	$[Rh(nbd)Cl]_2$/bdpp/NEt_3	82 *S*	70
2	$PhCOCH_2NEt_2 + H_2 \rightarrow PhCH(OH)CH_2NEt_2$	$[Rh(nbd)Cl]_2$/diop	93 +	127
3	$MeCOCOOMe + H_2 \rightarrow MeCH(OH)COOMe$	$[Rh(cod)Cl]_2$/mccpm	87 *R*	128
4	$PhCOCOPh + H_2 \rightarrow PhCH(OH)COPh$	$[Co(dmg)_2]$/quinine	78 *S*	129
5	$PhC(Me){=}NCH_2Ph + H_2 \rightarrow PhCH(Me)NHCH_2Ph$	$[Rh(nbd)Cl]_2$/bdpp	73 *R*	70

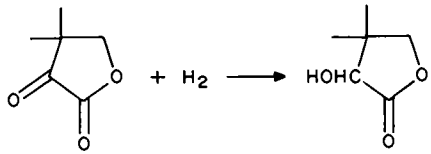
[a]For the formulae of the ligands see Tables 1 and 2; the ligand mccpm is a bppm derivative (see text).

3. Ketones and imines

For the hydrogenation of prochiral C=O bonds, the conventional rhodium catalysts are less efficient than for the hydrogenation of C=C bonds, with respect to both rate and enantioselectivity. The catalysts can be improved by adding amines[122] or by using optically active phosphine ligands with alkyl substituents at phosphorus, e.g. the cyclohexyl derivatives of diop and bppm[123–126].

Table 8 gives examples for the enantioselective hydrogenation of prochiral keto groups. Acetophenone has been hydrogenated in 82% ee to 1-phenylethanol with a rhodium catalyst of bdpp (entry 1)[70]. Acetophenone functionalized in the methyl group by a diethylamino moiety gives an increased enantiomeric excess on hydrogenation, probably owing to additional coordination of the diethylamino substituent (entry 2)[127]. α-Keto esters, such as methyl pyruvate (entry 3), can be reduced in high enantiomeric excess, using rhodium complexes with ligands of the bppm family. The best results are obtained with mccpm, a compound in which the OCO-*t*-Bu group of bcpm (bottom formula in Table 6) is replaced with OCNHMe[128]. Benzil is hydrogenated to benzoin using a cobalt–dimethyl glyoximate/quinine system with 78% ee (entry 4)[129].

Ketopantolactone, which has an α-keto group similar to the α-keto ester and α,β-diketone in entries 3 and 4 in Table 8, has become one of the standard substrates for the enantioselective hydrogenation of keto groups (equation 3)[130]. With an $[Rh(cod)Cl]_2$/bppm catalyst 87% ee[131,132] and with a rhodium catalyst of bcpm (bottom formula in Table 6) 92% ee are achieved in the hydrogenation of ketopantolactone[133,134].



(3)

β-Hydroxy acids play an important part in the biosynthesis and metabolism of fatty acids and in the synthesis of natural products. The enantioselective hydrogenation of β-keto esters, e.g. methyl or ethyl acetoacetate to give 3-hydroxybutyrates (equation 4), is a model reaction for the preparation of these key intermediates, intensely studied since 1958 mainly with heterogeneous catalysts of the Raney nickel type modified with tartaric acid and NaBr[32–35]. The reaction has already been used in the enantioselective steps of natural product syntheses, e.g. the sex attractant of the pine sawfly[135].

$$MeCOCH_2COOR + H_2 \rightarrow MeCH(OH)CH_2COOR \qquad (4)$$

$$R = Me, Et$$

As usual, the separation of the heterogeneous catalyst from the reaction mixture is much easier than for a homogeneous catalyst. However, it is a problem to reuse the heterogeneous catalyst, because it loses its activity and stereoselectivity. Recently, heterogeneous Raney nickel–tartaric acid–NaBr systems have been stabilized by amine modification[136] or by embedding them in silicone rubbers[137] to make them keep their original performance even after repeated use, storage or exposure to air.

So far, optically active β-hydroxycarboxylic esters have been prepared primarily by heterogeneous enantioselective hydrogenation of acetoacetates using tartaric acid–NaBr–modified Raney nickel. However, according to a recent finding, these important compounds can also be obtained by homogeneous hydrogenation of 3-oxocarboxylic acid derivatives with catalysts of the type $RuCl_2$(binap) in up to 100% ee[138]. Importantly, the new approach is superior to biotechnological approaches, e.g. the use of baker's yeast, in

being clean, operationally simple, economical and allowing high substrate concentrations[138].

For the hydrogenation of the C=N bond in prochiral ketimines, which gives secondary amines, examples are scarce. According to entry 5 in Table 8 the imine of acetophenone and benzylamine can be reduced with 73% ee using a Rh–bdpp catalyst[70].

4. Transfer hydrogenation

In transfer hydrogenation a hydrogen donor, e.g. isopropanol or formic acid, takes the place of molecular hydrogen. Two hydrogen atoms are transferred from the hydrogen donor to the substrate. A typical transfer hydrogenation is the reduction of acetophenone with isopropanol to give the chiral α-phenylethanol and acetone (equation 5).

$$PhCOMe + Me_2CHOH \rightarrow PhCH(OH)Me + Me_2CO \qquad (5)$$

For the system isopropanol–aluminium isopropanolate this reaction type is known as the Meerwein–Ponndorf–Verley reduction[139]. In recent years transition metal catalysts have been developed which catalyse transfer hydrogenations enantioselectively and more effectively than Al(*i*-PrO)$_3$ in homogeneous and heterogeneous systems[140,141].

Rhodium and iridium catalysts with optically active P or N ligands transform prochiral ketones into secondary alcohols with optical inductions lying in the middle range[142–148]. The activation of the transfer hydrogenation catalysts may be such a critical step that an inversion of the direction of optical induction is observed under different conditions[149]. The transfer hydrogenation of keto groups can also be accomplished by other hydrogen donors and catalysts. Thus, the reduction of the α-keto group in methyl phenylglyoxylate by nadh to yield methyl mandelate in up to 55% ee is catalysed by the optishift reagents [Eu(tfc)$_3$] and [Eu(hfc)$_3$][150].

Hydrogen donors also can tranfer hydrogen to C=C bonds[151]. Recently, the systems HCOOH–HCOONa and the commercial azeotrope HCOOH–NEt$_3$ (5:2) have been introduced for the enantioselective transfer hydrogenation of the C=C bond in (*Z*)-α-acetamidocinnamic acid (equation 6) and other dehydroamino acids[152,153]. Some of the systems give higher enantiomeric excesses than the hydrogenation with gaseous hydrogen.

$$PhCH{=}C(NHCOMe)COOH + HCOOH{-}NEt_3 \rightarrow PhCH_2CH(NHCOMe)COOH + CO_2{-}NEt_3 \qquad (6)$$

5. Hydrosilylation

The Si—H bond in silanes is activated more readily than the H—H bond in molecular hydrogen. Many transition metal compounds catalyse the Si—H addition to C=C, C=N, and C=O bonds. Only the hydrosilylation of carbonyl compounds, the most important of these reactions, is dicussed in detail[14,60,154,155].

In the hydrosilylation of a carbonyl compound, the oxophilic Si fragment regiospecifically adds to the O atom and the H atom to the C atom of the C=O bond. As O—Si bonds in silyl ethers hydrolyse easily, the hydrosilylation of a prochiral ketone and the subsequent hydrolysis result in a reduction to the corresponding alcohol. The most frequently used substrate, also the first substrate used in an enantioselective hydrosilylation[156], is acetophenone, giving α-phenylethanol. Its hydrosilylation with diphenylsilane and the subsequent hydrolysis is shown in equation 7.

$$PhCOMe + H_2SiPh_2 \rightarrow PhCH(Me)OSiHPh_2 \xrightarrow{H_2O} PhCH(Me)OH \qquad (7)$$

TABLE 9. Hydrosilylation of ketones and keto esters[a].

Entry	Reaction			Catalyst	%ee	Ref.
1	$4\text{-}ClC_6H_4COMe$	1. H_2SiPh_2 / 2. H_2O	$4\text{-}ClC_6H_4CH(OH)Me$	$[Rh(cod)Cl]_2$/pythia	89 *R*	160
2	2-pyridyl-COMe	1. H_2SiPh_2 / 2. H_2O	2-pyridyl-CH(OH)Me	$[Rh(cod)Cl]_2$/pythia	89 *R*	160
3	Bu"COMe	1. H_2SiPh_2 / 2. H_2O	Bu"CH(OH)Me	$[Rh(cod)Cl]_2$/pythia	52 *R*	160
4	$MeCOCOOCHMe_2$	1. α-NpPhSiH$_2$ / 2. H_2O	$MeCH(OH)COOCHMe_2$	[(diop)Rh(S)Cl]	85 *R*	161
5	$MeCOCH_2COOCHMe_2$	1. α-NpPhSiH$_2$ / 2. H_2O	$MeCH(OH)CH_2COOHMe_2$	[(diop)Rh(S)Cl]	83 *S*	161

[a]For the formulae of the ligands in entries 1–5 see Table 1.

In the hydrosilylation of prochiral ketones only medium optical inductions can be achieved, irrespective of the choice of substituents at the carbonyl group and the silicon atom, as long as the conventional bisphosphine ligands in Table 1 are used, which have done such a good job in enantioselective hydrogenation. For the hydrosilylation of acetophenone with diphenylsilane, the highest reported enantiomeric excess is 77%, obtained with a rhodium catalyst containing glucophinite, a derivatized glucose converted into a bisphosphinite ligand[157]. The situation changed with the advent of nitrogen ligands, such as pyridine imines[158,159] and especially pyridine thiazolidines[30,31,160]. Rhodium complexes of the commercially available pyridine thiazolidine ligand pythia (Table 1) give much higher optical inductions in the hydrosilylation of prochiral ketones than the bisphosphines used up to now[31], the highest reported enantiomeric excess for the system acetophenone–diphenylsilane being close to 100%. To improve enantioselective catalysis with transition metal compounds it is obvious to replace expensive phosphorus ligands, accessible only in many-step syntheses, with readily available nitrogen ligands, such as pythia, accessible in one-step condensations.

Entries 1 and 2 in Table 9 show two prochiral aryl alkyl ketones which have been reduced by hydrosilylation and subsequent hydrolysis in high optical yield[160]. One of these, 2-acetylpyridine (entry 2), had previously been difficult to reduce enantioselectively[162]. The examples were selected from a series of 58 prochiral ketones which have been subjected to the standard procedure for the hydrosilylation with diphenylsilane using catalysts of the $[Rh(cod)Cl]_2$/pythia type, giving high enantiomeric excess in most cases[160]. Even alkyl alkyl ketones such as hexan-2-one in entry 3 can be reduced with reasonably high optical inductions.

In contrast to ketones, keto esters can be hydrosilylated in high optical yields using rhodium complexes of the conventional bisphosphines. The best success is achieved when the hydrosilylating agent diphenylsilane is replaced with α-$NpPhSiH_2$, containing a prochiral silicon atom. With this special silane *n*-propyl pyruvate is reduced with 85% ee (entry 4)[161]. Interestingly, the catalysts successful for α-keto esters can also be applied to β-keto esters. Thus, with a Rh–diop catalyst, *n*-propyl acetoacetate gives the reduction product in 83% ee (entry 5), which can be cyclized to the corresponding γ-lactone[161]. The reaction can be extended from α-keto esters to α-keto amides and α-keto acylamino acid derivatives. For substrates containing optically active amino acid derivatives, double stereoselection is possible and many examples of efficient catalyst control are known[60,154,155].

Besides the addition to the C=O bond discussed above, the Si—H bond can be enantioselectively added to olefins and imines[154]. Also, oximes can be enantioselectively reduced by catalytic hydrosilylation[163,164]. The reactions can be conducted such that optically active silicon compounds are formed[154]. Asymmetric 1,2- and 1,4-additions to α,β-unsaturated carbonyl compounds are possible[154,165]. All these hydrosilylation variants are mentioned only briefly here because the optical inductions do not exceed the medium range. The reader is referred to recent reviews for further information[2–6].

B. Oxidation

Unlike reduction, oxidation of organic compounds tends to remove chiral centres. In specific oxidation reactions, however, new asymmetric centres can be formed during transition metal catalysis, one of which, the Sharpless epoxidation, has become a valuable tool in enantioselective organic syntheses.

1. Epoxidation

C=C bonds are catalytically oxidized to epoxides with a variety of oxidants, e.g. *tert*-butyl hydroperoxide. The reaction is known as Sharpless epoxidation if the C=C bond is

part of an allylic alcohol moiety. Titanium alkoxides–tartaric acid esters are used as enantioselective catalysts (equation 8).

$$RCH{=}CHCH_2OH + t\text{-}BuOOH \rightarrow RCH\text{—}CHCH_2OH + t\text{-}BuOH \quad (8)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad \backslash O /$$

Sharpless epoxidations of allylic alcohols have usually been carried out with stoichiometric amounts or even an excess of titanium alkoxides–tartaric acid esters[36–41]. Therefore, the applications of the stoichiometric and over-stoichiometric variants do not belong to the scope of this review, which is confined to sub-stoichiometric amounts of catalyst.

Already in the first publications on the Sharpless epoxidation the possibility of carrying out the reactions with sub-stoichiometric amounts of catalyst was apparent[166,167] and occasionally catalytic variants of the Sharpless epoxidation with sub-stoichiometric amounts of catalyst and inductor have been used[39,40,168,169]. More recently, a procedure allowing the asymmetric epoxidation of allyl alcohols with 5–10 mol-% of catalyst was developed by Sharpless and coworkers, the key feature of which is the use of molecular sieves[170,171]. The new procedure facilitates the work-up and gives optical inductions close to those of the stoichiometric systems.

Table 10 gives seven representative examples[171]. In entry 1 the epoxidation of allyl alcohol to the corresponding epoxide is shown. Up to now, such low molecular weight allyl alcohols have presented problems in the work-up. It is one of the many cases where the catalytic variant is superior to the stoichiometric reaction. The epoxidation of the

TABLE 10. Sharpless epoxidation of allylic alcohols with *tert*-butyl hydroperoxide using sub-stoichiometric amounts of Ti(*i*-PrO)$_4$–diethyl tartrate or diisopropyl tartrate catalyst in the presence of molecular sieves[171]

Entry	Reaction	Chemical yield (%)	Optical yield (% ee)
1	$H_2C{=}CHCH_2OH \rightarrow H_2C\text{—}CHCH_2OH$ (O)	65	90
2	(*E*)-$C_3H_7CH{=}CHCH_2OH \rightarrow C_3H_7CH\text{—}CHCH_2OH$ (O)	85	94
3	(*E*)-$PhCH{=}CHCH_2OH \rightarrow PhCH\text{—}CHCH_2OH$ (O)	89	> 98
4	(*Z*)-$C_7H_{15}CH{=}CHCH_2OH \rightarrow C_7H_{15}CH\text{—}CHCH_2OH$ (O)	74	86
5	$H_2C{=}C(Pr)CH_2OH \rightarrow H_2C\text{—}C(Pr)CH_2OH$ (O)	88	95
6	(*E*)-$PhCH{=}C(Me)CH_2OH \rightarrow PhCH\text{—}C(Me)CH_2OH$ (O)	79	> 98
7[a]	(*E*)-$RCH{=}CHCH_2OH \rightarrow RCH\text{—}CHCH_2OH$ (O)	95	91

[a] $R = Me_2C{=}CHCH_2CH_2$.

E-configured epoxy alcohols in entries 2 and 3 is rapid and complete, whereas the *Z*-configurated allyl alcohol in entry 4 is epoxidized only slowly. Entry 5 is the epoxidation of an unsymmetrically disubstituted allyl alcohol. It reacts slowly but gives the epoxide in high chemical and optical yield. For such substrates the stoichiometric reaction is accompanied by extensive ring opening. Entries 6 and 7 demonstrate that trisubstituted allyl alcohols react rapidly with optical inductions slightly lower than those in the stoichiometric reaction. Also, kinetic resolutions of secondary allylic alcohols with 10 mol-% of catalyst have been reported[171].

These developments have set the stage to make sub-stoichiometric variants of the Sharpless epoxidation increasingly popular. Thus, the epoxidation of (*E*)-nona-2,3-dien-1-ol, in which only the double bond of the allylic alcohol moiety was attacked, with *tert*-butyl hydroperoxide gave a 96%ee[172]. Similarly, the catalytic epoxidation of the corresponding allylic alcohols provided the enantioselective steps in the synthesis of anthracyclines[173], anthracyclinone[174], digitoxose[175], *endo*-brevicomin[176], and cyclosporins[177]. Also, the C_4 unit of insect pheromones was synthesized by catalytic asymmetric epoxidation[178].

In contrast to the Sharpless epoxidation of the C=C bond in allylic alcohols, the enantioselective epoxidation of the C=C bond in simple olefins is still a problem. Thus, the epoxidation of *p*-chlorostyrene with iodosylbenzene at best gives about 50%ee using chirally modified iron porphyrin catalysts[179,180].

2. *Sulphide oxidation*

Sulphides can be oxidized to sulphoxides, which are configurationally stable molecules. The oxidation of methyl phenyl sulphide is shown in equation 9.

$$\text{PhSMe} + t\text{-BuOOH} \rightarrow \text{PhSOMe} + t\text{-BuOH} \qquad (9)$$

All the transition metal systems used to catalyse the sulphide→sulphoxide reaction gave limited optical inductions[181] until the system Ti(*i*-PrO)$_4$–diethyl tartrate brought a breakthrough[42,43,182–186]. Recently it has been demonstrated that cumene hydroperoxide is superior to *tert*-butyl hydroperoxide and that the reaction can be carried out catalytically using 25 mol-% of catalyst[42,43]. All the other recent transition metal systems are less efficient than the Ti(*i*-PrO)$_4$–diethyl tartrate system in the enantioselective oxidation of sulphides[187,188].

C. C—C Bond Formation

The catalytic formation of new C—C bonds with concomitant introduction of optical activity is a concept which tackles two major problems in modern synthetic organic chemistry. As far as transition metal catalysis is concerned, enantioselective C—C bond forming reactions subdivide into a number of totally different types.

1. *Hydroformylation and hydrocarboxylation*

Hydroformylation of olefins is an industrially important reaction, which is usually carried out with a 1:1 mixture of carbon monoxide and hydrogen. In the olefin hydroformylation a hydrogen atom and a formyl group are added to the C—C bond. Usually two regioisomers, linear and branched, result; these may be chiral depending on the structure of the olefin used[189–192]. A detailed review is available in Chapter 8 of Volume 3 of this series as well as elsewhere[193].

In the hydroformylation of styrene, the usual model reaction (equation 10), only the

branched chain product is chiral.

$$PhCH{=}CH_2 + CO{-}H_2 \rightarrow PhCH(Me)CHO + PhCH_2CH_2CHO \quad (10)$$

The first enantioselective hydroformylation of styrene with low optical induction was described in 1972[194]. The optical yields have been increased steadily over the years by improving the catalyst, usually rhodium and platinum compounds, the latter frequently in combination with $SnCl_2$[195]. An example is the $[(bppm)PtCl_2]/SnCl_2$ catalyst, which for the branched isomer gives up to 96%ee on low conversion and 70–80%ee on high conversion (entry 1, Table 11)[196,197]. Under similar reaction conditions substituted styrenes, e.g. 4-acetylstyrene (entry 2), are hydroformylated in up to 85%ee. High optical inductions are obtained in the hydroformylation of vinylnaphthalenes, some of which can be converted into the drugs ibuprofen, naproxen, and suprofen[196]. With the successful catalyst $[(bppm)PtCl_2]/SnCl_2$, substrates such as allyl acetate (entry 3) and vinylphthalimide yield 82 and 73%ee, respectively[196].

In the hydroformylation of dimethyl itaconate (entry 4, Table 9) with the catalyst $[(diop)PtCl_2]/SnCl_2$ the 2-formyl product is the only hydroformylation product obtained in 82%ee[198]. The competitive hydrogenation, a frequent side-reaction in hydroformylation, gives dimethyl 2-methylsuccinate in 51%ee. Rh–diop catalysts form both compounds in only low enantiomeric excess[199].

Usually, hydroformylation reactions are carried out in solvents such as benzene or toluene. Special success has been reported recently for enantioselective hydroformylation in triethyl orthoformate. In this solvent the hydroformylation of styrene at 100% conversion yields the optically pure acetal of the branched aldehyde, which can be hydrolysed to the aldehyde without racemization[196]. Similarly, 6-methoxy-2-vinyl-naphthalene, *N*-vinylphthalimide, and vinyl acetate are hydroformylated to give the optically pure acetals of the corresponding branched oxo-aldehydes[196].

In addition to hydrogenation, the hydroformylation reaction has mainly been used to test many heterogeneous catalysts, e.g. the $PtCl_2/SnCl_2$ complexes of polymeric diop- and bppm-derived systems. Usually they give enantioselectivities comparable to those with the corresponding homogeneous systems[189,197,200–204]. A quadrant rule has been developed to predict the direction of optical induction in the hydroformylation reaction which most of the systems obey[192,193,198,205].

In the hydrocarboxylation or hydroesterification reaction an olefin is converted into a carboxylic acid ester by treatment with carbon monoxide in an alcoholic solvent. Control of the regioselectivity is possible by proper choice of the alcohol[191,192]. An example is the

TABLE 11. Hydroformylation of olefins with $CO{-}H_2$[a]

Entry	Reaction	Catalyst	%ee	Ref.
1	$PhCH{=}CH_2 + CO{-}H_2$	$[(bppm)PtCl_2]/SnCl_2$/bppm	96	196
	→ PhCH(Me)CHO	$[(bppm)PtCl_2]/SnCl_2$	80	197
2	$4\text{-}AcC_6H_4CH{=}CH_2 + CO{-}H_2$ → $4\text{-}AcC_6H_4CH(Me)CHO$	$[(bppm)PtCl_2]/SnCl_2$	85	196
3	$CH_2{=}CHOAc + CO{-}H_2$ → $MeCH(OAc)CHO$	$[(bppm)PtCl_2]/SnCl_2$	82	196
4	$CH_2{=}C(COOMe)CH_2COOMe + CO{-}H_2$ → $MeC(CHO)(COOMe){-}CH_2COOMe$	$[(diop)PtCl_2]/SnCl_2$	82	198

[a]The chiral aldehyde shown is accompanied by its regioisomer and usually by some hydrogenation product. For the formulae of the ligands see Table 1.

hydroesterification of α-methylstyrene, shown in equation 11, which gives 69%ee[206,207].

$$PhC(Me)=CH_2 + CO\text{–}Me_3COH \rightarrow PhCH(Me)CH_2COOCMe_3 \qquad (11)$$

2. *Grignard cross-coupling*

The reaction of vinyl halides and aryl halides with Grignard reagents can be catalysed by transition metal compounds. On modification of the catalysts with optically active ligands enantioselective product formation is observed, ferrocenylphosphines and β-dimethylaminoalkylphosphines being the most successful ligands usually applied in nickel and palladium complexes[76,208–211]. The cross-coupling of 1-phenylethyl-Grignard with vinyl bromide (equation 12) is a frequently studied model reaction.

$$PhCH(Me)MgCl + BrCH=CH_2 \rightarrow PhCH(Me)CH=CH_2 + MgBrCl \qquad (12)$$

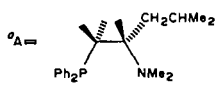
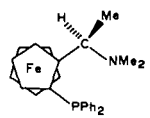
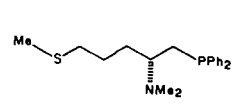
Reaction 12 was the first (1973) enantioselective Grignard cross-coupling[212,213]. The reaction type can be extended to other Grignard and organozinc reagents and alkenyl halides. Sometimes the optical purity and even the configuration of the products change with an exchange of the halide in the Grignard reagent or its coupling partner[214]. The Grignard cross-coupling reaction is an asymmetric transformation involving racemization of the chiral Grignard reagent during the reaction[208]. An impressive number of examples have been accumulated[208], the most spectacular of which are summarized in Table 12.

In entry 1 the results for the system of equation 12 are shown using powerful nickel and palladium catalysts with ligands A, B, and C, depicted in the footnote; leuphos (A) is derived from the amino acid leucine[215,219] and ppfa (B) is a member of the bppfa family[76,216,218], both PN ligands which are especially suitable in the Grignard cross-coupling reaction.

New families of macrocyclic ligands with sulphide and amine binding sites have been synthesized. Their nickel catalysts give high optical inductions in the cross-coupling of equation 12. The best enantiomeric excess of 88% is obtained with a $NiCl_2$ catalyst containing ligand C (homomethphos), designed to act as a tricoordinate ligand[217]. The idea is supported by the observation that ligands with shorter spacers between the PN moiety and the S atom are much less enantioselective.

TABLE 12. Grignard cross-coupling of various racemic Grignard reagents and alkenyl halides

Entry	Reaction	Catalyst[a]	%ee	Ref.
1	$PhCH(Me)MgCl + BrCH=CH_2$ $\rightarrow PhCH(Me)CH=CH_2 + MgBrCl$	$NiCl_2$/A	94 *R*	215
		$PdCl_2$/B	95 *R*	216
		$NiCl_2$/C	88 *R*	217
2	$PhCH(SiMe_3)MgBr + BrCH=CH_2$ $\rightarrow PhCH(SiMe_3)CH=CH_2 + MgBr_2$	$PdCl_2$/B	95 *R*	218
3	$PhCH(SiMe_3)MgBr + BrCH=CHPh$ $\rightarrow PhCH(SiMe_3)CH=CHPh + MgBr_2$	$PdCl_2$/B	95 *R*	218

[a] A=  (leuphos); B=  (ppfa); C=  (homomethphos)

Asymmetric Grignard cross-coupling has been extended to silyl derivatives. The reaction of 1-(trimethylsilyl)benzyl Grignards with alkenyl bromides (entries 2 and 3) gives optical inductions up to 95% ee with palladium catalysts containing ferrocenylphosphine ligands of type B[216,218]. The coupling products are useful intermediates in organic synthesis with the asymmetric centre directly bonded to the silicon atom.

A series of chiral and prochiral allylic electrophiles have been cross-coupled with Grignard reagents, leading to the allyl alkylations discussed in the next section. Nickel complexes of the ligand chiraphos give up to 90.4% ee in the methylation of the cyclic allyl phenyl ether according to equation 13[220]. The reaction has been used to prepare olefins from allylic alcohol derivatives and Grignard reagents in high optical yields[221,222].

(13)

Allylic alkylations with hard nucleophiles such as Grignard reagents or organozinc compounds follow mechanisms different from that of the palladium-catalysed substitution of allylic acetates by soft nucleophiles, discussed in the next section. They involve the formation of a bond between the transition metal atom of the catalyst and the nucleophile. The product is formed from this intermediate by a reductive elimination in which the nucleophile approaches the allylic moiety from the side of the η^3-coordinated metal atom[208], contrary to the mechanism of allylic alkylation with soft nucleophiles considered in Section IV.

3. *Allyl alkylation with soft nucleophiles*

The alkylation of allyl acetates with soft nucleophiles such as sodium acetylacetonate (equation 14) is best catalysed by palladium complexes[208]. It involves the formation of an η^3-allyl palladium complex inverting the configuration of the asymmetric carbon atom. As the soft nucleophile attacks the η^3-allyl complex from the side opposite to the palladium atom, another inversion takes place, giving the product with formal retention compared with the chiral allyl acetate used as a starting material. For R = R′ in equation 14 the η^3-allyl palladium substructure is symmetrical and the optical induction in the product comes solely from the optically active ligand bound to the palladium atom.

$$\begin{aligned}\mathrm{RCH(OAc)CH{=}CHR' + NaCH(COMe)_2 \rightarrow RCH[CH(COMe)_2]CH{=}CHR'} \\ \mathrm{+ RCH{=}CHCH[CH(COMe)_2]R'}\end{aligned} \tag{14}$$

Table 13 contains recent examples spectacular with respect to a high degree of optical induction. One of the most developed systems, triphenylpropenyl acetate–sodium dimethylmalonate, gives optical inductions up to 86% ee (entry 1)[223]. The mechanism of this palladium-catalysed allylic alkylation is discussed in Section IV[208,223,226,227].

The special ferrocenylphosphine A, depicted in the footnote to Table 13, is an advanced ligand derived from bppfa (Table 1). Designed to interact with the substrate within the catalyst, it gives high optical inductions for a variety of propenyl acetates (entries 2 and 3)[224,225]. In a kinetic resolution, palladium catalysts of ferrocenylphosphine A (Table 13) have been applied to give up to 99%ee for the recovered allyl acetate and 98%ee for the substitution product[228].

4. *Cyclopropanation*

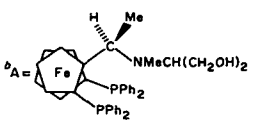
In the reaction of an olefin with a diazo compound, such as diazo acetate, nitrogen is eliminated and cyclopropanes are formed when catalysed with copper or other transition

TABLE 13. Alkylation of allylic acetates with soft nucleophiles.

Entry	Reaction	Catalyst	%ee	Ref.
1[a]	$PhCH(OAc)CH{=}CPh_2 + NaCH(COOMe)_2$ $\rightarrow PhCH[CH(COOMe)_2]CH{=}CPh_2 + NaOAc$	$[(\eta^3\text{-}C_3H_5)Pd(chiraphos)]ClO_4$	86	223
2[b]	$NpCH(OAc)CH{=}CHNp + NaCH(COMe)_2$ $\rightarrow NpCH[CH(COMe)_2]CH{=}CHNp + NaOAc$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/A	92	224
3[b,c]	$PhCH(OAc)CH{=}CHAr + NaCH(COMe)_2$ $\rightarrow PhCH[CH(COMe)_2]CH{=}CHAr$ $+ NaOAc + PhCH{=}CHCH[CH(COMe)_2]Ar$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$/A	95 80	225 225

[a] For the formula of chiraphos see Table 1.

[b] A =



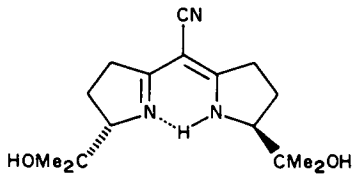
[c] Ar = 3-$MeOC_6H_4$.

metal catalysts, as shown in equation 15 for styrene.

$$PhCH{=}CH_2 + N_2CHCOOEt \rightarrow PhCH\!-\!CH_2 + N_2 \quad (15)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad \backslash\ /$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad CHCOOEt$$

Cyclopropane derivatives based on chrysanthemum acid are used as insecticides (pyrethroids), the activity being strongly dependent on the configuration of the asymmetric centres in the three-membered ring[229]. It was a cyclopropanation reaction which in 1966 was the first enantioselective homogeneous catalysis using a transition metal compound to be described. Meanwhile cyclopropanation has become one of the standard reactions in enantioselective catalysis. Recently, new olefins and diazo compounds have been introduced as substrates[230–232], including compounds which allow the synthesis of ring B of the steroid skeleton[51]. Almost complete optical induction was obtained in the reaction of styrene with 2-diazodimedone using an immobilized copper β-diketonate catalyst[230]. Reviews are available[233–235].

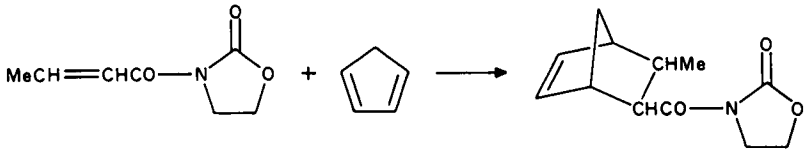
Efficient copper catalysts have been developed for the cyclopropanation of styrene with diazoacetates. The new semicorrin ligand **1**, derived from L-pyroglutamic acid, gives up to 97% ee for the *cis* and *trans* isomers of phenylcarbalkoxycyclopropanes, the *trans* isomer being formed in excess[236]. The substrates butadiene and hept-1-ene also allow enantiomeric excesses exceeding 90%[236].



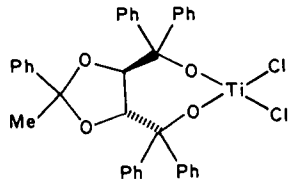
(1)

5. *Diels–Alder reactions*

The enantioselective Diels–Alder reaction, a domain of organic chemistry, has recently been opened up to transition metal catalysis[237]. In the Diels–Alder reaction in equation 16 the optical purity of the adduct increases from 9 to 91% ee when, in addition to 10 mol-% of the titanium reagent **2**, molecular sieves are added[238,239].

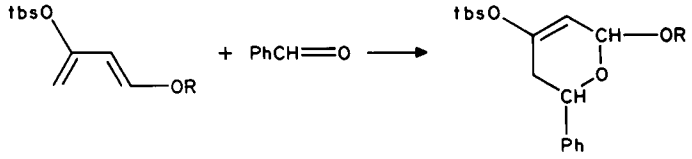


(16)



(2)

Europium optishift reagents catalyse the enantioselective cycloaddition of aldehydes with oxygenated butadienes (equation 17). The combinations of optically active europium shift reagents with achiral dienes and achiral europium shift reagents with optically active dienes give only modest enantioselectivities. Surprisingly, the combination of optically active dienes with (+)-[Eu(hfc)$_3$] exhibits striking interactivities and results in optical inductions of up to 95%[240]. The cycloadducts can be converted into L-glycolipids and L-glucose.

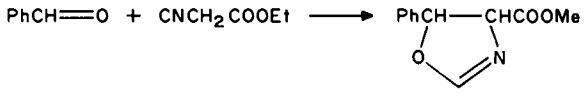


(17)

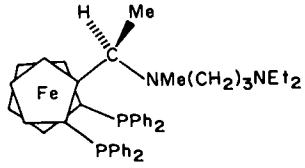
In the Diels–Alder reaction of 1-substituted butadienes with carbonyl dienophiles, catalysed by optishift reagents, the cycloadducts were obtained in up to 64% ee[241].

6. *Aldol reaction*

In recent years enantioselective variants of the aldol reaction catalysed by transition metal systems have been reported[242,243]. In a recent approach, close to 100% ee was obtained in the aldol reaction of benzaldehyde with methyl isocyanoacetate using gold/bppfa-type catalysis (equation 18)[244]. The additional diethylamino group present in the ferrocenylphosphine ligand **3** specifically interacts with the substrate and participates in the enolate formation of the coordinated isocyanoacetate. High enantioselectivities and high *trans* selectivities are obtained with other secondary and tertiary alkyl aldehydes and α,β-unsaturated aldehydes[244].



(18)



(**3**)

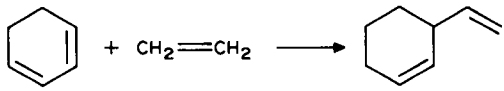
7. *Cyanohydrin formation*

Me_3SiCN can be added to C=O bonds. In an enantioselective approach, the substrate 3-methylbutyraldehyde gives the cyanhydrin adduct in 82% ee according to equation 21[242]. As the catalyst 20 mol-% of the chiral Lewis acid **2** is used.

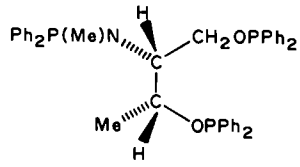
$$Me_2CHCH_2CHO + Me_3SiCN \rightarrow Me_2CHCH_2CH(CN)OSiMe_3 \qquad (19)$$

8. Olefin dimerization

The dimerization or oligomerization of olefins is characterized by a low selectivity giving rise to a variety of products. For the hydrovinylation of olefins such as cycloocta-1,3-diene, norbornene, or norbornadiene with ethylene using $[(\eta^3\text{-}C_3H_5)NiCl]_2$/$AlEtCl_2$/menthylphosphine catalysts, up to 70–80%ee were obtained in the early 1970s[245,246]. The record for the hydrovinylation of cyclohexadiene with ethylene (equation 20) at present is 93%ee using $[Ni(cod)_2]$/$AlEt_2Cl$ catalysts together with the aminophosphine ligand **4**[247].



(20)



(4)

D. Carbon—Heteroatom Bond Formation

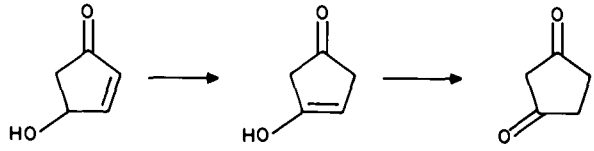
1. Isomerization of functionalized olefins

In 1976, the isomerization of prochiral allylic alcohols to optically active aldehydes in low enantiomeric excess with an Rh–diop catalyst was the first transition metal-catalysed enantioselective olefin isomerization[248]. A recent example is the rearrangement of diethylgeranylamine to the corresponding enamine (reaction 21). Such reactions are catalysed by cobalt and rhodium phosphine complexes[249–252], the Rh–binap system being unrivalled in showing high catalytic activity and selectivity[253–255]. In reaction 21 the optical induction is virtually quantitative, provided that a pure geometrical isomer with respect to the allylamine double bond is used. Hydrolysis of the enamine gives optically pure citronellal, whereas natural citronellal has an optical purity of only 75–80%[254].

$$Me_2C{=}CH(CH_2)_2C(Me){=}CHCH_2NEt_2 \rightarrow$$
$$Me_2C{=}CH(CH_2)_2CH(Me)CH{=}CHNEt_2 \qquad (21)$$

The enantioselective catalytic isomerization of diethylgeranylamine with Rh–binap catalysts is the key step in the commercial production of 1000 tons per annum of menthol, one third of the present world production. In this reaction a nitrogen-triggered 1,3-hydrogen shift takes place in the allylamine part of diethylgeranylamine; the other double bond is not affected.

The isomerization of the allyl alcohol moiety has been used for a kinetic resolution (equation 22). A Rh–binap catalyst gives a 5:1 enantiomeric discrimination, allowing the recovery of the starting material 4-hydroxycyclopent-2-enone, a key chiral building block in prostaglandin synthesis, in 91%ee[256].



(22)

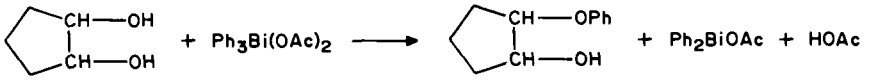
2. *Sulphonylation of allyl acetates*

Racemic allyl *p*-toluenesulphinates can be rearranged with $[Pd(PPh_3)_4]$. Addition of chiral ligands such as diop gives optically active allyl sulphones in up to 87% ee[257]. These compounds can also be prepared in the same optical purity from allylic acetates and sodium *p*-toluenesulphinate using a $[Pd(PPh_3)_4]$/diop catalyst (equation 23).

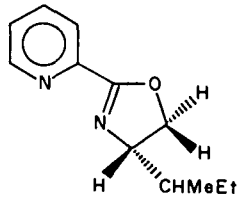
$$MeCH{=}CHCH_2OAc + TolSO_2Na \rightarrow TolSO_2CH(Me)CH{=}CH_2 + NaOAc \quad (23)$$

E. Future Prospects

For all the reactions discussed up to now, exceedingly high optical inductions have been reported. In addition to these 'show-window' reactions, many other reaction types have been subjected to enantioselective transition metal catalysis. An example from the author's laboratory is the monophenylation of *meso*-diols. *cis*-Cyclopentanediol is monophenylated with $Ph_3Bi(OAc)_2$ to give *cis*-1-phenoxycyclopentan-2-ol (equation 24). *In situ* catalysts consisting of $[Cu(OAc)_2]$ and the pyridineoxazoline ligand **5** give 50% ee in this reaction, in which two new chiral centres are formed[258]. However, the optical induction has to be raised.



(24)



(5)

The same is true for a variety of other transition metal-catalysed reactions, the optical inductions of which up to now do not exceed the medium range. Recent examples are the hydrocyanation of olefins[259], cyclization of unsaturated aldehydes (hydroacylation)[260–262], chlorosulphonylation of olefins[263,264], carbon dioxide fixation with halohydrins[265], decarboxylation of substituted malonic hemiesters[266], ring opening of epoxides with amines and thiols[52,267], oxidative cyclization of allylphenols[268–270], Michael-addition of 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds[271,272], reduction of cyclic anhydrides to lactones[273–275], and hydrosilylation of oximes[163,164]. For further details the reader is referred to the references cited or to recent reviews[2–9].

IV. MECHANISMS

For some of the reactions discussed in Section III detailed information concerning the mechanisms is available. The two most prominent examples, hydrogenation and allylic alkylation, are discussed below. However, for most of the reactions the mechanisms are either not known in detail or are completely unknown.

A. Hydrogenation of Dehydroamino Acid Esters

The mechanism of the enantioselective hydrogenation of dehydroamino acid derivatives has been unravelled in the last decade, especially by the work of Halpern[276–282]. The present status of the mechanism is shown in Scheme 1.

The catalytically active species is a rhodium(I) complex **I** containing an optically active bisphosphine, abbreviated to P*—P, and two solvent molecules S. The two solvent molecules are replaced by the substrate, methyl (*Z*)-α-acetamidocinnamate (**II**), which binds in a bidentate way through the olefinic double bond and the oxygen atom of the *N*-acetyl group. Two diastereoisomers, **IIIa** and **IIIb**, are formed which differ only in the face of the olefin bonded to the rhodium atom. Via dissociation of the olefin there is equilibration between the two diastereomeric rhodium complexes **IIIa** and **IIIb**. The next step is the oxidative addition of the hydrogen molecule to the two diastereomers, normally the rate-determining step, to give the octahedral *cis*-dihydro species **IVa** and **IVb**. **IVa** and **IVb** undergo a rearrangement to the σ-alkyl species **Va** and **Vb**, which reductively eliminate the hydrogenation products **VIa** and **VIb**, regenerating the catalytically active species which re-enters the catalytic cycle.

In the diastereomer equilibrium **IIIa**⇌**IIIb**, diastereoisomer **IIIa** dominates, if P*—P is (*R*, *R*)-dipamp (Table 1). The pure diastereoisomer **IIIa** has been isolated and characterized by X-ray crystallography. Surprisingly, diastereomer **IIIa** is not the species which in the hydrogenation reaction forms the major product enantiomer **VIb**. Therefore, it must be assumed that diastereomer **IIIb** present in the equilibrium in only small amounts is so much more reactive than **IIIa** in the rate-determining hydrogen addition that the major product enantiomer **VIb** originates from it. The situation can be reversed by increasing the hydrogen pressure. Then, the rate of the oxidative addition step is increased and the equilibration **IIIa**⇌**IIIb** may become the slow step in Scheme 1.

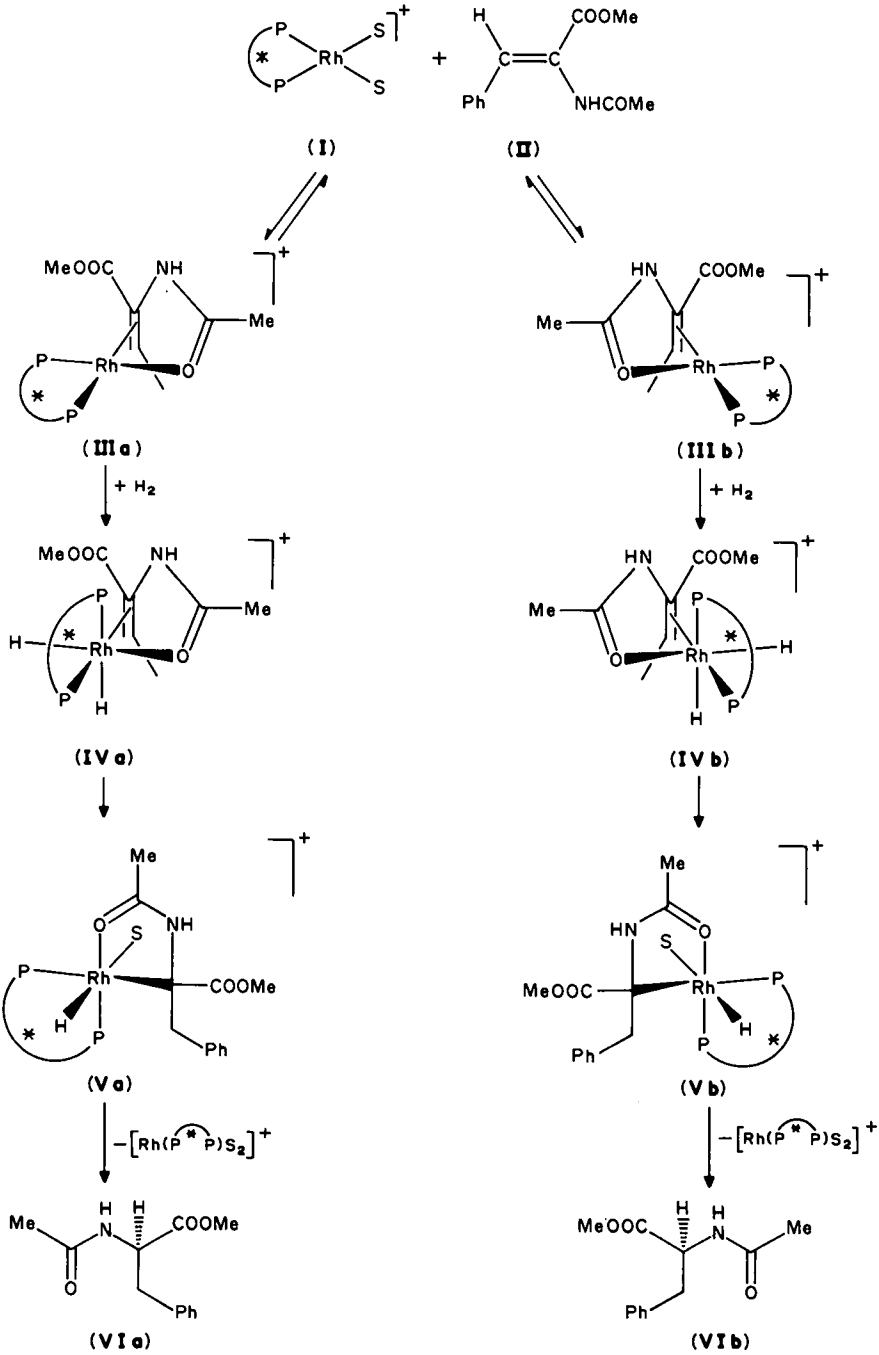
B. Alkylation of Allyl Acetates With Soft Nucleophiles

The mechanism of the palladium-catalysed allylic alkylation with soft nucleophiles has been elucidated by Bosnich[5,208,223,226,227]. By reaction with the nucleophile the catalyst $[(\eta^3\text{-}C_3H_5)Pd(S,S\text{-chiraphos})]ClO_4$ is converted into the $Pd^0/P^*\!-\!P$ species **I** (Scheme 2).

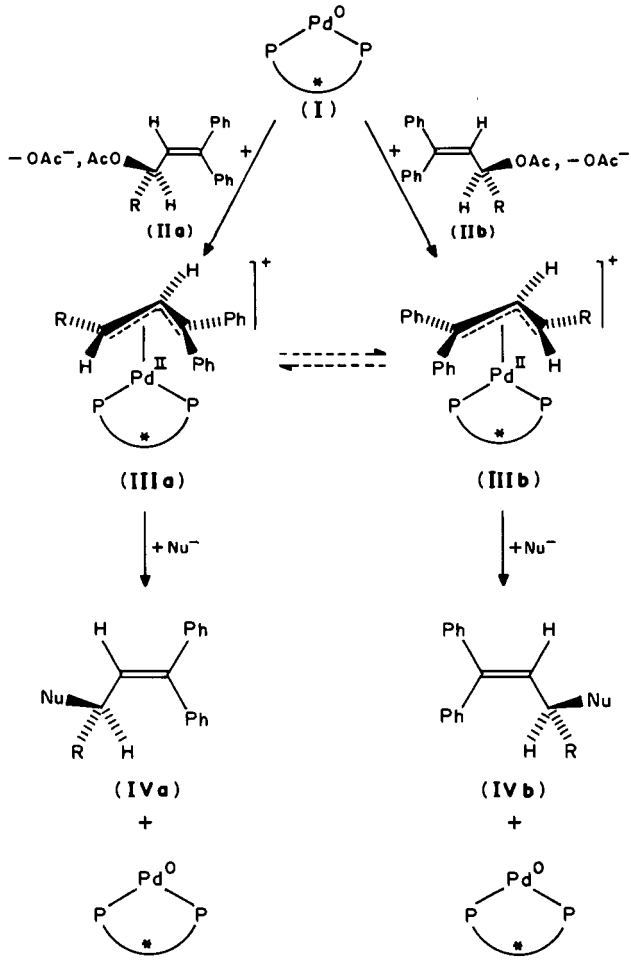
$Pd^0/P^*\!-\!P$ reacts with the substrate triphenylprop-2-enyl acetate (R = Ph) (**IIa/IIb**) to give the new η^3-allyl complexes **IIIa** and **IIIb**. The attack of **IIIa** and **IIIb** by the nucleophile, e.g. the acetylacetonate anion, regenerates $Pd^0/P^*\!-\!P$ (**I**), leading to the enantiomers **IVa** and **IVb** of the substitution product, in which the 3,3-diphenyl group directs the nucleophile to the less hindered position.

It has already been mentioned in Section III.C.3 that the formation of the η^3-allyl complexes **IIIa** and **IIIb** occurs with inversion of configuration, if chiral allyl acetates are used and that the nucleophile attacks the η^3-allyl intermediates **IIIa** and **IIIb** from the side opposite to the palladium atom leading to another inversion. Hence the palladium-catalysed allylation actually is a double inversion[223,226,283–285].

In the catalytic cycle shown in Scheme 2, the rate-determining step is the reaction of the η^3-allyl intermediates **IIIa** and **IIIb** with the nucleophile. This step is slow compared with the oxidative addition of the allyl acetate **IIa/IIb** to $Pd^0/P^*\!-\!P$ and also compared with the epimerization of the diastereomers **IIIa** and **IIIb**.



SCHEME 1



SCHEME 2

The two diastereomers **IIIa** and **IIIb** in Scheme 2 differ only in the face of the allyl group bonded to the palladium atom. There is equilibration between the two diastereomers **IIIa** and **IIIb** and, similarly to the hydrogenation mechanism, the equilibrium is shifted to one side. For P–*–P = (*S*, *S*)-chiraphos, it is **IIIb** that dominates the equilibrium **IIIa** ⇄ **IIIb**. As the reaction of the two diastereomers **IIIa** and **IIIb** with the nucleophile is strongly exothermic, the chiral discrimination in the ground-state intermediates **IIIa** and **IIIb** is reflected in the corresponding diastereomeric transition states. For Scheme 2 it has been established that the major product enantiomer **IVb** originates from the major diastereomer **IIIb**. Hence the enantioselective step in the palladium-catalysed alkylation is under reactant control, whereas the rhodium-catalysed hydrogenation discussed before is under product control. Hence both mechanisms are based on two equilibrating diastereomers, but in the hydrogenation the major product enantiomer arises from the minor diastereomer whereas in the allylic alkylation the major product enantiomer arises

from the major diastereomer. The lesson is that generalizations are dangerous and each individual mechanism has to be checked carefully.

V. REFERENCES

1. T. Wynberg, *Top. Stereochem.*, **16**, 87 (1986).
2. H. Brunner, *Synthesis*, 645 (1988).
3. H. Brunner, *Top. Stereochem.*, **18**, (1988).
4. M. Nógrádi, *Stereoselective Synthesis*, VCH, Weinheim, 1987.
5. B. Bosnich, *Asymmetric Catalysis*, NATO ASI Series E 103, Martinus Nijhoff, Dordrecht, 1986.
6. J. D. Morrison, *Asymmetric Synthesis, Vol. 5, Chiral Catalysis*, Academic Press, Orlando, 1985.
7. P. Pino and G. Consiglio, *Pure Appl. Chem.*, **55**, 1781 (1983).
8. H. B. Kagan, in *Comprehensive Organometallic Chemistry* (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Vol. 8, Pergamon Press, Oxford, 1982, p. 463.
9. B. Bosnich and M. D. Fryzuk, *Top. Stereochem.*, **12**, 119 (1981).
10. S. Akabori, S. Sakurai, Y. Izumi, and Y. Fujii, *Nature (London)*, **178**, 323 (1956).
11. H. Nozaki, S. Moriuti, H. Takaya, and R. Noyori, *Tetrahedron Lett.*, 5239 (1966).
12. L. Horner, H. Siegel, and H. Büthe, *Angew. Chem., Int. Ed. Engl.*, **7**, 942 (1968).
13. W. S. Knowles and M. J. Sabacky, *Chem. Commun.*, 1445 (1968).
14. H. Brunner, *Angew. Chem., Int. Ed. Engl.*, **22**, 897 (1983).
15. M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **100**, 5491 (1978).
16. M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977).
17. W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2567 (1975).
18. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **99**, 5946 (1977).
19. H. Brunner and W. Pieronczyk, *Angew. Chem., Int. Ed. Engl.*, **18**, 620 (1979).
20. H. Brunner, W. Pieronczyk, B. Schönhammer, K. Streng, I. Bernal, and J. Korp, *Chem. Ber.*, **114**, 1137 (1981).
21. H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).
22. B. A. Murrer, J. M. Brown, P. A. Chaloner, P. N. Nicholson, and D. Parker, *Synthesis*, 350 (1979).
23. K. Achiwa, *J. Am. Chem. Soc.*, **98**, 8265 (1976).
24. T. Hayashi, T. Mise, S. Mitachi, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 1133 (1976).
25. T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto, and M. Kumada, *Bull. Chem. Soc. Jpn.*, **53**, 1138 (1980).
26. A. Mijashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, and R. Noyori, *J. Am. Chem. Soc.*, **102**, 7932 (1980).
27. H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, and R. Noyori, *J. Org. Chem.*, **51**, 629 (1986).
28. U. Nagel, *Angew. Chem., Int. Ed. Engl.*, **23**, 435 (1984).
29. U. Nagel, E. Kinzel, J. Andrade, and G. Prescher, *Chem. Ber.*, **119**, 3326 (1986).
30. H. Brunner, G. Riepl, and H. Weitzer, *Angew. Chem., Int. Ed. Engl.*, **22**, 331 (1983).
31. H. Brunner, R. Becker, and G. Riepl, *Organometallics*, **3**, 1354 (1984).
32. Y. Izumi, *Adv. Catal.*, **32**, 215 (1983).
33. E. I. Klabunovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 505 (1984); *Chem. Abstr.*, **101**, 54069b (1984).
34. W. M. H. Sachtler, in Chemical Industries/22, *Catalysis of Organic Reactions* (Ed. R. L. Augustine), Marcel Dekker, Inc., New York, Basel, 1985, p. 189.
35. A. Tai and T. Harada, in *Tailored Metal Catalysts* (Ed. J. Iwasawa), Reidel, Dordrecht, 1986, p. 265.
36. K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem.*, **55**, 1823 (1983).
37. *Aldrichim. Acta*, **18**, 53 (1985).
38. B. E. Rossiter, in Chemical Industries/22, *Catalysis of Organic Reactions* (Ed. R. L. Augustine), Marcel Dekker, Inc., New York, Basel, 1985, p. 295.
39. B. E. Rossiter, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 193.
40. M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 247.

41. A. Pfenninger, *Synthesis*, 89 (1986).
42. H. B. Kagan, E. Dunach, C. Nemecek, P. Pitchen, O. Samuel, and S.-H. Zhao, *Pure Appl. Chem.*, **57**, 1911 (1985).
43. S. H. Zhao, O. Samuel, and H. B. Kagan, *C. R. Acad. Sci., Ser. 2*, **304**, 273 (1987).
44. H. Brunner, *J. Organomet. Chem.*, **300**, 39 (1986).
45. H. B. Kagan, *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 1.
46. T. Harada and Y. Izumi, *Chem. Lett.*, 1195 (1978).
47. Y. Izumi, *Angew. Chem., Int. Ed. Engl.*, **10**, 871 (1971).
48. T. Harada, M. Yamamoto, S. Onaka, M. Imaida, H. Ozaki, A. Tai, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **54**, 2323 (1981).
49. M. Inoue, K. Ohta, N. Ishizuka, and S. Enomoto, *Chem. Pharm. Bull.*, **31**, 3371 (1983).
50. N. Ishizuka, M. Togashi, M. Inoue, and S. Enomoto, *Chem. Pharm. Bull.*, **35**, 1686 (1987).
51. A. R. Daniewski and T. Kowalczyk-Przewloka, *J. Org. Chem.*, **50**, 2976 (1985).
52. H. Yamashita and T. Mukaiyama, *Chem. Lett.*, 1634 (1985).
53. C. U. Pittman, Jr, in *Comprehensive Organometallic Chemistry* (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Vol. 8, Pergamon Press, Oxford, 1982, p. 553.
54. A. Kinting, H. Krause, and M. Capka, *J. Mol. Catal.*, **33**, 215 (1985).
55. U. Nagel and E. Kinzel, *J. Chem. Soc., Chem. Commun.*, 1089 (1986).
56. R. Selke, *J. Mol. Catal.*, **37**, 227 (1986).
57. H. B. Kagan and T. P. Dang, *Chem. Commun.*, 481 (1971).
58. W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *J. Chem. Soc., Chem. Commun.*, 10 (1972).
59. K. E. Koenig, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 71.
60. I. Ojima, *Pure Appl. Chem.*, **56**, 99 (1984).
61. J. Halpern, *Pure Appl. Chem.*, **55**, 99 (1983).
62. W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983).
63. V. Caplar, G. Comisso, and V. Sunjic, *Synthesis*, 85 (1981).
64. R. E. Merrill, *ChemTech*, 118 (1981).
65. K. E. Koenig, M. J. Sabacky, G. L. Bachman, W. C. Christopfel, H. D. Barnstoff, R. B. Friedman, W. S. Knowles, B. R. Stults, B. D. Vineyard, and D. J. Weinkauff, *Ann. N. Y. Acad. Sci.*, **333**, 16 (1980).
66. L. Horner, *Pure Appl. Chem.*, **52**, 843 (1980).
67. H. Brunner, *Chem. unserer Zeit*, **14**, 177 (1980).
68. T. P. Dang, J. C. Poulin, and H. B. Kagan, *J. Organomet. Chem.*, **91**, 105 (1975).
69. T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, and S. Akutagawa, *J. Chem. Soc., Chem. Commun.*, 922 (1985).
70. J. Bakos, I. Tóth, B. Heil, and L. Markó, *J. Organomet. Chem.*, **279**, 23 (1985).
71. U. Nagel and E. Kinzel, *Chem. Ber.*, **119**, 1731 (1986).
72. B. D. Zwick, A. M. Arif, A. T. Patton, and J. A. Gladysz, *Angew. Chem., Int. Ed. Engl.*, **26**, 910 (1987).
73. R. Selke and H. Pracejus, *J. Mol. Catal.*, **37**, 312 (1986).
74. A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, **40**, 1245 (1984).
75. P. A. McNeil, N. K. Roberts, and B. Bosnich, *J. Am. Chem. Soc.*, **103**, 2280 (1981).
76. T. Hayashi and M. Kumada, *Acc. Chem. Res.*, **15**, 395 (1982).
77. R. Selke, *J. Mol. Catal.*, **37**, 227 (1986).
78. U. Nagel and E. Kinzel, *J. Chem. Soc., Chem. Commun.*, 1098 (1986).
79. H. B. Kagan, *Ann. N. Y. Acad. Sci.*, **333**, 1 (1980).
80. W. S. Knowles, B. D. Vineyard, M. J. Sabacky, and B. R. Stults, in *Fundamental Research in Homogeneous Catalysis* (Eds Y. Ishii and M. Tsutsui), Vol. 3, Plenum Press, New York, 1979, p. 537.
81. D. A. Slack, I. Greveling, and M. C. Baird, *Inorg. Chem.*, **18**, 3125 (1979).
82. H. Brunner, B. Schönhammer, B. Schönhammer, and C. Steinberger, *Chem. Ber.*, **116**, 3529 (1983).
83. S. Takeuchi and Y. Ohgo, *Bull. Chem. Soc. Jpn.* **57**, 1920 (1984).
84. C. Cativiela, J. A. Mayoral, E. Meléndez, L. A. Oro, M. T. Pinillos, and R. Usón, *J. Org. Chem.*, **49**, 2502 (1984).
85. D. G. Allen, S. B. Wild, and D. L. Wood, *Organometallics*, **5**, 1009 (1986).
86. K. Saito, S. Saijo, K. Kotera, and T. Date, *Chem. Pharm. Bull.*, **33**, 1342 (1985).

87. U. Schmidt, A. Lieberknecht, H. Griesser, and F. Bartkowiak, *Angew. Chem., Int. Ed. Engl.*, **23**, 318 (1984).
88. W. S. Knowles, *J. Chem. Educ.*, **63**, 222 (1986).
89. U. Schmidt and U. Schanbacher, *Justus Liebigs Ann. Chem.*, 1205 (1984).
90. D. G. Melillo, R. D. Larsen, D. J. Mathre, W. F. Shukis, A. W. Wood, and J. R. Colleluori, *J. Org. Chem.*, **52**, 5143 (1987).
91. H. Parnes and E. J. Shelton, *Int. J. Pept. Protein Res.*, **27**, 239 (1986); *Chem. Abstr.*, **105**, 134134a (1986).
92. H. Parnes and E. J. Shelton, *Synth. Appl. Isot. Labeled Comp. Proc. Int. Symp., 2nd (1985)*, 159 (Pub. 1986); *Chem. Abstr.*, **106**, 214337w (1987).
93. H. Parnes, E. J. Shelton, and G. T. Huang, *Int. J. Pept. Protein Res.*, **28**, 403 (1986); *Chem. Abstr.*, **107**, 59430w (1987).
94. S. El-Baba, J. M. Nuzillard, J. C. Poulin, and H. B. Kagan, *Tetrahedron*, **42**, 3851 (1986).
95. I. Ojima, N. Yoda, M. Yatabe, T. Tanaka, and T. Kogure, *Tetrahedron*, **40**, 1255 (1984).
96. J. M. Nuzillard, J. C. Poulin, and H. B. Kagan, *Tetrahedron Lett.*, **27**, 2993 (1986).
97. S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985).
98. I. Ojima, *Pure Appl. Chem.*, **56**, 99 (1984).
99. M. Yatagai, M. Zama, T. Yamagishi, and M. Hida, *Bull. Chem. Soc. Jpn.*, **57**, 739 (1984).
100. T. Yamagishi, M. Yatagai, H. Hatakeyama, and M. Hida, *Bull. Chem. Soc. Jpn.*, **57**, 1897 (1984).
101. M. Yatagai, M. Zama, T. Yamagishi, and M. Hida, *Chem. Lett.*, 1203 (1983).
102. M. Yatagai, T. Yamagishi, and M. Hida, *Bull. Chem. Soc. Jpn.*, **57**, 823 (1984).
103. K. E. Koenig, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 76.
104. U. Schöllkopf, I. Hoppe, and A. Thiele, *Justus Liebigs Ann. Chem.*, 555 (1985).
105. K. E. Koenig, G. L. Bachman, and B. D. Vineyard, *J. Org. Chem.*, **45**, 2362 (1980).
106. K. Achiwa, *Chem. Lett.*, 561 (1978).
107. H. Kawano, Y. Ishii, T. Ikariya, M. Saburi, S. Yoshikawa, Y. Uchida, and H. Kumobayashi, *Tetrahedron Lett.*, **28**, 1905 (1987).
108. H. Takahashi and K. Achiwa, *Chem. Lett.*, 1921 (1987).
109. I. Ojima and N. Yoda, *Tetrahedron Lett.*, **21**, 1051 (1980).
110. R. Noyori, M. Ohta, Y. Hsiao, and M. Kitamura, *J. Am. Chem. Soc.*, **108**, 7117 (1986).
111. M. Kitamura, Y. Hsiao, R. Noyori, and H. Takaya, *Tetrahedron Lett.*, **28**, 4829 (1987).
112. D. Sinou and H. B. Kagan, *J. Organomet. Chem.*, **114**, 321 (1976).
113. U. Matteoli, P. Frediani, and M. Bianchi, *J. Mol. Catal.*, **12**, 265 (1981).
114. T. Ohta, H. Takaya, M. Kitamura, K. Nagai, and R. Noyori, *J. Org. Chem.*, **52**, 3174 (1987).
115. H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, and R. Noyori, *J. Am. Chem. Soc.*, **109**, 1596 (1987).
116. I. Thanos and H. Simon, *Angew. Chem., Int. Ed. Engl.*, **25**, 462 (1986).
117. D. A. Evans, M. M. Morrissey, and R. L. Dow, *Tetrahedron Lett.*, **26**, 6005 (1985).
118. J. M. Brown and I. Cutting, *J. Chem. Soc., Chem. Commun.*, 578 (1985).
119. J. M. Brown, I. Cutting, P. L. Evans, and P. J. Maddox, *Tetrahedron Lett.*, **27**, 3307 (1986).
120. S. Inoue, M. Osada, K. Koyano, H. Takaya, and R. Noyori, *Chem. Lett.*, 1007 (1985).
121. Y. Kawabata, M. Tanaka, and I. Obata, *Chem. Lett.*, 1213 (1976).
122. B. Heil, S. Törös, J. Bakos, and L. Markó, *J. Organomet. Chem.*, **175**, 229 (1979).
123. K. Yamamoto and Saeed-Ur-Rehman, *Chem. Lett.*, 1603 (1984).
124. K. Tani, T. Ise, Y. Tatsuno, and T. Saito, *J. Chem. Soc., Chem. Commun.*, 1641 (1984).
125. H. Takahashi, M. Hattori, M. Chiba, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **27**, 4477 (1986).
126. T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, and K. Achiwa, *Chem. Lett.*, 2061 (1986).
127. S. Törös, L. Kollar, B. Heil, and L. Markó, *J. Organomet. Chem.*, **232**, C17 (1982).
128. H. Takahashi, T. Morimoto, and K. Achiwa, *Chem. Lett.*, 855 (1987).
129. Y. Ohgo, Y. Natori, S. Takeuchi, and J. Yoshimura, *Chem. Lett.*, 1327 (1974).
130. B. Heil, *Wiss. Z. Tech. Hochsch. Chem. Carl Schorlemmer Leuna-Merseburg*, **27**, 739 (1985); *Chem. Abstr.*, **106**, 18637e (1987).
131. I. Ojima, T. Kogure, T. Terasaki, and K. Achiwa, *J. org. Chem.*, **43**, 3444 (1978).
132. I. Ojima, T. Kogure, and Y. Yoda, *Org. Synth.*, **63**, 18 (1985).
133. H. Takahashi, M. Hattori, M. Chiba, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **27**, 4477 (1986).

134. T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, and K. Achiwa, *Chem. Lett.*, 2061 (1986).
135. T. Kikukawa, M. Imaida, and A. Tai, *Bull. Chem. Soc. Jpn.*, **57**, 1954 (1984).
136. A. Tai, K. Tsukioka, H. Ozaki, T. Harada, and Y. Izumi, *Chem. Lett.*, 2083 (1984).
137. A. Tai, K. Tsukioka, Y. Imachi, Y. Inoue, H. Ozaki, T. Harada, and Y. Izumi, *Int. Congr. Catal. (Proc.), V521, 8th, 1984, 5*; *Chem. Abstr.*, **106**, 83812x (1987).
138. R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa, *J. Am. Chem. Soc.*, **109**, 5856 (1987).
139. L. Wilds, *Org. React.*, **2**, 178 (1944).
140. V. M. Gryaznov, *Fiz. Khim. (Moscow)*, 96 (1982); *Chem. Abstr.*, **100**, 208650c.
141. R. A. W. Johnstone, A. H. Wilby, and I. D. Entwistle, *Chem. Rev.*, 129 (1985).
142. P. Kvintovics, J. Bakos, and B. Heil, *J. Mol. Catal.*, **32**, 111 (1985).
143. H. W. Krause and A. K. Bhatnagar, *J. Organomet. Chem.*, **302**, 265 (1986).
144. C. Botteghi, G. Chelucci, G. Chessa, G. Delogu, S. Gladiali, and F. Soccolini, *J. Organomet. Chem.*, **304**, 217 (1986).
145. R. Spogliarich, J. Kaspar, M. Graziani, F. Morandini, and O. Piccolo, *J. Catal.*, **94**, 292 (1985).
146. S. Gladiali, G. Chelucci, G. Chessa, G. Delogu, and F. Soccolini, *J. Organomet. Chem.*, **327**, C15 (1987).
147. G. Zassinovich and G. Mestroni, *J. Mol. Catal.*, 42, 81 (1987).
148. P. Kvintovics, B. R. James, and B. Heil, *J. Chem. Soc., Chem. Commun.*, 1810 (1986).
149. R. Spogliarich, J. Kaspar, M. Graziani, and F. Morandini, *J. Organomet. Chem.*, **306**, 407 (1986).
150. S. Zehani and G. Gelbard, *J. Chem. Soc., Chem. Commun.*, 1162 (1985).
151. K. Yoshinaga, T. Kito, and K. Ohkubo, *J. Chem. Soc., Perkin Trans. 2*, 469 (1984).
152. H. Brunner and M. Kunz, *Chem. Ber.*, **119**, 2868 (1986).
153. H. Brunner and W. Leitner, *Synthesis*, in press.
154. I. Ojima and K. Hirai, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 103.
155. I. Ojima, *Strem Chem.*, **8**, 1 (1980).
156. K. Yamamoto, T. Hayashi, and M. Kumada, *J. Organomet. Chem.*, **46**, C65 (1972).
157. T. H. Johnson, K. C. Klein, and S. Thomen, *J. Mol. Catal.*, **12**, 37 (1981).
158. H. Brunner and G. Riepl, *Angew. Chem., Int. Ed. Engl.*, **21**, 377 (1982); *Angew. Chem. Suppl.*, 769 (1982).
159. H. Brunner, B. Reiter, and G. Riepl, *Chem. Ber.*, **117**, 1330 (1984).
160. H. Brunner and A. Kürzinger, *J. Organomet. Chem.*, **346**, 413 (1988).
161. I. Ojima, T. Kogure, and M. Kumagai, *J. Org. Chem.*, **42**, 1671 (1977).
162. K. Soai, S. Niwa, and T. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 801 (1987).
163. H. Brunner and R. Becker, *Angew. Chem., Int. Ed. Engl.*, **23**, 222 (1984).
164. H. Brunner, R. Becker, and S. Gauder, *Organometallics*, **5**, 739 (1986).
165. I. Ojima and T. Kogure, *Organometallics*, **1**, 1390 (1982).
166. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
167. V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981).
168. W. R. Roush and R. J. Brown, *J. Org. Chem.*, **48**, 5093 (1983).
169. J. G. Hill and K. B. Sharpless, *Org. Synth.*, **63**, 66 (1985).
170. R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, **51**, 1922 (1986).
171. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).
172. P. C. B. Page, C. M. Rayner, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1408 (1986).
173. M. Sodeoka, T. Iimori, and M. Shibasaki, *Tetrahedron Lett.*, **26**, 6497 (1985).
174. T. Izawa, Z. Wang, Y. Nishimura, S. Kondo, and H. Umezawa, *Chem. Lett.*, 1655 (1987).
175. R. E. Babine, *Tetrahedron Lett.*, **27**, 5791 (1986).
176. A. C. Oehlschlager and B. D. Johnston, *J. Org. Chem.*, **52**, 940 (1987).
177. R. D. Tung and D. H. Rich, *Tetrahedron Lett.*, **28**, 1139 (1987).
178. J. M. Chong and S. Wong, *J. Org. Chem.*, **52**, 2596 (1987).
179. J. T. Groves and R. S. Myers, *J. Am. Chem. Soc.*, **105**, 5791 (1983).
180. D. Mansuy, P. Battioni, J.-P. Renaud, and P. Guerin, *J. Chem. Soc., Chem. Commun.*, 155 (1985).
181. F. Di Furia, G. Modena, and R. Seraglia, *Synthesis*, 325 (1984).
182. P. Pitchen and H. B. Kagan, *Tetrahedron Lett.*, **24**, 1049 (1984).
183. P. Pitchen, M. Deshmukh, E. Dunach, and H. B. Kagan, *J. Am. Chem. Soc.*, **106**, 8188 (1984).

184. E. Dunach and H. B. Kagan, *Nouv. J. Chim.*, **9**, 325 (1985).
185. C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, and H. B. Kagan, *J. Am. Chem. Soc.*, **108**, 2353 (1986).
186. H. B. Kagan, *Phosphorus Sulfur*, **27**, 127 (1986).
187. K. Nakajima, M. Kojima, and J. Fujita, *Chem. Lett.*, 1483 (1986).
188. A. Colombo, G. Marturano, and A. Pasini, *Gazz. Chim. Ital.*, **116**, 35 (1986).
189. J. K. Stille, in Chemical Industries/22, *Catalysis of Organic Reactions* (Ed. R. L. Augustine), Marcel Dekker, Inc., New York, Basel, 1985, p. 23.
190. J. K. Stille, S. J. Fritschel, N. Takaishi, T. Masuda, H. Imai, and C. A. Bertelo, *Ann. N. Y. Acad. Sci.*, **333**, 35 (1980).
191. I. Ojima and K. Hirai, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 103.
192. G. Consiglio and P. Pino, *Adv. Chem. Ser.*, No. 196, 371 (1982).
193. G. Consiglio and P. Pino, *Top. Curr. Chem.*, **105**, 77 (1982).
194. C. Botteghi, G. Consiglio, and P. Pino, *Chimia*, **26**, 141 (1972).
195. M. Petit, A. Mortreux, F. Petit, G. Buono, and G. Peiffer, *Nouv. J. Chim.*, **7**, 593 (1983).
196. G. Parrinello and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 7122 (1987).
197. J. K. Stille and G. Parrinello, *J. Mol. Catal.*, **21**, 203 (1983).
198. L. Kollár, G. Consiglio, and P. Pino, *J. Organomet. Chem.*, **330**, 305 (1987).
199. L. Kollár, G. Consiglio, and P. Pino, *Chimia*, **40**, 428 (1986).
200. J. K. Stille, in *The Chemistry of the Metal Carbon Bond* (Ed. S. Patai), Vol. 2, Wiley, New York, 1985, p. 625.
201. J. K. Stille, S. J. Fritschel, N. Takaishi, T. Masuda, H. Imai, and C. A. Bertelo, *Ann. N. Y. Acad. Sci.*, **333**, 35 (1980).
202. G. Parrinello and J. K. Stille, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.*, **27**, 9 (1986); *Chem. Abstr.*, **107**, 58192h (1987).
203. R. Deschenaux and J. K. Stille, *J. Org. Chem.*, **50**, 2299 (1985).
204. C. U. Pittman, Jr, L. I. Flowers, and Q. Ng, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **27**, 614 (1982); *Chem. Abstr.*, **101**, 6263p (1984).
205. G. Consiglio, F. Morandini, M. Scalone, and P. Pino, *J. Organomet. Chem.*, **279**, 193 (1985).
206. T. Hayashi, M. Tanaka, and I. Ogata, *Tetrahedron Lett.*, 3925 (1978).
207. T. Hayashi, M. Tanaka, and I. Ogata, *J. Mol. Catal.*, **26**, 17 (1984).
208. T. Hayashi and M. Kumada, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 147.
209. R. M. Kellog, *Angew. Chem., Int. Ed. Engl.*, **23**, 782 (1984).
210. T. Hayashi, in *Asymmetric Reactions and Processes in Chemistry* (Eds E. L. Eliel and S. Otsuka), ACS Symp. Ser., No. 185, American Chemical Society, Washington, DC, 1982, p. 177.
211. T. Hayashi and M. Kumada, in *Fundamental Research in Homogeneous Catalysis* (Eds Y. Ishii and M. Tstsui), Vol. 2, Plenum Press, New York, 1978, p. 159.
212. G. Consiglio and C. Botteghi, *Helv. Chim. Acta*, **56**, 460 (1973).
213. Y. Kiso, K. Tamao, N. Miyake, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 3 (1974).
214. G. Consiglio, F. Morandini, and O. Piccolo, *Tetrahedron*, **39**, 2699 (1983).
215. T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki, and M. Kumada, *J. Org. Chem.*, **48**, 2195 (1983).
216. T. Hayashi, M. Konishi, H. Ito, and M. Kumada, *J. Am. Chem. Soc.*, **104**, 4962 (1982).
217. B. K. Vriesema and R. M. Kellogg, *Tetrahedron Lett.*, **27**, 2049 (1986).
218. T. Hayashi, M. Konishi, Y. Okamoto, K. Kabeta, and M. Kumada, *J. Org. Chem.*, **51**, 3772 (1986).
219. T. Hayashi, M. Fukushima, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, **21**, 79 (1980).
220. G. Consiglio, O. Piccolo, L. Roncetti, and F. Morandini, *Tetrahedron*, **42**, 2043 (1986).
221. G. Consiglio, F. Morandini, and O. Piccolo, *J. Chem. Soc., Chem. Commun.*, 112 (1983).
222. T. Hiyama and N. Wakasa, *Tetrahedron Lett.*, **26**, 3259 (1985).
223. P. R. Auburn, P. B. Mackenzie, and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2033 (1985).
224. T. Hayashi, A. Yamamoto, T. Hagihara, and Y. Ito, *Tetrahedron Lett.*, **27**, 191 (1986).
225. T. Hayashi, A. Yamamoto, and Y. Ito, *Chem. Lett.*, 177 (1987).
226. P. B. Mackenzie, J. Whelan, and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2046 (1985).
227. B. Bosnich and P. B. Mackenzie, *Pure Appl. Chem.*, **54**, 189 (1982).
228. T. Hayashi, A. Yamamoto, and Y. Ito, *J. Chem. Soc., Chem. Commun.*, 1090 (1986).

229. D. Arlt, M. Jautelat, and R. Lantzsch, *Angew. Chem., Int. Ed. Engl.*, **20**, 703 (1981).
230. S. A. Matlin, W. J. Lough, L. Chan, D. M. H. Abram, and Z. Zhou, *J. Chem. Soc., Chem. Commun.*, 1038 (1984).
231. D. A. Laidler and D. J. Milner, *J. Organomet. Chem.*, **270**, 121 (1984).
232. H. Kanai and H. Matsuda, *J. Mol. Catal.*, **29**, 157 (1985).
233. T. Aratani, *Pure Appl. Chem.*, **57**, 1839 (1985).
234. G. Maas, *Top. Curr. Chem.*, **137**, 75 (1987).
235. M. P. Doyle, *Chem. Rev.*, **86**, 919 (1986).
236. H. Fritschi, U. Leutenegger, and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, **25**, 1005 (1986).
237. K. Krohn, *Nachr. Chem. Tech. Lab.*, **35**, 840 (1987).
238. K. Narasaka, M. Inoue, and N. Okada, *Chem. Lett.*, 1109 (1986).
239. K. Narasaka, M. Inoue, and T. Yamada, *Chem. Lett.*, 1967 (1986).
240. M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **108**, 7060 (1986).
241. M. Quimpère and K. Jankowski, *J. Chem. Soc., Chem. Commun.*, 676 (1987).
242. M. T. Reetz, S.-H. Kyung, C. Bolm, and T. Zierke, *Chem. Ind. (London)*, 824 (1986).
243. M. T. Reetz and A. E. Vougioukas, *Tetrahedron Lett.*, **28**, 793 (1987).
244. Y. Ito, M. Sawamura, and T. Hayashi, *J. Am. Chem. Soc.*, **108**, 6405 (1986).
245. B. Bogdanovic, B. Henc, A. Tösler, B. Meister, H. Pauling, and G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **12**, 954 (1973).
246. B. Bogdanovic, *Adv. Organomet. Chem.*, **17**, 105 (1979).
247. G. Buono, C. Siv, G. Peiffer, C. Triantaphylides, P. Denis, A. Mortreux, and F. Petit, *J. Org. Chem.*, **50**, 1781 (1985).
248. C. Botteghi and G. Giacomelli, *Gazz. Chim. Ital.*, **106**, 1131 (1976).
249. S. Otsuka, *Fundam. Res. Homogeneous Catal.*, **4**, 145 (1984); *Chem. Abstr.*, **101**, 54229d (1984).
250. S. Otsuka and K. Tani, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 171.
251. H. Kumobayashi, S. Akutagawa, and S. Otsuka, *J. Am. Chem. Soc.*, **100**, 3949 (1978).
252. H. Kumobayashi, S. Akutagawa, and S. Otsuka, *J. Am. Chem. Soc.*, **102**, 7932 (1980).
253. K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, and R. Noyori, *J. Chem. Soc., Chem. Commun.*, 600 (1982).
254. K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, and S. Otsuka, *J. Am. Chem. Soc.*, **106**, 5208 (1984).
255. K. Tani, T. Yamagata, Y. Tatsuno, Y. Yamagata, K. Tomita, S. Akutagawa, H. Kumobayashi, and S. Otsuka, *Angew. Chem., Int. Ed. Engl.*, **24**, 217 (1985).
256. M. Kitamura, K. Manabe, R. Noyori, and H. Takaya, *Tetrahedron Lett.*, **28**, 4719 (1987).
257. K. Hiroi and K. Makino, *Chem. Lett.*, 617 (1986).
258. H. Brunner, U. Obermann, and P. Wimmer, *J. Organomet. Chem.*, **316**, C1 (1986).
259. M. Hodgson and D. Parker, *J. Organomet. Chem.*, **325**, C27 (1987).
260. S. Sakane, K. Maruoka, and H. Yamamoto, *Tetrahedron*, **42**, 2203 (1986).
261. B. R. James and C. G. Young, *J. Chem. Soc., Chem. Commun.*, 1215 (1983).
262. B. R. James and C. G. Young, *J. Organomet. Chem.*, **285**, 321 (1985).
263. M. Kameyama, N. Kamigata, and M. Kobayashi, *Chem. Lett.*, 527 (1986).
264. M. Kameyama, N. Kamigata, and M. Kobayashi, *J. Org. Chem.*, **52**, 3312 (1987).
265. T. Takeichi, Y. Ozaki, and Y. Takayama, *Chem. Lett.*, 1137 (1987).
266. O. Toussaint, P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, **28**, 539 (1987).
267. H. Yamashita, *Chem. Lett.*, 525 (1987).
268. T. Hosokawa, Y. Imada, and S.-I. Murahashi, *Bull. Chem. Soc. Jpn.*, **58**, 3282 (1985).
269. T. Hosokawa, T. Uno, and S. I. Murahashi, *J. Chem. Soc., Chem. Commun.*, 475 (1979).
270. T. Hosokawa, C. Okuda, and S.-I. Murahashi, *J. Org. Chem.*, **50**, 1282 (1985).
271. H. Brunner and B. Hammer, *Angew. Chem., Int. Ed. Engl.*, **23**, 312 (1984).
272. V. M. Potapov, G. V. Panova, and E. G. Solozhenko, *Zh. Obshch. Khim.*, **54**, 665 (1984); *Chem. Abstr.*, **101**, 110455p (1984).
273. T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, and S. Akutagawa, *J. Chem. Soc., Chem. Commun.*, 922 (1985).
274. K. Osakada, M. Obana, T. Kariya, M. Saburi, and S. Yoshikawa, *Tetrahedron Lett.*, **23**, 4227 (1982).
275. T. Ikariya, K. Osakada, Y. Ishii, S. Osawa, M. Saburi, and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **57**, 897 (1984).

276. J. Halpern, in Chemical Industries/22, *Catalysis of Organic Reactions* (Ed. R. L. Augustine), Marcel Dekker, Inc., New York, Basel, 1985, p. 3.
277. J. Halpern, *Pure Appl. Chem.*, **55**, 99 (1983).
278. J. Halpern, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, Orlando, 1985, p. 41.
279. J. Halpern, *Inorg. Chim. Acta*, **50**, 11 (1981).
280. J. Halpern, *Science*, **217**, 401 (1982).
281. J. Halpern, *Acc. Chem. Res.*, **15**, 332 (1982).
282. C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, **109**, 1746 (1987).
283. T. Hayashi, A. Yamamoto, and T. Hagihara, *J. Org. Chem.*, **51**, 723 (1986).
284. T. Hayashi, M. Konishi, and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 107 (1984).
285. T. Hayashi, T. Hagihara, M. Konishi, and M. Kumada, *J. Am. Chem. Soc.*, **105**, 7767 (1983).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 5

Organometallic oxidation catalysts

GÁBOR SPEIER

Institute of Organic Chemistry, Veszprém University of Chemical Engineering, Veszprém 8200, Hungary

I. INTRODUCTION

The oxidation of organic compounds catalysed by metal complexes constitutes a large part of the field of homogeneous catalytic processes used in either laboratory or industrial reactions. The discovery of the Mid-Century process[1] for the production of terephthalic acid, the Wacker process[2] for the production of acetaldehyde, and the Celanese process[3] for the liquid-phase oxidation of *n*-butane to acetic acid gave an enormous impetus to the pursuit of research on metal-catalysed oxidations. Although much information had been gathered before on the autoxidation of organic compounds with radical chain mechanisms, the application of metal catalysts afforded more selectivity to these processes and opened up new non-radical routes for diverse oxidation reactions. The scope of these reactions is wide and is still being extended. They can be classified in different ways, by organic substrate, by the type of primary oxidants, or by the type of catalyst used. The role of the catalyst can also be diverse, activating either the oxidants or the substrate, and catalysing the decomposition of the primary products formed initially. Almost all of the special topics of metal-catalysed oxidation reactions have been covered by more or less recent reviews and books, which will be cited at the appropriate places. The aim of this chapter is to discuss the most important aspects and recent developments in homogeneous metal-catalysed oxidation reactions involving oxidative change(s) at carbon atom(s) of the substrate, or having a metal carbon association during either a stoichiometric or a catalytic process.

II. PRIMARY OXIDANTS AND THEIR MOST COMMON MECHANISTIC ASPECTS

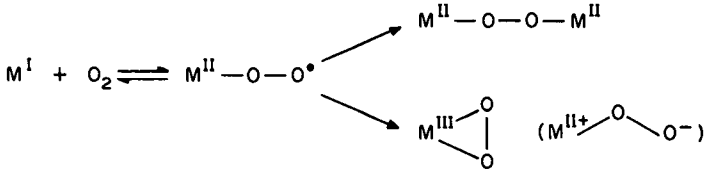
In metal-catalysed oxidations of organic compounds a variety of primary oxidants are suitable. By definition they are reagents consumed and expressed in the overall stoichiometry in a catalytic process. In this part, the oxidants are classified in terms of the main characteristics of the mechanism of oxidation, bearing in mind both catalytic and stoichiometric reactions. Some species are therefore only intermediates in the catalytic cycles, but their structure is a key factor in the whole process.

A. Dioxygen as Primary Oxidant

Many liquid-phase autoxidations proceed under relatively mild conditions. The reaction of simple hydrocarbons with dioxygen provided the basis for the development and understanding of free radical chain theory[4–6]. Autoxidations lead to thermodynamically stable products but they are unfavourable kinetically, requiring high activation energies[7]. They are often subject to autocatalysis by the products. The primary products are hydroperoxides from alkanes and peracids from aldehydes. In these autoxidations, metal catalysts are used only to influence the product distribution and selectivities by means of catalytic decomposition of the primary hydroperoxides (see below).

The direct participation of dioxygen in the oxidation of organic compounds is possible only via its activation by metal complexes[8–10]. The successive one-electron transfer from

the metal species to dioxygen gives superoxo and peroxo complexes (equation 1). The superoxo complexes play an important role in biomimetic oxygenation reactions[11], while those of peroxo complexes with low-valent ions (Pt, Pd, Co) attack substrates in a nucleophilic manner[12], whereas high-valent metal peroxide complexes (Mo, V, Co) tend to give electrophilic attack[13].



(1)

B. Peroxidic Primary Oxidants

Among the peroxidic primary oxidants, the most important are hydrogen peroxide[14] and alkyl hydroperoxides[15]. Fundamentally, metal-catalysed reactions of H_2O_2 involve homolytic, one-electron processes in which free radicals are intermediates. The best known of this class of reaction are those with Fenton's reagent[14], consisting of iron(II) and H_2O_2 generating hydroxyl radicals via a radical chain process (equation 2). In the presence of organic substrates, organic free radicals are produced, which undergo dimerization, oxidation by iron(III), or reduction by iron(II). In the reaction of $HO^{\bullet}$ with iron(III) ferryl species can also be formed (equation 3), which have relevance in biochemical oxygen transfer reactions[16].

$$Fe^{II} + H_2O_2 \longrightarrow Fe^{III}OH + OH^{\bullet} \quad (2)$$

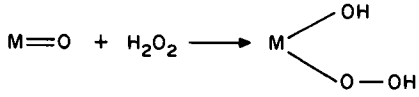
$$Fe^{III} + HO^{\bullet} \longrightarrow O{=}Fe^{IV} + H^{+} \quad (3)$$

With alkyl hydroperoxides, metal ions act as initiators either by reduction (equation 4) or by oxidation (equation 5), generally catalysing autoxidations by generating chain-initiating radicals[13]. The relative rates depend on the redox potential of the M^{III}/M^{II} couples[17].

$$RO_2H + M^{II} \longrightarrow RO^{\bullet} + M^{III} + HO^{-} \quad (4)$$

$$RO_2H + M^{III} \longrightarrow RO^{\bullet}_2 + M^{II} + H^{+} \quad (5)$$

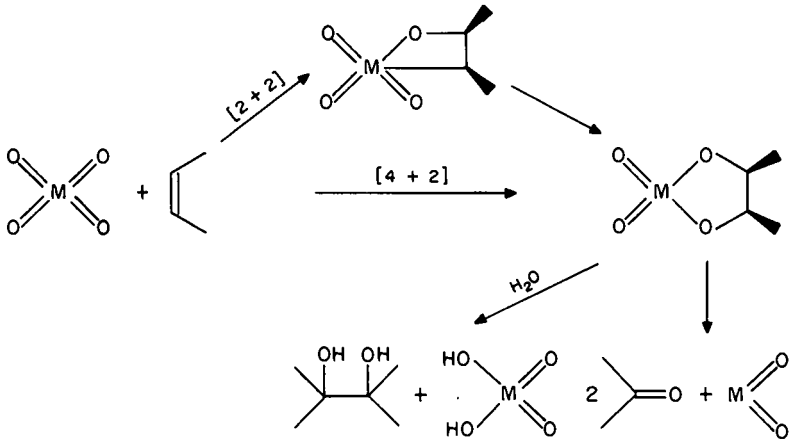
Acidic metal oxides, such as MoO_3, WO_3, V_2O_5, and SeO_2, catalyse oxygenation with H_2O_2 by forming inorganic peracids[18]. These are formed by addition of H_2O_2 to an M=O group (equation 6), where the latter renders the peroxidic oxygens more electrophilic. They resemble organic peracids[19]. Other per compounds, such as peracids, dialkyl peroxides, organometallic peroxides, and persulphates, are of minor importance.



(6)

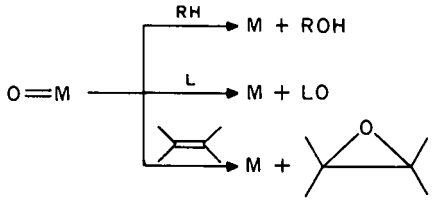
C. 'Oxenoid'-type Primary Oxidants

Oxometal reagents such as permanganate[20], chromic acid and chromyl compounds[21], SeO_2[22,23], OsO_4[24], RuO_4[25], MnO_2[26,27], and oxoiron species[16] are well known stoichiometric oxidants for organic substrates. The dioxo species of Os, Ru, and Mn form cyclic esters as intermediates with olefins and acetylenes[28], which give glycols on



SCHEME 1

hydrolysis or carbonyl compounds by C—C bond cleavage. Alternatively, [2 + 2] cycloaddition followed by reductive insertion by OsO_4 has also been proposed[28] (Scheme 1). Oxometal groups are also capable of effecting hydroxylation of alkanes and aromatics, transferring oxygen to phosphines, sulphides, and sulphoxides, and epoxidizing olefins to oxiranes[16] (equation 7).



(7)

Oxometal species of iron, manganese, the chromium with porphyrin ligands are formed in catalytic reactions with molecular oxygen, iodosylbenzene, NaOCl, amine oxides, and hydroperoxides[29].

D. High- and Low-valent Metal Complexes as Primary Oxidants

These metal-catalysed oxidation reactions can be designated as homolytic or heterolytic. The former are characterized by recycling of several oxidation states of metal catalyst ions by one-equivalent changes, forming free radicals as intermediates (Mn, Co, Fe, Cu) (equation 8)[30,31]. These oxidants are strong electrophiles, attacking the substrate electrophilically or by way of one-electron transfer (equation 9).

$$RH + M^{III} \rightarrow R^{\cdot} + M^{II} + H^{+} \quad (8)$$

$$R^{\cdot} + M^{III} \rightleftharpoons R^{+} + M^{II} \quad (9)$$

Hard ligands favour electron transfer (acetate), whereas soft ligands favour ligand transfer[32] (equation 10).

$$R^{\cdot} + M^{III}X \rightleftharpoons RX + M^{II} \quad (10)$$

Oxidative processes with metal oxidants in a low oxidation state with a soft centre

[palladium(II)], which are not strong electrophiles, react with the substrate, in most cases with olefins, through π-complex formation. In this way the substrate is activated toward nucleophilic substitution of hydrogen and a two-electron heterolytic reduction of the metal ion involving organometallic intermediates[13].

III. METAL-CATALYSED OXIDATIONS

A. Alkanes

The most important large-scale industrial metal-catalysed oxidations are used for the production of acetic acid from *n*-butane[3] and of adipic acid from cyclohexane[33]. Alkanes are generally not readily susceptible to oxidative attack owing to the strength of their C—H bonds. The role of the metal catalysts in these reactions lies (i) in the controlled decomposition of peroxides (H_2O_2, RO_2H) resulting in either the products or active metal species capable of reacting with alkanes, or in homolytic attack by high-valent metal ions or in (more or less) the activation of alkanes by oxidative addition of C—H bonds towards soft metal centres; (ii) in forming oxometal species with different primary oxidants mimicking biological oxygenations; and (iii) in miscellaneous oxygenations and dehydrogenations.

1. Peroxide decompositions and homolytic reactions

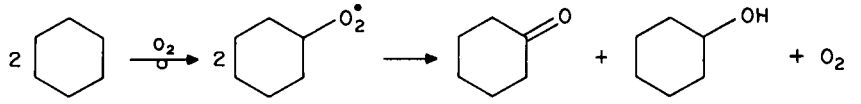
The metal-catalysed homolytic decomposition of alkyl hydroperoxides is the most common pathway of homogeneous oxidation[34,35]. The metal acts here as an initiator rather than as a catalyst. The two principal reactions are reactions 4 and 5. *t*-BuO_2H decomposes thermally to yield *t*-BuOH almost quantitatively[36] (equation 11). With a catalytic amount of cobalt(II) salt, the decomposition to *t*-BuOH (86%), $(t\text{-Bu})_2O$ (12%), and dioxygen (93%) is rapid at 25 °C[37]. The activity of the metal cation in the decomposition of *t*-BuO_2H is related to its redox potential[38]. The one-step conversion of alkanes to alcohols could be feasible under conditions where hydroperoxides also decompose. At higher temperatures and metal catalyst concentrations the intermediate alkoxy radicals undergo β-scission to give ketones (equation 12). Liquid-phase oxidation of isobutane showed that $Mn(OAc)_2$ increased the selectivity for HCO_2H and AcOMe at the expense of Me_2CO formation. A lower conversion of isobutane was obtained with $Mn(OAc)_2$[39]. Alkyl hydroperoxide decomposition to the corresponding alcohol is also catalysed by selenium[40] and boron[41] compounds. In the presence of H_3BO_3, HBO_2, or B_2O_3 the intermediate hydroperoxides are reduced to alkyl borates, dioxygen, and water[42] (equation 13), and the alkylperoxy radicals react with boron(III) compounds to give alkylperoxyboron(III) compounds, which are subsequently transformed to alkyl borates and then hydrolysed to the alcohol and boric acid[43]. A great variety of catalysts have been tested for product distribution. Cobalt naphthenate affects the hydroperoxide accumulation by the autoxidation of cyclododecane and phenylcyclohexane[44]. Cobalt salts affect the rate and selectivity of the oxidation of octane at 1–100 ppm concentrations[45]. Metal stearates (St) also greatly influence the product compositions, e.g. $AlSt_3$ interacts with the hydroperoxide, formed initially from cyclohexane, to yield cyclohexanol and cyclohexanone, while $CoSt_2$ accelerates oxidation by the simultaneous formation of hydroperoxide, alcohol, and ketone[46].

$$2RO_2H \longrightarrow 2ROH + O_2 \tag{11}$$

$$Me_3CO^{\cdot} \longrightarrow Me_2C{=}O + Me^{\cdot} \tag{12}$$

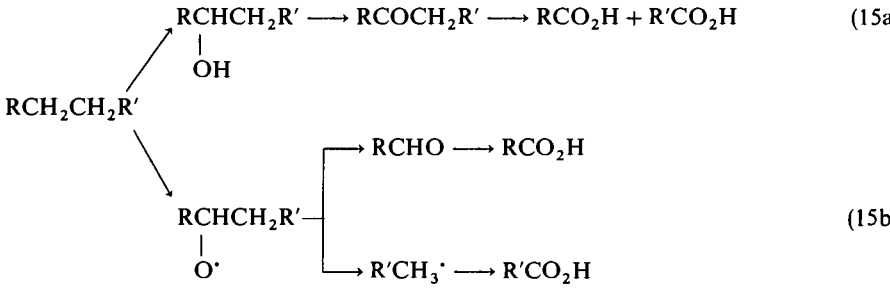
$$6RO_2H + B_2O_3 \longrightarrow 2(RO)_3B + 3H_2O + 3O_2 \tag{13}$$

The oxidation of cyclohexane to cyclohexanol and cyclohexanone is important industrially[47,48]. In the Dutch State Mine process[48] cyclohexane is oxidized by air at 155 °C and 8–10 bar in the presence of a cobalt catalyst (equation 14). Cyclohexane conversion is approximately 10%, the selectivity is 70%, and the cyclohexanol to cyclohexanone ratio is 1–2:1 with by-products such as *n*-butyric, *n*-valeric, succinic, glutaric, and adipic acids. Boric acid addition increases the cyclohexanol to cyclohexanone ratio to 10:1 and the selectivity to 90%[47,49].



(14)

The primary products, alcohols and ketones, can be oxidized further to carboxylic acids by C—C bond cleavage. The C—C bond scission can occur in a stepwise reaction sequence as shown in equation 15a or by fragmentation of the alkoxy radicals (equation 15b). Acetic acid is produced industrially by the autoxidation of *n*-butane at 180 °C and 60 bar in acetic acid with cobalt acetate as the catalyst[50]. Above 90% conversion of *n*-butane the selectivity for acetic acid is 57% with by-products such as formic acid, acetaldehyde, methanol, acetone, methyl ethyl ketone, and esters.



(15a)

(15b)

Simple alkanes can be selectively oxidized by dioxygen in the presence of high concentrations of cobalt(III) acetate in acetic acid[51,52]. For example, the oxidation of *n*-butane with methyl ethyl ketone as promoter proceeds at 100–125 °C to afford acetic acid with 83% selectivity and 80% conversion. The maximum rate is attained after the oxidation of cobalt(II) to cobalt(III), which is in accord with a mechanism involving direct homolytic oxidation of *n*-butane by cobalt(III).

Cyclohexane is also readily oxidized by cobalt(III) acetate in acetic acid at 80 °C, resulting in cyclohexyl acetate and 2-acetoxycyclohexanone as the main products[52]. If dioxygen is present adipic acid is the major product formed with 80% conversion and 75% selectivity[53,54].

In these reactions no deuterium kinetic isotope effect is observed, which is in agreement with a mechanism of a reversible one-electron transfer[51,52]. This is followed by loss of proton to give an alkyl radical. The sequence of reactions under such conditions is outlined in Scheme 2. The relative rates of various cycloalkane oxidations by cobalt(III) in acetic acid suggest that complex formation between cobalt(III) and alkane is rate determining, strongly influenced by steric factors[53,54]. Cobalt(III) acts as the chain-transfer agent in these reactions. The rate of oxidation of alkanes (e.g. cyclohexane) by cobalt(III) is enhanced in the presence of bromide ions[55,56] in acetic acid and also in the presence of strong acids such as trifluoroacetic acid. When *n*-heptane is oxidized at

$$RH + Co^{III} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RH^{+\cdot} + Co^{II} \quad (16)$$

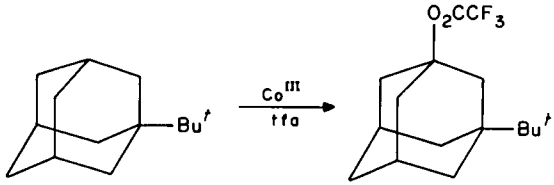
$$RH^{+\cdot} \xrightarrow{k_2} R^{\cdot} + H^{+} \quad (17)$$

$$R^{\cdot} \xrightarrow{Co^{III}} R^{+} \xrightarrow{AcOH} ROAc \quad (18)$$

$$R^{\cdot} \xrightarrow{O_2} RO_2^{\cdot} \longrightarrow \text{products} \quad (19)$$

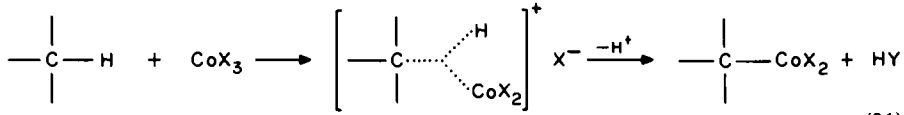
SCHEME 2

25 °C by cobalt(III) in a mixture of trifluoroacetic acid and acetic acid, 2-heptyl acetate is the major product (81% selectivity). In the presence of dioxygen heptan-2-one is formed with 83% selectivity[57]. Alkyladamantanes afford adamantyl trifluoroacetates in high yields when oxidized by cobalt(III), manganese(III), or lead(IV) acetates[58] (equation 20). Anodic oxidations give fragmentations, where the *t*-Bu group is substituted by

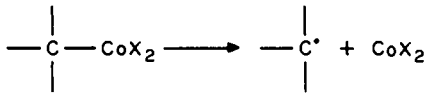


(20)

O_2CCF_3. The product distributions suggest the absence of cation radical intermediates in the metal-catalysed oxidations. These were regarded as electrophilic substitutions at saturated carbon centres (at the C—H bond) with a trigonal transition state as shown in Scheme 3[59–61].



(21)



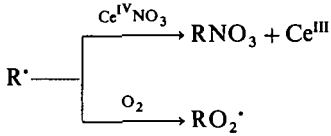
(22)

SCHEME 3

The oxidation of adamantane, norbornane, and cyclohexane can be accomplished photochemically, promoted by cerium(IV) ammonium nitrate in acetonitrile at room temperature (equation 23–26)[62]. Both processes are extremely efficient and selective with adamantane.

$$Ce^{IV}NO_3 \longrightarrow Ce^{III} + NO_3^{\cdot} \quad (23)$$

$$RH + NO_3^{\cdot} \longrightarrow R^{\cdot} + HNO_3 \quad (24)$$

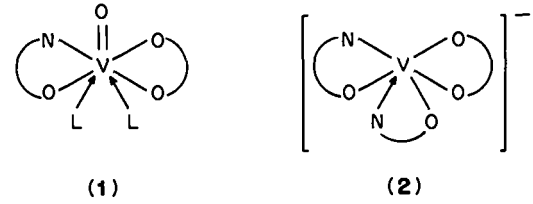


(25)

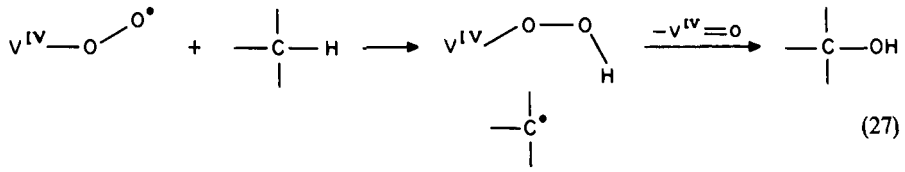
(26)

Oxidations with the $Fe(ClO_4)_3$–H_2O_2–MeCN system were compared with the corresponding alkyl hydroperoxide system[63]. Adamantane underwent more extensive oxygenation at its secondary carbon atoms through a radical process than in the $Fe(acac)_3$–RO_2H systems. The reaction here involves both radical and non-radical processes.

The vanadium complexes **1** and **2** are efficient for the biomimetic hydroxylation of alkanes[64]. The mechanism of the reaction is believed to proceed as shown in equation 27.

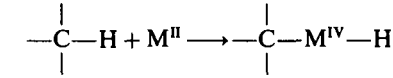


(1) (2)

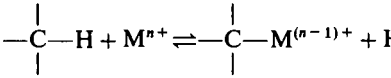


(27)

The activation of alkanes by transition metals could also be feasible by the oxidative addition reaction of sp^3-hybridized C—H and C—C bonds, as found with dihydrogen in many cases (equation 28)[65,66]. The C—H bond in alkanes can also be cleaved by strong electrophiles (equation 29) since M—C bonds are almost as stable as M—H bonds[67]. This type of reaction has been discussed before; electrophile attack on the C—H bond by low-valent, e.g. palladium(II) and platinum(II), complexes will be treated later when considering alkane dehydrogenation.

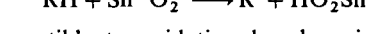


(28)



(29)

C_1–C_4 olefins are oxidized to alcohols by dioxygen in the presence of a stoichiometric amount of $SnCl_2$ at 25 °C in MeCN[68]. The product distribution is close to those found in free-radical reactions. Therefore, a free-radical mechanism with a key step as shown in equation 30 has been suggested[69]. The industrially important syntheses of acetic and adipic acid have been thoroughly discussed in the pertinent literature[13,70].



(30)

Alkanes are also susceptible to oxidation by chromium(VI) and manganese(VII)

complexes, usually under acidic conditions. The order of reactivity is tertiary > secondary > primary. With *n*-alkanes the reaction rate is proportional to the number of methylene groups in the molecule[71] and the acidity. Protonated species participate in the oxidation and the reaction seems to proceed by abstraction of a hydrogen atom by the oxygen attached to chromium (equation 31). The radicals formed remain in the cage, which is supported by rentention of configuration in the oxidation of optically active hydrocarbons, e.g. (+)-3-methylheptane[72].

$$RH + O{=}Cr(OH)_3^+ \longrightarrow R^\cdot + HOCr^V(OH)_3^+ \qquad (31)$$

Permanganate in trifluoroacetic acid interacts with alkanes at room temperature[73]. The rate increases with increase of acidity, which implies that the MnO_3^+ cation, which is a strong electrophile, is the active species. The rate constants of $KMnO_4$ oxidations with *n*-alkanes, isoalkanes, and cycloalkanes were determined in aqueous acidic solution[74]. $HMnO_4$ is ca 10^3 times more active than MnO_4^-. The substrate selectivity and H/D isotope effects are similar with both species, although cycloalkanes and methylcycloalkanes react more rapidly with $HMnO_4$ than with MnO_4^-. Ruthenium(IV)[75] and iridium(IV)[76] complexes also catalysed the oxidation of alkanes by manganese(III) in sulphuric acid and by chromic acid, respectively. Other oxidants such as HNO_3 and $HClO_4$ may also be used. The role of the catalyst is the formation of an oxidant–catalyst complex. In the case of chromium(VI) a two-centre Cr^{VI}–Ru^{IV} complex is formed, which attacks the C—H bond of the alkane, with the OCr group (in a similar way to that in equation 31) abstracting a hydrogen atom via an oxidative homolytic mechanism.

The oxometal species of ruthenium(IV) *cis*-$[Ru^{IV}(6,6'\text{-}Cl_2(bpy)_2O_2]^{2+}$ is also capable of oxidizing the unactivated C—H bonds in cyclohexane to yield cyclohexanone (57%)[77]. The transition metal-substituted heteropolytungstate complexes $[PW_{11}(M)O_{39}]^{5-}$ with $M = Co^{II}$, Mn^{II}, Cu^{II}, or Fe^{II}, catalyse the oxo-transfer oxidation of alkanes by *t*-BuO_2H[78]. With cyclohexane mainly cyclohexanol and cyclohexanone (in the ratio ca 2:1) and with adamantane adamantan-1- and -2-ol and adamantan-2-one (in the ratio of 49:7:14) are formed. The primary kinetic isotope effect of 6.5 for cyclohexane suggests a mechanism (equation 32) involving abstraction of H from the alkane to the oxometal species, resulting in R$^\cdot$, which in a further reaction of the hydroxo metal species forms alcohol and the catalyst. The intermediate oxometal species can be regenerated by homolytic O—O cleavage in $[-Co^{III}-O_2R]$ or by a mechanism proposed by Mimoun *et al.*[64].

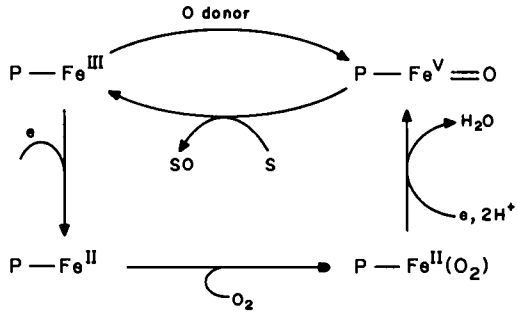
$$[-Co^{III}-O^\cdot] + RH \rightarrow [-Cu^{III}-OH] + R^\cdot \rightarrow [-Co^{III}] + ROH \qquad (32)$$

2. Oxometal complexes

Oxometal complexes, especially those containing porphyrin ligands, have attracted intense interest owing to their relevance to metal-containing enzymes involved in the oxidation of biological systems[79]. The immense importance of the use of metalloporphyrins as catalysts in the oxygenation of hydrocarbons leads to an understanding of the chemistry of enzyme-catalysed reactions (mainly cytochrome P-450) through studies of chemical models and the search for catalyst systems able to catalyse the hydroxylation of saturated hydrocarbons selectively under ambient conditions. A series of metalloporphyrins were prepared and tested as catalysts using primary oxidants such as PhIO, NaOCl, O_2, RO_2H, H_2O_2, amine *N*-oxides, and other inorganic per compounds. The common feature of these reactions is the formation of a M=O species as the reactive entity interacting with hydrocarbons. In alkane hydroxylations equation 33 is useful to account for removal of H$^\cdot$ from the substrate[78,79]. The catalytic cycles in these reactions are shown in Scheme 4. The formation of oxometalporphyrins either from single oxygen

donors or dioxygen can proceed directly or by the use of electron donors[79].

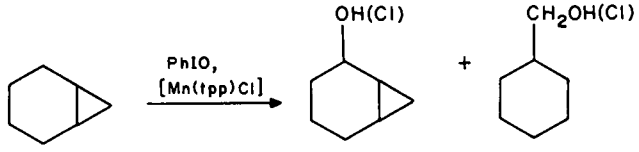
$$M^{n+1}{=}O \rightleftharpoons M^{n}{-}O^{\bullet} \tag{33}$$



SCHEME 4

Groves and Nemo's system[80], PhIO–[Fe(tpp)Cl], oxidizes cyclohexane to a mixture of cyclohexanol and cyclohexanone (in the ratio 15:1). Atropoisomers $\alpha,\alpha,\alpha,\beta$ and $\alpha,\alpha,\beta,\beta$ of the [Fe(tpp)Cl] complex catalyse the hydroxylation of cyclohexane better than [Fe(tpp)Cl], hinting at control of complex periphery resulting in retention of configuration[81]. *cis*-Decalin gives a mixture of decal-9-ol (*cis*-to-*trans* ratio 9:1). The kinetic isotope ratio k_H/k_D is 12.9 ± 1 for cyclohexane. These results support a two-step mechanism of abstraction of H$^{\bullet}$ and then the recombination of R$^{\bullet}$ with P—Fe^{IV}—OH without racemization of R$^{\bullet}$ (equation 34). The [Mn(Por)Cl]–PhIO system hydroxylates norcarane and other alkanes in both benzene and chlorinated solvents to give the corresponding alcohols (equation 35) and some alkyl halides (Cl stemming from either the solvent or the iron complex)[82,83]. The halogen incorporation occurs via a norcarane radical not involving carbocations. Ruthenium porphyrins with PhIO are also capable of hydroxylating hydrocarbons, but their catalytic activity and the number of catalytic cycles are small compared with those for iron or manganese porphyrins[84].

$$P{-}Fe^{V}{=}O + RH \longrightarrow P{-}Fe^{IV}{-}OH\text{------}R^{\bullet} \longrightarrow P{-}Fe^{III} + ROH \tag{34}$$



(35)

Cyclohexane can be tosylamidated with catalysis by iron and manganese porphyrins (equation 36)[85]. With [Mn(ofpp)Cl] or [Mn(tfpp)Cl] and NaOCl, adamantane is hydroxylated mainly at the tertiary C—H bond[86]. This is reminescent of a radical mechanism. Comparative studies with PhIO and NaOCl showed the latter to be less effecective owing to deterioration of the catalysts and the need for a more pronounced 'cage effect'[87].

$$C_6H_{12} + PhI{=}NSO_2C_6H_4Me\text{-}p \longrightarrow C_6H_{11}NHSO_2C_6H_4Me\text{-}p \tag{36}$$

The [Mn(tpp)Cl]–O_2–H_2–Pt system is capable of hydroxylating adamantane[88]. The

primary kinetic isotope effect of the tertiary C—H bond is 3.3. The [Mn(tpp)]–O_2–ascorbate system oxidizes alkanes to the corresponding ketones[89]. Secondary and tertiary C—H bonds (in the ratio 2.3:1) are attacked in methylcyclohexane whereas primary C—H bonds are not affected. Iron porphyrin with superoxide ion and the subsequent use of carboxylic acid halides also gives a ferryl oxo species, which hydroxylates alkanes[90]; 70% retention in the case of *cis*-dimethylcyclohexane has been found[91]. Hydrogen persulphate associated with [Mn(tfpp)Cl] in aqueous solution or in dichloromethane is a potent oxidizing agent, showing 33–55% conversion with cyclohexane and 50–94% with adamantane. The latter gives mainly adamantan-1-ol (32%) and to a lesser extent adamantan-2-ol (4%) and adamantanone (5%)[92]. [Mn(tpp)Cl] irradiated in the Soret band or the LMCT bands in the presence of ClO_4^- or IO_4^- ions is able to transform cyclopentane into cyclopentanone[93].

3. Miscellaneous oxidations and dehydrogenations

Yakovlev *et al.*[94] studied the reaction of alkanes with ozone in the presence of transition metal catalysts. It was found that cyclohexane is oxygenated by ozone when metal complexes are present. The activity of the catalysts used decreased in the order $[Cr(CO)_6]$ > $[Co(acac)_3]$ > $[CrSt_3]$ > $[Cr(OAc)_3]$ > $[Mn(acac)_3]$ > $[CoSt_2]$. $[Cr(CO)_6]$ and $[CrSt_3]$ are particularly selective for cyclohexanone formation. With $[Cr(CO)_6]$ cyclohexanone is formed with a selectivity of 84–89% at 8.7% conversion[95]. Chromium(III), chromium(IV), and chromium(VI) species are present in the system.

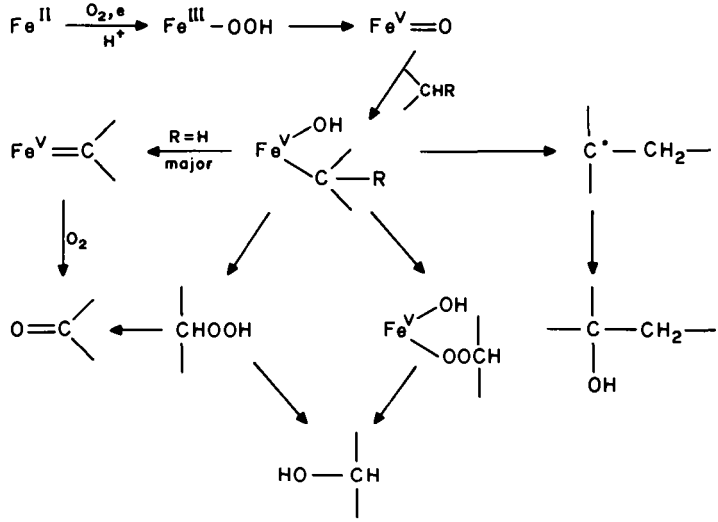
a. Oxidation by 'Gif'-type systems. The oxidation of adamantane can be achieved with unusual efficiency using dioxygen and a system consisting of hydrogen sulphide, iron powder, pyridine, acetic acid, and a small amount of water[96]. The products are adamantan-2-ol, adamantan-1-ol (ratio ca 3:1), and adamantanone. Cyclohexane, methylcyclohexane, 2-methylpentane, and cyclooctane are also effectively oxygenated[97]. In this system the reducing agent is not the sulfide but the iron metal. It was also shown that iron powder is not only the reducing agent but also serves as the source of iron for the formation of an iron cluster $[Fe_3O(OAc)_6py_{3.5}]$[98]. The iron cluster could be isolated and it was shown that it is the catalyst in a similar system consisting of zinc powder, acetic acid, (aqueous) pyridine, and dioxygen. Total yield is 13.8% with a turnover number of over 2000.

The selectivity of products in the oxidation of saturated hydrocarbons by dioxygen in pyridine–acetic acid in the presence of the iron catalyst $[Fe_3O(OAc)_3py_3]_2py$ and zinc is strongly dependent on the reaction mixture and reaction conditions[99]. Using air and slow stirring, attack is almost exclusively at secondary positions in adamantane and *trans*-1,4-dimethylcyclohexane.

The high selectivity of the Gif system for hydrocarbon oxidation was shown to depend on the capture of tertiary radicals by pyridine[100]. Coupled products such as 2,2′-bipyridine and adamantylpyridines could be detected. The mechanism for the secondary oxidation products has only a minor radical component. The mechanism of the Gif system is shown in Scheme 5. In the Gif system for selective hydrocarbon oxidation, the zinc can be replaced with a cathodic electrochemical reaction[101]. It gives largely ketones with only a small amount of aldehyde. The yields (20–30%) and selectivities obtained are very similar to those in previous systems.

The 'Gif–Orsay' system[102] uses cathodic reduction and paraquat or bipyridine as electron-transfer reagent. In this case the reduction of O_2 to O_2^- is mediated by the electron-transfer reagent and the latter oxidizes iron(II) to oxoiron(IV) as the oxidizing species. In another example methylviologen as a mediator and acetic anhydride as the acylating agent have been used with Zn–Hg as reducing agent[103]. Hydroxylation of

alkanes using dioxygen and zinc as reducing agent was achieved by using manganese porphyrin catalyst in the presence of 1-methylimidazole and acetic acid with yields of up to 50%[104].



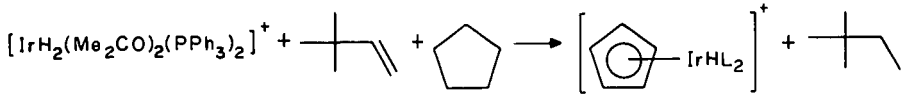
SCHEME 5

b. Dehydrogenations. Some metal compounds dehydrogenate alkanes, usually cycloalkanes, by concomitant reduction of the metals. Palladium(II) trifluoroacetate oxidizes alkanes (*n*-hexane or cyclohexane) in trifluoroacetic acid at 92 °C[105]. Palladium(II) is reduced to palladium(0) and cyclohexane is oxidatively dehydrogenated to benzene (equation 37). Palladium(II) phosphate in H_3PO_4–BF_3 and also in sulphuric acid effects similar dehydrogenations[106].

$$3Pd(CF_3CO_2)_2 + C_6H_{12} \rightarrow 3Pd(0) + C_6H_6 + 6CF_3CO_2H \qquad (37)$$

H_2PtCl_6 in the presence of platinum(II) complexes can attack alkanes in benzene at 100–120 °C[107]. Cycloalkanes (cyclohexane, decalin) give high yields of aromatic hydrocarbons (benzene, naphthalene) when oxidized with H_2PtCl_6–Na_2PtCl_4 in aqueous solutions[108].

Crabtree *et al.*[109] reported the dehydrogenation of a number of alkanes by $[IrH_2(Me_2CO)_2L_2]BF_4$ (L = PPh_3) and *tert*-butylethylene in chlorinated solvents (e.g. equation 38). The reaction is believed to proceed through successive oxidative addition of C—H bonds on the metal to give metal hydrides, which are then dehydrogenated by *tert*-butylethylene[110,111].



(38)

This type of *tert*-butylethylene chemistry could be extended to $[ReH_7(PPh_3)_2]$[112]. With cyclohexane the same products as obtained with iridium are formed. C_6–C_8 cycloalkanes gave olefins in stoichiometric[113] and also in catalytic[114] reactions.

B. Side-chains in Aromatics

1. Oxidation of alkylbenzenes to carboxylic acids

The autoxidation of methylbenzenes to carboxylic acids in the presence of metal catalysts is a poor, inefficient process. The cobalt-catalysed autoxidation of *p*-(*tert*-butyl)-toluene to *p*-(*tert*-butyl)benzoic acid results in only 69% conversion and 67% selectivity at 168 °C[115]. The oxidation of xylene to terephthalic acid is an even more difficult problem owing to the electron-withdrawing effect of the carboxy group. The kinetic data obtained for the oxidation of a mixture of *p*-xylene and *p*-toluic acid catalysed by cobalt(II) at 160 °C are consistent with a free-radical mechanism. The abstraction of H from the methyl group by $RCO_2^{\bullet}$ is rate determining[116]. Carboxylic acid formation in the liquid-phase oxidation of *p*-xylene with dioxygen catalysed by cobalt salts proceeds via two different mechanisms, namely the oxidation of the aldehyde either by a primary hydroperoxide or to peracid and subsequent oxidation of aldehyde to the latter[117].

Bromide ions promote cobalt-catalysed autoxidations of alkylbenzenes[118]. Generally they are carried out using low cobalt concentrations at ca 200 °C and 30 bar. The cobalt-catalysed autoxidation of *p*-xylene using bromide as promoter is used for the industrial manufacture of terephthalic acid[119,120]. The oxo-centred, trinuclear cobalt(III) clusters $[Co_3O(OAc)_6py_3]PF_6$ and $[Co_3O(OAc)_5OHpy_3]PF_6$ have been prepared, characterized, and utilized as catalysts in the presence of LiBr for the oxidation of xylene[121]. They are better catalysts than $CoBr_2$. During the autoxidation Br^- is oxidized first to $Br^{\bullet}$, which acts as a chain initiator and abstracts hydrogen from the toluene to give a radical which forms a hydroperoxide on reacting with dioxygen and then the final oxidation product.

p-Xylene can be oxidized to terephthalic acid in acetic acid at 110 °C when high concentrations of cobalt(III) acetate are used either in the absence[122] ir in the presence of promoters such as bromide[123], ethyl methyl ketone[124], or ozone[125]. With acetaldehyde as the co-substrate and in the presence of high cobalt concentrations the *p*-xylene oxidation is also efficient[126]. In these cases there is a homolytic reaction of the substrate with cobalt(III) leading to the corresponding aldehyde and subsequently to the carboxylic acid (equations 39–43). The function of the promoters is to effect the oxidation of cobalt(II) to cobalt(III).

$$ArCH_3 + Co^{III} \longrightarrow ArCH_3^{+\bullet} + Co^{II} \quad (39)$$

$$ArCH_2^{+\bullet} \longrightarrow ArCH_2- + H^+ \quad (40)$$

$$ArCH_2^{\bullet} + O_2 \longrightarrow ArCH_2O_2- \quad (41)$$

$$ArCH_2O_2^{\bullet} + Co^{II} \longrightarrow ArCHO + Co^{III}OH \quad (42)$$

$$ArCHO + O_2 \longrightarrow \longrightarrow ArCOOH \quad (43)$$

Mixed-metal catalysts show synergistic effects. Replacing one fifth of the cobalt for manganese by the catalyst $Co(OAc)_2$–NaBr gives a 5-fold increase in reaction rate[126]. The addition of zirconyl acetate[127] in the oxidation of alkylaromatic compounds by $Co(OAc)_2$, or of metal acetate additives (Na, K, Ba, Zn, Co, Mn)[128] when the catalyst is $CoBr_2$, or of diethylaniline[129,130] to the $Co(OAc)_2$–NaBr system all result in shortened induction periods and significantly enhanced reaction rates.

The relative rates of reaction of primary and secondary side-chains depend on the catalyst system used. For example, using the $Co(OAc)_3$–ethyl methyl ketone system[131] toluene is more reactive than cumene since the rate-determining step is electron transfer of the substrate by cobalt(III), whereas with the $Co(OAc)_2$–NaBr system, where bromine acts as a chain-transfer agent, the reverse activity order has been found[55]. The combination of

$Co(OAc)_2$ with $Mn(OAc)_2$ is an appropriate catalyst for the autoxidation of isopropylbenzenes to the corresponding carboxylic acids via ketone intermediates[132]. The role of the manganese is believed to be to catalyse the autoxidation of the ketones to carboxylic acids[133]. In a similar way, alkylpyridines can be oxidized in acetic acid in the presence of cobalt(III) acetate to the corresponding carboxylic acids[134].

Methyl-substituted benzene derivatives are oxidized to the corresponding carboxylic acids in yields of over 90% under phase-transfer conditions with NaOCl as the oxidant and ruthenium salts and quaternary ammonium salts as co-catalysts. The RuO_4 abstracts hydride ion from the methyl group as the initial step[135].

A great number of heterogeneous catalytic processes are applied industrially in which oxometal catalysts are utilized for the oxidation of the alkyl chain in aromatic compounds, but they are outside the scope of this chapter[13].

2. *Oxidation of alkylbenzenes to aldehydes and ketones*

In the autoxidation of methylbenzenes the benzaldehydes first formed are oxidized further to carboxylic acids owing to their greater reactivity. Using high concentrations of the cobalt catalyst the rate-determining step is electron-transfer oxidation of the substrate by cobalt(III) (equations 44 and 45). Because of the electron-withdrawing effect of the carbonyl group the benzaldehyde intermediate is less reactive than the substrate and reaction 44 takes place faster than reaction 45. This makes the selective oxidation of alkylbenzenes to benzaldehydes possible.

$$XCo^{III}— \xrightarrow{ArCH_3} ArCH_3^{+\cdot} + Co^{II} + X^- \quad (44)$$

$$XCo^{III}— \xrightarrow{ArCHO} ArCHO^{+\cdot} + Co^{II} + X^- \quad (45)$$

Alkoxy- and aryloxytoluenes are selectively oxidized (50–75% at 40–80% conversion) to the corresponding aldehydes in acetic acid at ca 100 °C using high concentrations of $Co(OAc)_2$[136]. Under similar conditions *p*-methoxytoluene and *m*-phenoxytoluene are efficiently oxidized to *p*-anisaldehyde and *m*-phenoxybenzaldehyde, respectively. Toluene is oxidized to benzaldehyde (71%) and benzyl acetate (24%) when stoichiometric amounts of $Mn(OAc)_3$–H_2SO_4 are used in acetic acid under dioxygen[137]. The autoxidation of ethylbenzene in the presence of high concentrations of $Co(OAc)_3$ in acetic acid at 60 °C gives mainly acetophenone and small amounts of α-phenylethyl acetate and the corresponding alcohol[138]. Ketones are the major products in the autoxidation of primary alkylbenzenes catalysed by $Co(OAc)_2Br$. α-Tetralone is formed from tetralin under mild conditions[123].

Methylbenzenes give benzaldehydes and *p*-methoxytoluene gives *p*-anisaldehyde when oxidised by manganese(III) sulfate in sulphuric acid[139]. Oxidation of tetralin by dioxygen in the presence of $Co(acac)_2$ is inhibited by free-radical inhibitors. Using $Co(acac)_3$ as catalyst the inhibitors increase the rate of the oxidation. This effect is believed to be due to the change in the catalyst by the initiator[140]. Polymeric Schiff-base complexes of vanadium(II) and manganese(II) bind dioxygen reversibly as peroxide and catalyse the oxidation of cumene to acetophenone and 2-phenylpropan-2-ol[141]. Only traces of the hydroperoxide can be detected. At higher temperatures the amount of acetophenone rises.

Benzylic methylene groups can be oxidized to carbonyl functions by *t*-BuO_2H in CH_2Cl_2 with cyclic chromate esters as catalysts. Alkyl *tert*-butyl peroxides are assumed to be intermediates[142]. Tetralin derivatives are oxidized by *t*-BuO_2H catalysed by $[Cr(CO)_6]$ to give the corresponding α-tetralones in good yields. The presence of active chromium(0)

species is assumed[143]. Xylene oxidations by acidic $[Fe(CN)_6]^{3-}$ yielding aldehydes as the main products are first order with respect to substrate, oxidant, and acid. E.s.r. spectroscopy revealed the presence of radical intermediates. $[HFe(CN)_6]^{2-}$ reacts with the substrate to yield a radical, which is oxidized by iron(III) to R^+[144].

Cerium(IV) in aqueous methanesulphonic acid and trifluoromethanesulphonic acid are excellent reagents for the oxidation of alkyl and polycyclic aromatics to aromatic aldehydes, ketones, and quinones. The cerium(III) is then regenerated by anodic oxidation to cerium(IV)[145]. Dimethylanisoles in which one of the methyl groups is *meta* and the other is *ortho* or *para* are regioselectively oxidized in good yields to the corresponding *ortho*- and *para*-substituted aldehydes by copper(II) and $S_2O_8^{2-}$[146]. Subsequent oxidation of the aldehydes with $NaClO_3$ furnishes the corresponding carboxylic acids.

Using 70% *t*-BuO_2H and catalytic amounts of chromic anhydride, benzylic methylene groups are oxidized at room temperature to carbonyl functions in fair yields[147]. Indans and tetralins are oxidized to indan-1-ones and tetral-1-ones by Jones' reagent[148]. Selective oxidation of doubly benzylic secondary carbons to ketones, of doubly benzylic tertiary carbons to alcohols, and of singly benzylic secondary alcohols to ketones in a biphasic system with $KMnO_4$ using a phase-transfer catalyst can be achieved[149].

3. Oxidation of alkylbenzenes to benzylic acetates

The oxidation of methylbenzenes can lead to benzylic acetates in the presence of high concentrations of cobalt(III) and manganese(III) catalysts. Equations 18 and 19 in Scheme 2 are competitive. Benzyl acetate is derived from the subsequent reaction of the benzyl radical with cobalt(III) acetate and then with acetic acid. Using Co(OAc)Br as the catalyst in the autoxidation of alkylbenzenes in the presence of NaOAc under anhydrous conditions benzylic acetates are the main products[123]. Methylbenzenes give benzyl acetates on oxidation at 100 °C in acetic acid in the presence of a $Pd(OAc)_2$–$Sn(OAc)_2$ catalyst[150]. Side-chain oxidation of 5-substituted 1,2,3-trimethylbenzenes by cerium(IV) ammonium nitrate and cobalt(III) acetate gives benzylic acetates. The regioselectivity of the reactions shows that the cobalt containing system operates by electron transfer while the other abstracts a hydrogen atom[151]. Substituted biphenylenes are oxidized by $Mn(OAc)_3$ in AcOH to give 2-substituted biphenylenes and biphenylene-2,3-dione[152]. Methyl substituents are transformed to formyl and acetoxymethyl groups.

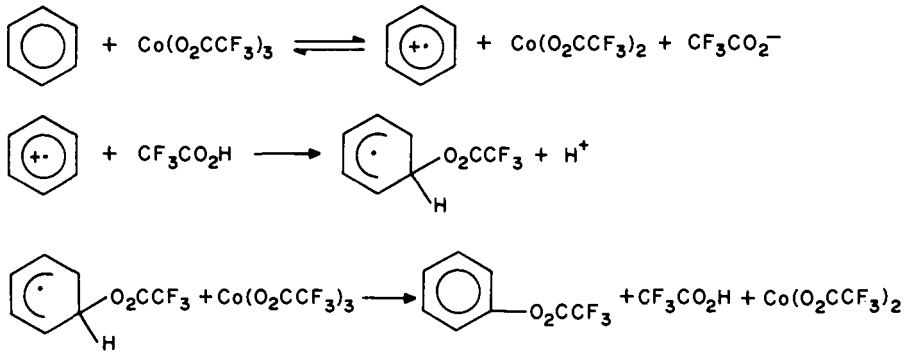
Oxidation of xylenes by palladium(II) complexes in acetic acid was found to proceed by two different mechanisms. One involves an organometallic intermediate leading to a chain arylated product and palladium(IV), and the other involves a cation radical which again gives chain arylated products with aromatics or benzyl acetates[153]. The mixed metal acetate complex $K_2[Pd(OAc)_4]$ is an efficient catalyst for the benzylic acyloxylation of toluene with dioxygen in carboxylic acid solvents at ca 170 °C. Minor by-products are benzaldehyde, benzoic acid and carbon dioxide[154]. $Cu(OAc)_2$ increases the efficiency of $Pd(OAc)_2$ as a catalyst for benzylic acetoxylation of methylbenzenes at 170 °C under dioxygen in carboxylic acids. Benzylic carboxylates are the main products with minor amounts of by-products such as aromatic aldehydes and carboxylic acids[155].

The mixed-metal complex $PdPb(OAc)_4 \cdot AcOH$ or mixtures of palladium and lead acetates catalyse the benzylic acyloxylation of toluene at 170 °C with a selectivity 98%[156]. Methylbenzenes are oxidized to the corresponding benzyl acetates with $S_2O_8^{2-}$ in the presence of copper(II) and sodium acetate[157]. 9-Methylanthracene is oxidized with $S_2O_8^{2-}$ catalysed by copper(II) in MeCN–AcOH and aqueous MeCN to give lepidopterene (a dimer) and OAc- and NHAc-substituted side-chain products[158]. The initially formed radical cation undergoes competing proton loss and reversible nucleophilic addition to form an anthracenylmethyl radical and the nucleophile adduct radicals. The oxidation of the latter by copper(II) or $S_2O_8^{2-}$ gives the products.

C. Aromatics

1. Oxidative substitution

Electron-poor arenes, such as benzene, are oxidized at room temperature by cobalt(III) in trifluoroacetic acid to aryl trifluoroacetates[159]. In acetic acid no reaction occurs. The mechanism, shown in Scheme 6, based on e.s.r. and kinetic studies is consistent with two one-electron transfers, probably preceded by a charge-transfer complex[160]. The analogous oxidation with lead(IV) trifluoroacetate in trifluoroacetic acid can be understood in terms of an electrophilic substitution mechanism (equations 46 and 47[161,162]). Phenyl acetate is also formed in the reaction of benzene with $Pd(OAc)_2$[163]. In this case a more stable aryl—metal bond results with soft metals such as lead(IV), thallium(III), and palladium(II), which gives arylmetal intermediates. Nucleophilic displacement at the α-carbon of σ-arylpalladium complexes is feasible.



SCHEME 6

$$ArH + Pb(O_2CCF_3)_4 \longrightarrow ArPb(O_2CCF_3)_3 + CF_3CO_2H \quad (46)$$

$$ArPb(O_2CCF_3)_3 \longrightarrow ArOCCF_3 + Pb(O_2CCF_3)_2 \quad (47)$$

Oxidative substitution with X = OAc, N_3, Cl, NO_2, CN, and SCN using oxidants such as $K_2Cr_2O_7$, $Pb(OAc)_4$, $KMnO_4$, $NaClO_3$, and $NaNO_3$ according to equations 48 and 49 have been reported[164]. It has been found that acetoxylation of arenes is promoted by palladium(II) in the presence of dioxygen and the absence of excess acetate[165,166].

$$ArH + PdX_2 \xrightarrow{-HX} ArPdX \xrightarrow[\text{oxidant}]{X^-} ArX + PdX_2 \quad (48)$$

$$PdX_2 + \text{oxidant} \xrightarrow{X^-} PdX_4 \xrightarrow{ArH} ArX + PdX_2 + X^- \quad (49)$$

Oxidative acetoxylation of aromatic substrates can be carried out with $S_2O_8^{2-}$ in acetic acid using silver[167] or copper[168] salts as catalysts. The reactions involve $SO_4^{-\cdot}$ attack on the substrate and formation of a cation-radical by electron transfer. Direct alkoxylations of anthracene with some lower alcohols and ethylene glycol monoalkyl ethers can be achieved in the presence of cerium(IV) trifluoroacetate, giving the corresponding 9-alkoxy anthracenes[169]. The yields range from 10 to 75% with the side-product anthraquinone. Benzene is trifluoroacetylated with the oxidants H_2O_2, peracetic acid, trifluoroperacetic acid, or acetalaldehyde and dioxygen in trifluoroacetic acid in the

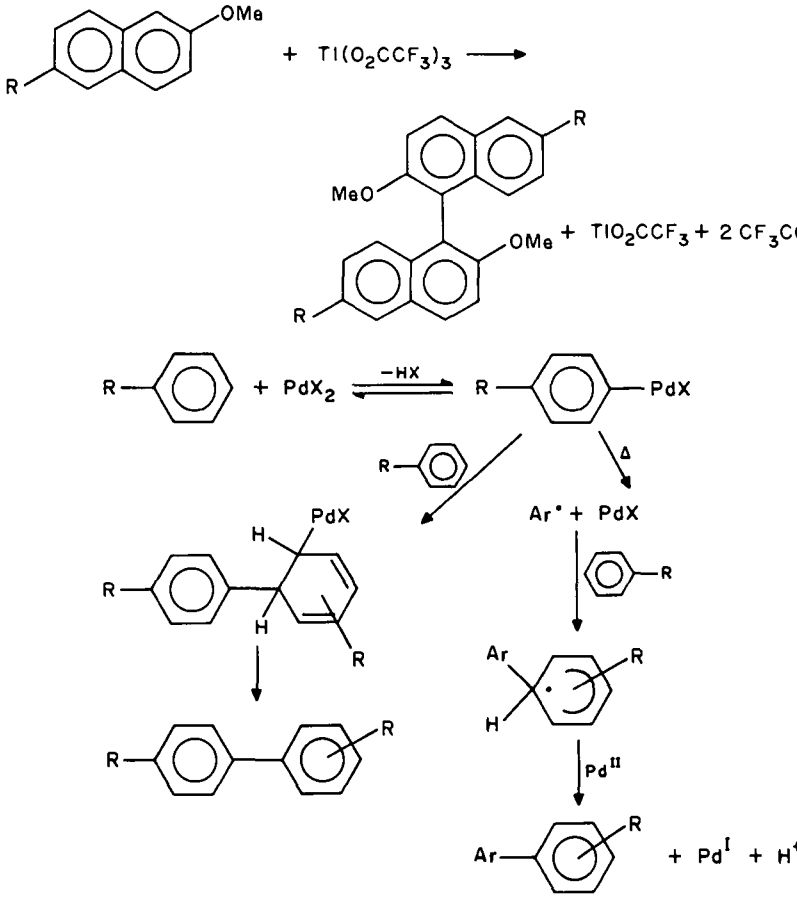
presence of cobalt(III) trifluoroacetate according to the net equation 50[170].

$$PhH + MeCHO + CH_3CO_2H + O_2 \longrightarrow PhO_2OCF_3 + MeCO_2H + H_2O \quad (50)$$

2. *Oxidative dimerization*

Benzene is oxidatively coupled to biphenyl in the presence of $PdCl_2$ and NaOAc in acetic acid at 90 °C[171] (equation 51). The reaction rate is strongly enhanced by strong acids such as perchloric[163] and trifluoroacetic acids[172]. The proposed mechanism, as shown in Scheme 7, involves an arylpalladium(II) intermediate, which undergoes either 1,2-addition to the arene or homolysis of the arylpalladium(II) intermediate, followed by addition of the aryl radical to the arene and electron transfer of the resulting cyclohexadienyl radical to palladium(II)[173]. Arenes with electron-releasing substituents are oxidatively dehydrodimerized in the presence of thallium(III) trifluoroacetate in trifluoroacetic acid[174] (equation 52).

$$2PhH + PdCl_2 + 2NaOAc \longrightarrow Ph_2 + Pd + 2NaCl + 2HOAc \quad (51)$$



(52)

SCHEME 7

Thallium(III) trifluoroacetate[174] and ruthenium trifluoroacetate[175] are good catalysts for the synthesis of some isoquinoline alkaloids such as ocoteine, neolitsine, aporphine, and homoaporphine. The autoxidation of 5,6-dihydroxyindole-2-carboxylic acid in the presence of metal ions, e.g. cobalt(II), leads to a mixture of oligomers, the major of which has been isolated and identified as 5,6,5′,6′-tetraacetoxy-2,2′-dicarbomethoxy-4,4′-biindolyl[176].

3. Hydroxylation (and O-functionalization)

The aromatic ring has only a low reactivity and alkylperoxy radicals do not effect hydrogen abstraction from the nucleus. On the other hand, phenolic products are more reactive than the starting aromatic nucleus.

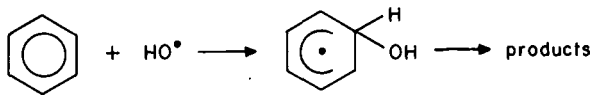
Udenfriend's *et al.* classical system, consisting of iron(II), EDTA, ascorbic acid, and dioxygen at neutral pH, hydroxylates arenes to phenols under mild conditions[177]. The ascorbic acid can be replaced with other hydrogen donors. Similar systems containing low-valent transition metals, dioxygen, and hydrogen donors have been developed[178]. The mechanism of these reactions is uncertain. The formation of H_2O_2 and then hydroxyl radicals is probable but they are not the only hydroxylating species in view of the isomer distribution in the hydroxylation of arenes[179]. It does not induce an NIH shift, which may suggest a different mechanism than that for enzymatic hydroxylation[180].

Oxygenation of benzene to phenol with air is catalysed by copper(I) salts in dilute sulphuric acid with an 8.3% yield based on the catalyst. Addition of H_2O_2 increased the yield[181]. Oxidation of benzene to phenol and hydroquinone with dioxygen in the presence of copper(I) ions can be effected when the copper(II) is continuously regenerated electrochemically[182]. Aerial oxidation of benzene in a mixture of CuCl, H_2SO_4, and MeOH–H_2O yields phenol and, through a direct route, 1,4-dihydroxybenzene under ambient conditions according to equation 53[183]. At pH 5 the hydroxylation efficiency is 42%. Tracer studies using ^{18}O show no scrambling in either phenol and hydroquinone. This is consistent with a mechanism, as shown in equations 54–56, in which hydroquinone is derived from the oxygen adduct of a hydroxycyclohexadienyl radical almost exclusively[184]. Arenes, such as benzene, chlorobenzene, and toluene, are effectively monohydroxylated with a system consisting of [Mn(tpp)], *N*-methylimidazole, colloidal platinum, O_2, and H_2[185]. Addition of benzoic anhydride and/or HCl favoured *ortho*- and *para*-hydroxylation. Water-soluble iron porphyrin complexes with quaternary ammonium functionalities catalyse the hydroxylation of phenylalanine to tyrosine and dihydroxyphenylalanine in ca 70% yields[186].

$$PhH + 2Cu^{I} + 2H_3O^{+} + O_2 \longrightarrow PhOH + 2Cu^{II} + 3H_2O \quad (53)$$

$$2Cu^{I} + O_2 + 2H^{+} \longrightarrow 2Cu^{II} + H_2O_2 \quad (54)$$

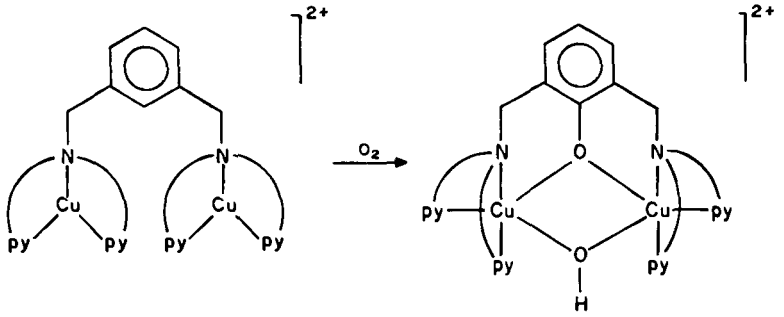
$$Cu^{I} + H_2O_2 + H^{+} \longrightarrow Cu^{II} + H_2O + HO- \quad (55)$$



(56)

Arene hydroxylation has been established in a dinuclear copper complex system as shown in equation 57[187].

Aromatic substrates undergo nuclear hydroxylation with Fenton's reagents, which consist of iron(II) salts and H_2O_2. In these systems hydroxyl radicals are produced via free-radical chain processes[188,189] (equation 58). Copper salts can also be used[189] or their addition enhances the yield of phenols in the iron-containing system. Higher iron(III) concentrations favour phenol formation. Aromatic compounds are also hydroxylated

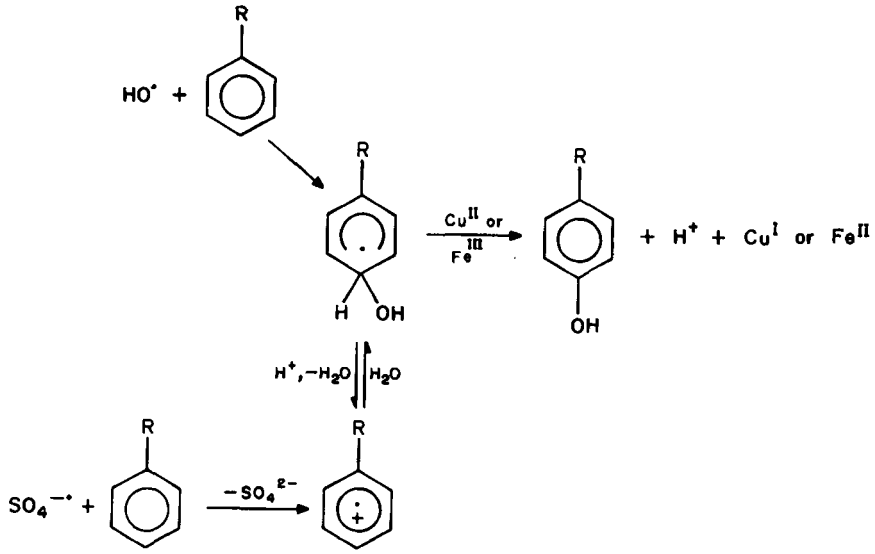


(57)

with the related Fe^{II}–$S_2O_8^{2-}$ system[190]. Here the reactive species is the $SO_4^{-\cdot}$ formed in equation 59. The mechanisms operating in these systems are shown in Scheme 8. The key intermediate is the hydroxycyclohexadienyl radical. In the hydroxylation with Fenton's reagent under aprotic conditions high-valent oxoiron complexes as hydroxylating species may also be involved[191].

$$Fe^{II} + H_2O_2 \longrightarrow Fe^{III}OH + HO^{\cdot} \quad (58)$$

$$Fe^{II} + S_2O_8^{2-} \longrightarrow Fe^{III} + SO_4^{2-} + SO_4^{-\cdot} \quad (59)$$



SCHEME 8

The role of oxygen in the hydroxylation of benzene with Fenton's reagents has also been studied. The phenol to benzoquinone ratio is 10:1. The phenol selectivity is low, and conversion of H_2O_2 is unexpectedly high. Incorporation of ^{18}O in phenol is ca 20% whereas in benzoquinone it is 100%[192]. In the presence of quinones as co-catalysts the iron(III)-catalysed hydroxylation of benzene with H_2O_2 provides phenol in up to 30% yield. Only traces of biphenyl and hydroquinone as by-products are formed[193].

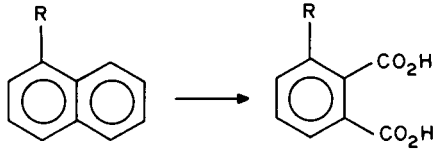
Benzene can be also hydroxylated with H_2O_2 in a benzene–water two-phase system in the presence of iron(III) and a variety of catechols. The efficiency of the catalyst is enhanced by the use of more hydrophobic catechols[194]. Benzene, toluene, and mesitylene are hydroxylated by complexes **1** and **2** to give hydroxylated products in good yields. Using benzene-d_6 in MeCN no kinetic isotope effect was observed, indicating that C—H bond cleavage is not rate determining[64].

Anthracene is oxidized to anthraquinone by dioxygen in the presence of $[Cu_2(OAc)_4]$ and LiCl in AcOH. The kinetics of the reaction at 90 °C using chlorocopper(II) complexes show that the reaction is first order in anthracene, 0.5–0 order with respect to the catalyst, and 0–1 order in NaCl[195,196]. 2-Methylnaphthalene is oxidized to 2-methyl-1,4-naphthoquinone in acetic acid with 60% H_2O_2 in the presence of palladium(II)–polystyrene sulphonic acid resin at 50 °C in 50–60% yield[197]. With $[RhCl(PPh_3)_3]$ as catalyst anthracene[198] and 2-substituted anthracenes[199] are oxidized to anthraquinones by t-BuO_2H in benzene at 70 °C in good to excellent yields. Indenopyrene is transformed into the quinone by first treating it with OsO_4 in pyridine and then oxidizing the resulting diol with activated MnO_2[200]. Polynuclear aromatic hydrocarbons are oxidized by $S_2O_8^{2-}$ with catalytic amounts of cerium(IV) and silver(I) in a two-phase system using $(Bu_4N)HSO_4$ as the phase-transfer catalyst[201].

4. Oxidative cleavage

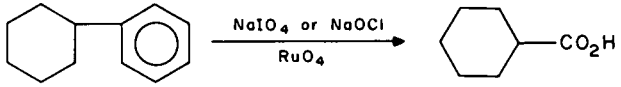
The aromatic ring is fairly stable and can only be cleaved with powerful oxidants. Industrial processes generally use heterogeneous catalysts.

Aromatic rings are oxidatively cleaved by RuO_4 under ambient conditions. The cleavage of naphthalene to phthalic acid by NaOCl and RuO_4 as catalyst proceeds in ca 65% yield[202]. In an analogous manner nitro- and hydroxynaphthalenes are converted to the corresponding phthalic acids (equation 60).



(60)

Aromatic rings can be converted to a carboxyl group by oxidation with $NaIO_4$ or NaOCl in the presence of catalytic amount of ruthenium compounds (equation 61)[203,204]. The addition of MeCN results in significantly enhanced yields[205].



(61)

D. Olefins

Olefins are the most important building units in organic synthesis and their conversion to oxygen-containing derivatives constitutes a basic process applied on both laboratory and industrial scales.

1. Epoxidation

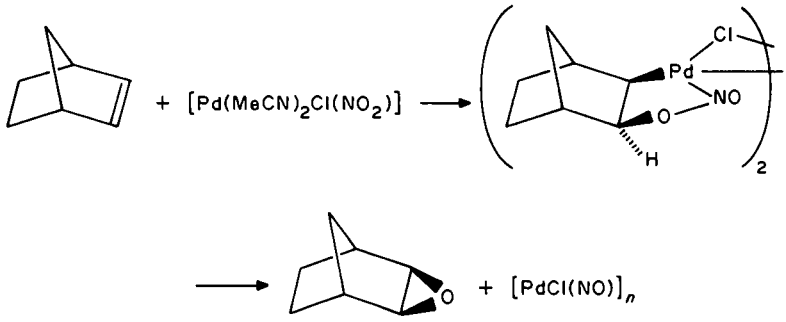
Ethylene and propylene oxide are important raw materials for a wide range of chemicals. Ethylene oxide is prepared industrially by the gas-phase oxidaion of ethylene

with dioxygen or air over a supported silver catalyst[206]. Higher olefins under these conditions give only low yields of epoxides (e.g. propylene oxide, ca 25%). There are continual efforts to utilize dioxygen as the primary oxidant for homogeneous catalytic olefin epoxidations.

The epoxidation of olefinic alcohol acetates such as geranyl acetate by O_2 is catalysed by $[Fe_3O(O_2CCMe_3)_6(MeOH)_3]Cl$ at 60 °C. Dioxygen is required at twice the ideal stoichiometry because half the oxygen is consumed in oxidative degradation of the substrate[207] (equation 62).

(62)

In the presence of colloidal platinum and H_2 [Mn(tpp)Cl] catalyses the epoxidation of olefins by O_2. The role of the platinum is to catalyse electron transfer from H_2 to [(tpp)Mn^{III}] to form [(tpp)Mn^{II}], which activates O_2[88]. The [Mn(tpp)Cl]–O_2–ascorbate system is also suitable for epoxidizing olefins, where about 100 mol of ascorbate are consumed per mole of epoxide formed[208]. Norbornene and its derivatives are epoxidized by O_2 in the presence of $[Pd(MeCN)_2Cl(NO_2)]$[209]. In a stoichiometric reaction a metallocycle is formed from norbornene which decomposes to *exo*-epoxynorbornene (equation 63). In the presence of air the reaction is catalytic[210].

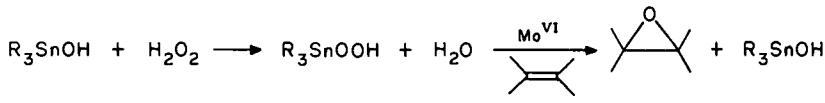


(63)

Hydrogen peroxide in the presence of metal catalysts, generally referred to as Milas reagents, interacts with olefins and is used extensively for the synthesis of glycols[14]. Acidic metal oxides such as OsO_4, MoO_3, WO_3, V_2O_5, and CrO_3 and non-metal oxides such as SeO_2 are used as components[211]. Many of these reactions proceed via epoxides which, under the acidic conditions employed, undergo subsequent hydrolysis. Under neutral and basic conditions selective epoxidations occur[211].

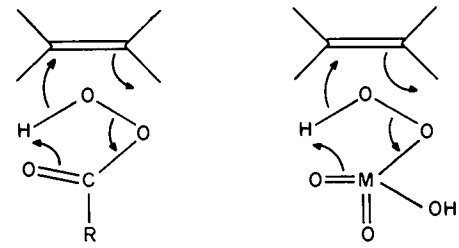
The epoxidation of allyl alcohol to glycidol using H_2O_2–Na_2WO_4 is used industrially[212]. The epoxidation of α,β-unsaturated carboxylic acids can be carried out with H_2O_2 in the presence of metal catalysts since they are inert towards alkyl hydroperoxides[213,214]. Non-functionalized and simple olefins also give good epoxide yields when the retarding effect of water is circumvented by its removal from the reaction medium. In this way, for example, propylene is epoxidized with H_2O_2 in 85% yield in the presence of molybdenum[215], boron[216], and arsenic[217] catalysts. The selective epoxidation of eight- and twelve-membered cyclic olefins with H_2O_2 in the presence of WO_3, H_2WO_4, H_2MoO_4, V_2O_5, and SeO_2 catalysts is also feasible, whereas smaller rings result in glycols under the same conditions[218]. Organometallic hydroperoxides formed from R_3SnOH and H_2O_2 are capable of epoxidizing olefins (equation 64)[219]. [(dppe)Pt(CF_3)(OH)] catalyses the

epoxidation of terminal alkenes with 35% H_2O_2 in the presence of water with a selectivity of over 39%[220]. The palladium–superoxo complex [$AcOPdO_2$] [prepared from $Pd(OAc)_2$ and H_2O_2] oxidizes ethylene to ethylene oxide and propene to propylene oxide and acetone[221].

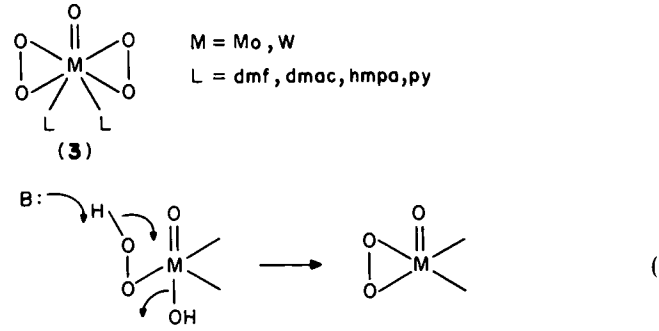


(64)

A plausible mechanism for these epoxidations is, after the formation of inorganic peracid, similar to that proposed for organic peracids as shown in Scheme 9[19]. Other suggestions have been also made for mechanistic consideration[211]. Covalent metal peroxides (**3**) are formed from inorganic peracids in the presence of bases (equation 65).



SCHEME 9



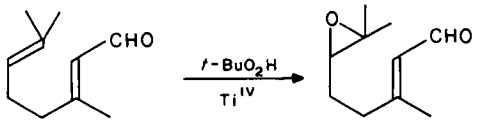
(65)

A series of molybdenum and tungsten peroxides are now available[222,223] which selectively epoxidize olefins[224]. For these epoxidations a cyclic mechanism involving 1,3-dipolar addition to the double bond after coordination of the olefins has been suggested[224]. ^{18}O labelling studies have shown that the epoxide oxygen arises exclusively from the peroxo oxygens when [MoO_5(hmpa)] is the oxidant[225]. Molybdenum(VI) and tungsten(VI) peroxide complexes also act as catalysts for the epoxidation of olefins with H_2O_2[226]. The use of concentrated H_2O_2 is necessary and side-products such as glycols are also formed.

The most important primary oxidants for the epoxidation of olefins are alkyl hydroperoxides in the presence of metal catalysts. Alkyl hydroperoxides are decomposed homolytically by certain metal complexes yielding radicals as discussed previously. In

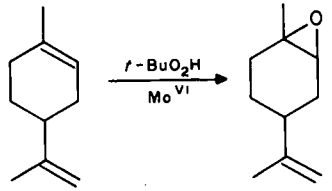
heterolytic reactions of alkyl hydroperoxides, the metal catalysts withdraw electrons from the O—O bond, making it more susceptible to heterolysis by attacking nucleophiles. Utilizing these systems a great number of chemoselective, regioselective, and enantioselective epoxidation reactions can be performed[13,15,211,227,228]. This method is also suitable for the industrial production of propylene oxide from propene[229].

Alkyl hydroperoxides have been widely used as primary oxidants for epoxidation reactions. The most important of these is t-BuO_2H, which has many advantages over other primary oxidants[15]. t-BuO_2H epoxidizes 2,4,4-trimethylpent-1-ene at 25 °C in the presence of molybdenum, vanadium, and chromium acetylacetonates in high yields[230]. Epoxy alcohols can be synthesized by the treatment of allylic hydroperoxides with a catalytic amount of a vanadium, molybdenum, and tungsten compound[231]. t-BuO_2H–metal catalyst reagents are especially useful in the case of acid-sensitive olefins and those with functional groups that react with peracids. Citral is selectively epoxidized with t-BuO_2H (equation 66)[232].



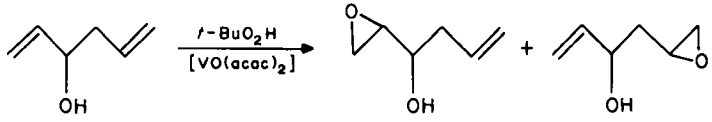
(66)

A wide variety of olefin epoxidations with alkyl hydroperoxide–metal catalysts[233] and with the t-BuO_2H–[$Mo(CO)_6$] system[15] in good yields have been published. Double bonds with increasing alkyl substitution exhibit higher reactivities. Non-conjugated dienes show selective monoepoxidation[227,233] (equation 67). Electron-withdrawing groups retard the rate of epoxidation. Propene is about ten times more reactive than allyl chloride[234], and acrylic esters and acrylonitrile[233] cannot be epoxidized by t-BuO_2H–Mo^{VI}. When the electron-withdrawing group is sufficiently far from the double bond, e.g. 4-cyanocyclohexene, the yields are good (e.g. 88%)[227]. Isolated double bonds are more reactive than conjugated ones. Monoepoxides are selectively formed[227,233]. The stereochemistry of these epoxidations is similar to that observed with peracids. There are, however, in cases of olefins with functional groups, great differences in the regio- and stereoselectivities.

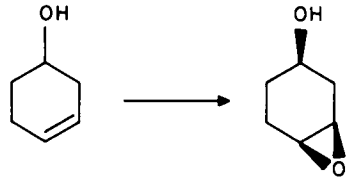


(67)

Reactions of allylic alcohols catalysed by vanadium compounds proceed with better yields and higher rates than those catalysed by molybdenum compounds[233] (e.g. equation 68). The high reactivity and selectivity in this case is due to a facile intramolecular oxygen transfer from the coordinated alkyl hydroperoxide to the double bond of an allylic alcohol coordinated to vanadium(V) through its OH group. The exploitation of this behaviour led to the regioselective epoxidation of geraniol and linalool[234]. High regioselectivities are also observed with homoallylic alcohols[234,235] (e.g. equation 69).

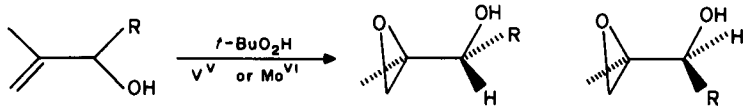


(68)

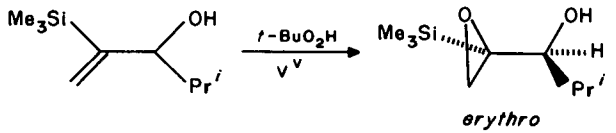


(69)

In the epoxidation of acyclic allylic alcohols with the alkyl hydroperoxide–metal catalyst system, in some cases high *erythro*- and *threo*-selectivities could be achieved. The *erythro*-epoxides are formed almost exclusively with allyl alcohols in equation 70 in comparison with those with *m*-chloroperbenzoic acid[236,237]. High diastereoselectivities are achieved in the vanadium(V)-catalysed epoxidation of acyclic allylic alcohols by *t*-BuO_2H[238] (equations 71 and 72).

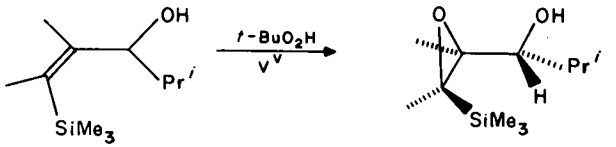


(70)



(71)

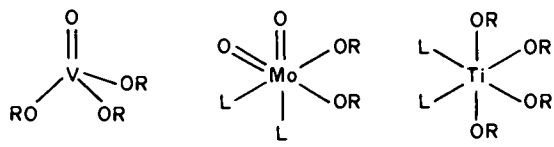
erythro



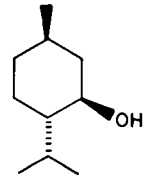
(72)

threo

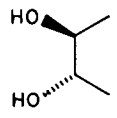
The enantioselective epoxidation of olefins using vanadium, molybdenum, and titanium compounds as catalysts, *t*-BuO_2H as primary oxidant, and chiral ligands has been achieved satisfactorily[239]. Complexes of the structures **4**, **5**[240], and **6**[241,242] have been used with combination of chiral ligands of types **7**–**12** and *t*-BuO_2H as the primary oxidant. The most effective epoxidation catalysts of this type involve [Ti(*i*-Pr)$_4$] or [Ti(*t*-Bu)$_4$] and chelating ligands of C_2 symmetry, mostly L-(+)-or L-(−)-diethyl tartrate. Enantiomeric excesses approaching 100% could be achieved[239,242].



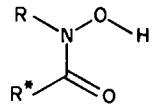
(4) (5) (6)



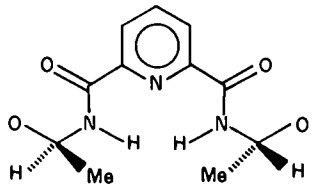
(7)



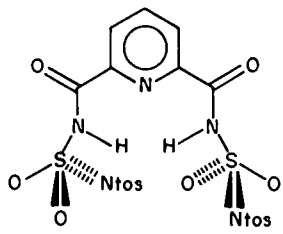
(8)



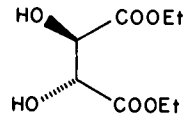
(9)



(10)

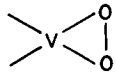


(11)

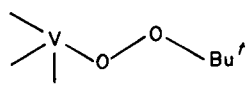


(12)

Studies concerning mechanistic aspects of the epoxidation reaction disclosed some feature of oxygen transfer and possible intermediates. Evidence concerning the nature of peroxometal intermediates in the epoxidation of olefins by H_2O_2 or t-BuO_2H in the presence of vanadium(V) compounds as catalysts indicates that H_2O_2 forms a side-bonded peroxometal complex (**13**), whereas t-BuO_2H forms a vanadium μ-perester (**14**)[243].



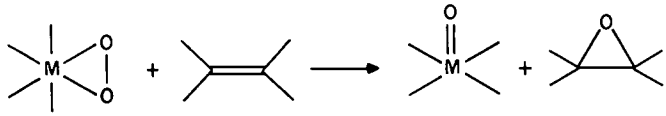
(13)



(14)

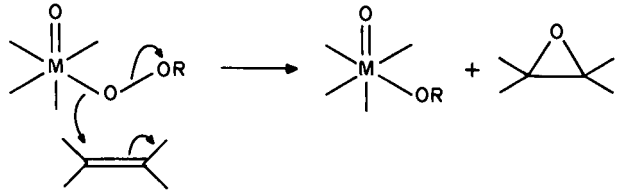
The complexes $[MoO(O_2)L_2Cl_2]$ (L = dmf, hmpa) epoxidize olefins to the epoxides and consecutively to cleaved products. Olefins are epoxidized by Ph_3COOH in the presence of $[MoO_2L_2Cl_2]$ catalysts, where the peroxo complexes are possibly intermediates in the catalytic process[244].

For the oxo transfer alternative mechanisms have been proposed. The metal–peroxide mechanism (equation 73) suggests the formation of metal peroxide intermediate which reacts directly with the olefin[224,245]. The metal–alkyl hydroperoxide complex mechanism, based on ^{18}O labelling studies, is similar to that proposed for the Prileschajew reaction 19 or alternatively those shown in equations 74 and 75[246].

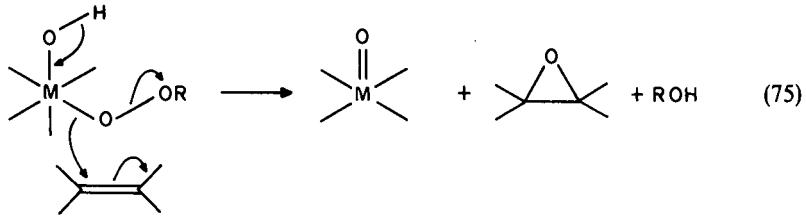


(73)

Porphyrins have been also applied as catalysts for olefin epoxidations using different primary oxidants[79]. [Mo(tpp)(O)OMe] and [Ti(tpp)O] catalyse the epoxidation of olefins using t-BuO_2H[247] and cumyl hydroperoxide[248]. PhIO and C_5F_5IO are suitable oxygen donors for epoxidation reactions in the presence of [Fe(dcpp)Cl][249].

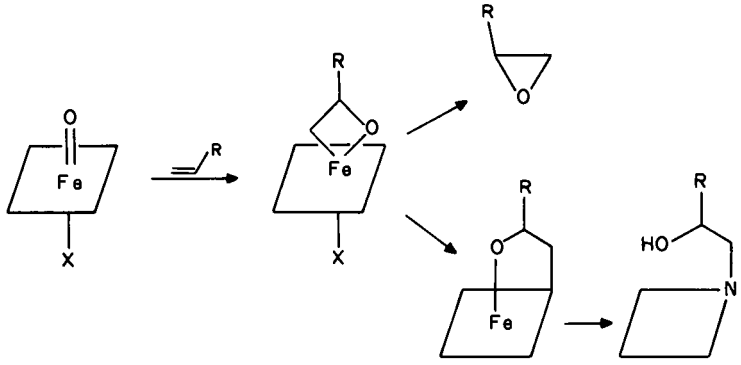


(74)



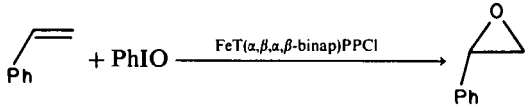
(75)

cis-Olefins are more reactive than their *trans*-isomers[250]. Kinetic studies revealed that oxygen transfer is the rate-determining step[251,252]. There is some deactivation of the catalysts due to the formation of *N*-alkylporphyrin[253]. A mechanism via oxametallacyclobutane intermediate as shown in equation 76 has been suggested[249,254].



(76)

Picket-fence porphyrins having binaphthyl groups alternating on the sides of the macrocyclic $H_2T(\alpha,\beta,\alpha,\beta\text{-binap})PP$ can be used for asymmetric epoxidation with PhIO reaching 48% ee (equation 77)[255]. Manganese porphyrins catalyse olefin epoxidation in a radical reaction leading to loss of stereochemistry[256]. Oxygenation of olefins is also observed when potassium hydrogen persulphate is used as the oxygen donor, and data support the role of oxometal species in these oxygen transfers mediated by manganese and iron bleomicin complexes[257]. The [Mn(Por)X]–NaOCl system is also able to epoxidize olefins[258], especially when improved by adding pyridine[259].



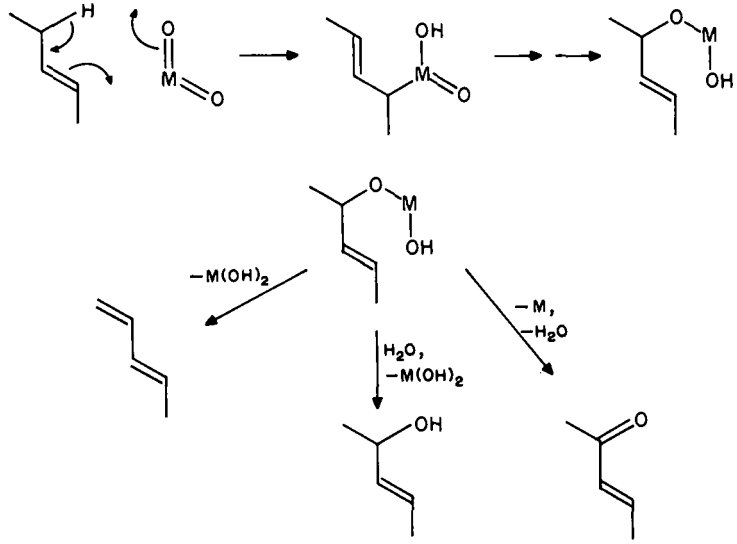
(77)

Olefins are epoxidized by PhIO in the presence of copper(II) in MeCN. Both stilbene isomers give *trans*-stilbene oxide. Using copper(I) an induction period and lower yields

result[260]. Using tripodal and nitrogen-containing crown ethers for binuclear copper(I) complexes with PhIO in MeCN better epoxidations are achieved than with mononuclear complexes[261]. Oxidation of styrene and stilbene by PhIO in the presence of $FeCl_3$, [Fe(acac)$_3$], and [Fe(tpp)Cl] gives mainly epoxides[262]. If O_2 is present autoxidation to benzaldehyde is predominant. The epoxidation of olefins is effected with $NaIO_4$ as oxidant in the presence of $RuCl_3 \cdot nH_2O$ and 2, 2′-bipyridine as catalyst. It is well suited for internal olefins showing *syn*-stereospecificity without isomerization[263]. Styrene is catalytically oxidized in the presence of iodosoarenes and square-planar cobalt(III) complexes of polyanionic chelating ligands. Possible intermediates in these oxygen atom-transfer reactions include cobalt(V) oxo complexes[264].

2. *Allylic oxidation*

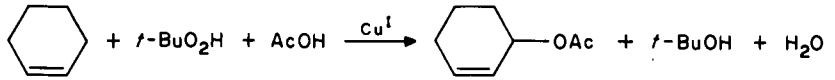
Oxometal compounds are the choice of reagent for the allylic oxidation of olefins. These reactions are conducted industrially using heterogeneous catalysts, e.g. over bismuth molybdate for the production of acrolein and acrylonitrile[265,266]. For laboratory purposes selenium dioxide is an alternative primary oxidant[23]. Both reactions seem to have a common mechanism involving an ene addition and sigmatropic rearrangement according to Scheme 10.



SCHEME 10

Terminal olefins yield primary allylic alcohols and disubstituted olefins are oxidized at the methylene group. Unsaturated carbonyl compounds and conjugated dienes are also formed in some cases. Allylic oxidation of olefins with *t*-BuO_2H using SeO_2 as catalyst gives allylic alcohols in moderate to good yields[267]. Enones are formed in the oxidation of olefins by *t*-BuO_2H in the presence of [$Cr(CO)_6$] or [$Cr(CO)_3(MeCN)_3$], even in the presence of oxidizable groups such as OH[268]. Treatment of cyclic olefins with *t*-BuO_2H in AcOH and [$Rh_3O(OAc)_6(H_2O)_3$]OAc as catalyst affords the corresponding α,β-unsaturated carbonyl compounds[269]. Allylic acetates are by-products. The oxidation of cyclic olefins in AcOH to the corresponding allylic acetates by *t*-BuO_2H is catalysed by

$PdCl_2$, AgOAc, and TeO_2[270]. Cyclohexene is transformed to 3-acetoxycyclohexene in 88% yield with t-BuO_2H in the presence of $CuCl$[271] (equation 78). Good yields of allylic acetates can be obtained in the reaction of olefins with peroxy esters in the presence of copper salts[272,273].



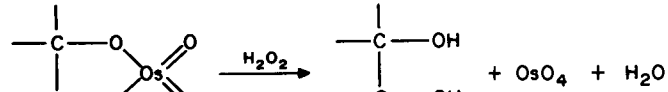
(78)

Olefins are converted to allylic acetates when treated with 1 equiv. of benzoquinone as the oxidant in the presence of catalytic amount of $Pd(O_2CCF_3)_2$. There is good selectivity for terminal methyl groups[274]. Metal acetates such as $Pb(OAc)_4$, $Te(OAc)_3$, $Hg(OAc)_2$, and $Pd(OAc)_2$ are also effective for the allylic acetoxydation of olefins[275]. Of these only the latter is catalytic. Alkenes undergo stoichiometric and catalytic oxidation (air as primary oxidant) in the presence of $[(MeCN)_2Pd(NO_2)Cl]$ to give allyl alcohols, α,β-unsaturated ketones, ketones, and epoxides with good selectivities[276]. Some cyclohexenones are oxidized by $K_2Cr_2O_7$ and air in the presence of molybdophosphoric acid and $CuSO_4 \cdot 5H_2O$ to cyclohexenediones in ca 60% yield[277]. Cationic rhodium complexes, $[Rh(LL)]BF_4$ [LL = dppe, $Ph_2P(CH_2)_2SPh$], promote the air oxidation of cycloolefins and branched terminal olefins to yield allylic oxidation products[278].

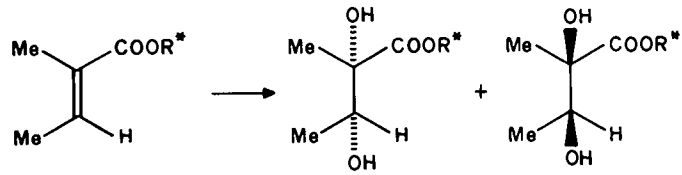
3. Glycol (ester) formation

H_2O_2 in combination with acidic metal oxides as catalysts (Milas reagent) are generally used for the hydroxylation of olefins to glycols. The intermediate formation of a cyclic osmate ester is assumed (equation 79), which after cleavage by H_2O_2 gives the glycol and OsO_4[24]. The formation of the osmate ester may be the result of a nucleophilic and electrophilic attack of OsO_4 on the double bond (further discussion is given in Section E).

Tiglate esters of chiral alcohols are hydroxylated with OsO_4 to give the diols (equation 80). The ratio of stereoisomeric products varies between 0.25 and 5, depending on the structure of the alcohol[279]. Other oxidants such as t-BuO_2H[280,281], $NaClO_3$[282], NaOCl[283], and amine oxides (N-methylmorpholine oxide)[284] may be used. OsO_4 catalyses efficiently the oxidation of olefins to glycols by O_2 in the presence of organic selenoxides as co-oxidants. The co-oxidant oxidizes soluble osmium(VI) to osmium(VIII) (equation 81) and the selenides can be reoxidized to selenoxides by photochemically generated singlet oxygen[285]. Terminal olefins are oxidized by $[Pd(MeCN)_2(NO_2)Cl]$ in acetic acid to a mixture of glycol monoacetate isomers as the main products. In the presence of O_2 the reaction is catalytic[286]. A mechanism involving an acetoxonium intermediate (**15**) has been proposed[287].

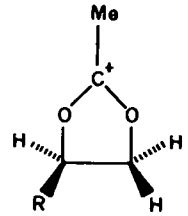


(79)



(80)

$$R_2SeO + OsO_4^{2-} + H_2O \longrightarrow R_2Se + OsO_4(OH)_2^{2-} \quad (81)$$



(15)

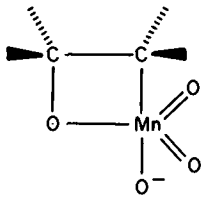
Meso-Tetra(2, 6-dichlorophenyl)porphinatoiron(III) chloride is an unusually efficient catalyst for alkene hydroxylation by C_6F_5IO. The turnover numbers are ca 10000. The high activity of the complex is attributed to its resistance against μ-oxo dimer formation and oxidative destruction[288]. Yields of *cis*-cyclohexane-1, 2-diol formed by the reaction of a $KMnO_4$ solution in MeOH–water with cyclohexene increased from nearly zero to 84% with efficient stirring and dilution. This is due to the formation of an intermediate hypomanganate ester which is hydrolysed by water to glycol but is further oxidized by excess MnO_4^- [289]. Oxidations of *cis*- and *trans*-2, 5-dihydro-2, 5-dimethoxyfurans with $KMnO_4$ proceed at comparable rates in aqueous ethanol or acetone. If aqueous thf is used as the solvent, only the *cis*-isomer is oxidized exclusively to the diol[290]. Oxidation of γ-butenolides with $KMnO_4$ in CH_2Cl_2 in the presence of a crown ether affords the corresponding 2, 3-*cis*-dihydroxy-γ-butyrolactones in 27–88% yields[291]. Treatment of alkenes with cetyltrimethylammonium permanganate in CH_2Cl_2 at 20 °C results in the corresponding *cis*-hydroxy compounds[292].

Oxidation of C_2–C_4 olefins with HIO_4 in AcOH solution and in the presence of $Pd(OAc)_2$ yields glycol acetates with high selectivity. From ethylene mainly ethylene glycol diacetate is formed whereas higher olefins give glycol monoacetates as the main products[293]. Alkenes are oxidized to glycol derivatives in AcOH with $Pd(OAc)_2$ and $LiXO_3$ (X = Cl, Br, I). The selectivity for glycol derivatives is 82%[294]. The oxidation of ethylene with nitric acid in acetic acid solutions to ethylene glycol monoacetate was studied in the presence of palladium(II) compounds as catalysts. An intermediate containing nitrite ion and ethylene coordinated to palladium is assumed[295].

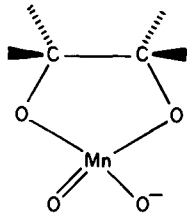
Oxidation of various aryl-conjugated olefins such as styrene with $Co(OAc)_3$ in wet AcOH under nitrogen gives the corresponding glycol monoacetates in good yield[296]. The oxidation of propene to propylene glycol acetates is catalysed by $CuCl_2$ and I_2 in AcOH solution. The results indicate that $CuCl_2 \cdot I_2 \cdot C_3H_6$ and $CuCl \cdot CuCl_2 \cdot I_2 \cdot C_3H_6$ are formed as intermediates[297,298]. Oxidation of ethene with SeO_2 in acetic acid at 100–125 °C in the presence of mineral acids affords ethylene glycol diacetate[23,299]. Styrene and butadiene similarly give 1,2-addition products[300].

4. Oxidative cleavage

Oxometal reagents effect the oxidative cleavage of double bonds when a *cis*-dioxometal functionality is available. The cleavage can occur via a [4 + 2]- or a [2 + 2]-cycloaddition[13]. When reoxidation of the reduced form of the oxidant is feasible, the process can be made catalytic. Olefins are cleaved at the C=C bond to yield aldehydes as main products with $KMnO_4$ in a dilute thf solution. Conjugation increases, whereas bulky substituents decrease, the yield[301]. The kinetics and mechanism of the permanganate ion oxidation of thienyl propionates show that the rate-limiting step is the formation of a metallacyclooxetane (**16**) or a cyclic manganese(V) diester (**17**)[302].



(16)



(17)

Oxidative cleavage of olefins to carboxylic acids can be accomplished in good yield with RuO_4 in CCl_4–H_2O when MeCN is added[303]. Oxidation of enolic olefins can be carried out in CCl_4–H_2O (1:1) with $NaIO_4$ and catalytic amounts of RuO_2. The actual oxidizing agent is RuO_4. Increasing the amount of $NaIO_4$ favours the formation of carboxylic acids at the expense of aldehydes[304].

Allylic double bonds can be cleaved with KIO_4 in the presence of dibenzo-18-crown-6 and OsO_4 to give the aldehydes[305]. Oxidation of alk-2-enyl and alk-4-enyl-di-*tert*-butylphenols promoted by [Co(salpr)] leads selectively to the corresponding carbonyl compounds due to oxidative cleavage[306]. Rhodium(I) complexes such as $[Rh(PPh_3)_3Cl]$ catalyse the oxygenation of olefins to give carbonyl compounds by C=C bond cleavage. 2,3-Dimethylbut-2-ene is transformed to acetone[307].

Styrene derivatives undergo C=C bond scission to give benzaldehyde and acetophenone when treated with *t*-BuO_2H in AcOH in the presence of $[Rh_3O(OAc)_3(H_2O)_3]OAc$[308]. The oxidative cleavage of styrene to benzaldehyde and formaldehyde by acidic $[Fe(CN)_6]^{3-}$ is first order in each of the substrate, oxidant, and acid. In the rate-determining step the formation of a cationic intermediate is assumed[309]. RuO_4 in conjunction with NaOCl is a potent oxidant system[310]. Olefins undergo oxidative cleavage to ketones or carboxylic acids in the presence of catalytic amounts of ruthenium salts[311]. Cyclohexene affords adipic acid in 86–95% yield in a similar manner[311]. Potassium oleate can be converted to a mixture of azealic and pelargonic acids[283].

Cycloolefins are oxidized to dicarboxylic acids with NaOCl and $RuCl_3 \cdot xH_2O$ as catalyst in a two-phase system. The best results are obtained with cyclopentene, where the yield of glutaric acid is 82%[312]. Cycloolefins are also oxidized to the corresponding dicarboxylic acids using dilute nitric acid in the presence of a vanadium(V) catalyst[313]. The oxidative cleavage of cyclododecene to dodecane-1,12-dioic acid could be accomplished[314] using a mixture of Re_2O_7 and H_2O_2 in acetic acid at ambient temperature in a yield of 30%.

5. *Oxidative ketonization*

The Wacker process, the palladium-catalysed oxidation of ethene to acetaldehyde, involves the smooth conversion of ethene by aqueous solutions of $PdCl_2$[2,315–318]. This is followed by reoxidation of the palladium(0) by molecular oxygen in the presence of copper salts. The reactions shown in equations 82–84 have been proposed. The yield of acetaldehyde is 95% with minor by-products such as acetic acid (ca 2%), CO_2 (ca 1%), and chlorinated compounds (ca 1%)[319].

$$C_2H_4 + PdCl_2 + H_2O \longrightarrow MeCHO + Pd + 2HCl \quad (82)$$

$$Pd + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl \quad (83)$$

$$2CuCl + 2HCl + 0.5O_2 \longrightarrow 2CuCl_2 + H_2O \quad (84)$$

Propene and but-1-ene or but-2-ene are similarly oxidized by dioxygen in the presence of $PdCl_2$–$CuCl_2$ to give acetone and ethyl methyl ketone[316,320,321]. The yields vary considerably with higher olefins owing to olefin isomerization[320]. Olefins branched at the double bond cannot give ketones but undergo allylic oxidation. Since isomerization of terminal olefins is an unwanted side-reaction, Wacker-type reactions can be achieved by using alcohols[322,323], dmf[324], or sulpholane[325] as cosolvents. On the other hand, copper(I) chloride is superior to copper(II) chloride as cocatalyst since chlorination of the ketones is hampered[326].

The kinetic data of the palladium(II)-catalysed oxidations of olefins support a mechanism involving the basic steps shown in equations 85–89[327]. The most important aspects of this mechanism are the enhanced electrophilicity of the coordinated double bond of the olefin, the π–σ rearrangement of the olefin, and the subsequent β-hydride elimination of the hydroxyethylpalladium(II) intermediate. The most recent mechanistic studies support a mechanism of π–σ rearrangement or hydroxypalladation (equation 87), which proceeds with *trans* stereochemistry by distal attack of nucleophile (H_2O) and not by rearrangement of the coordinated ligand (H_2O or OH)[328,329]. The failure to deserve a significant isotope effect with C_2D_4[321,330] and the absence of deuterium incorporation in the acetaldehyde formed in D_2O[327] support the mechanism shown in Scheme 11.

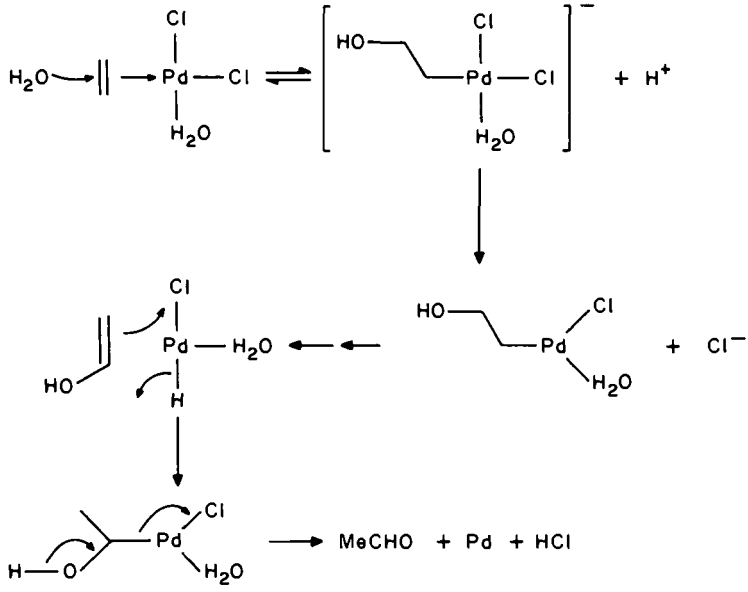
$$PdCl_4^{2-} + C_2H_4 \longrightarrow [PdCl_3(C_2H_4)]^- + Cl^- \quad (85)$$

$$[PdCl_3(C_2H_4)]^- + H_2O \longrightarrow [PdCl_2(H_2O)(C_2H_4)] + Cl^- \quad (86)$$

$$[PdCl_2(H_2O)(C_2H_4)] + H_2O \longrightarrow [HOCH_2CH_2PdCl_2(H_2O)]^- + H^+ \quad (87)$$

$$[HOCH_2CH_2PdCl_2(H_2O)]^- \longrightarrow HOCH_2CH_2PdCl(H_2O) + Cl^- \quad (88)$$

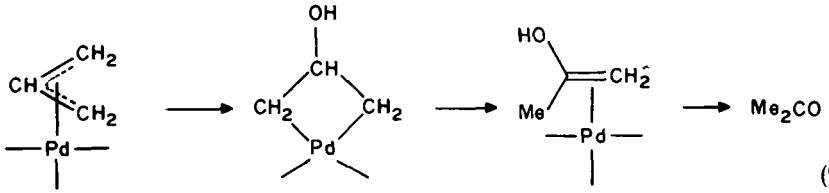
$$HOCH_2CH_2PdCl(H_2O) \longrightarrow MeCHO + Pd + HCl + H_2O \quad (89)$$



SCHEME 11

Hexa-1,5-diene is converted catalytically to acetone in an aqueous solution of $[Pd(PhCN)_2Cl_2]$, $CuCl_2$ and CuCl at 60 °C in the presence of O_2. A mechanism involving the formation of a (η^3-allyl)Pd(II) complex and the conversion of the η^3-allyl ligands to acetone has been suggested (equations 90 and 91). The Wacker oxidation of higher alk-1-enes to ketones proceeds also through η^3-allyl intermediates, in contrast to the case with ethene, where a π-bonded olefin is involved in the reaction with OH^- [331]. Terminal olefins can be converted to ketones by O_2 at 80 °C in a benzene–water two-phase system using $PdCl_2$ and $CuCl_2$ as catalysts and cetyltrimethylammonium bromide as phase-transfer agent[332]. [Mn(tpp)Cl] catalyses the oxidation of olefins to ketones by air in the presence of $(Bu_4N)(BH_4)$ in CH_2Cl_2 at room temperature. High O_2 concentrations inhibit the oxidation and the ketones are partly reduced to alcohols by $(Bu_4N)(BH_4)$[333].

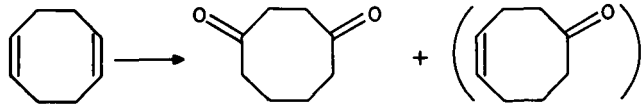
(90)



(91)

The hydride $[HIrCl_2(COD)(DMA)]$ catalyses the co-oxidation of cyclooctene and H_2 to cyclooctanone and water (equation 92). No oxygenation occurs in the absence of H_2. An iridium(III) hydroperoxide is a likely intermediate[334]. Cyclooctane-1,4-dione is formed from cod and O_2 in benzene containing PPh_3 and catalytic amounts of $[Rh(PPh_3)_3Cl]$ or $Rh(PPh_3)_3(O_2)Cl]$ (equation 93). The major product is the result of a homo-co-oxygenation at two olefinic centers in one molecule. The monoketone and Ph_3PO are formed in a hetero-co-oxygenation[335]. The complexes $[Rh(CN)(PPh_3)_3]$, $[Rh(OCN)(PPh_3)_3]$, and $[Rh(SCN)(PPh_3)_3]$ are catalysts for the co-oxidation of oct-1-ene and PPh_3 in benzene solution at 20–60 °C. Styrene shows a lower reactivity[336] (equation 94).

$$C_8H_{14} + O_2 + H_2 \longrightarrow C_8H_{14}O + H_2O \tag{92}$$



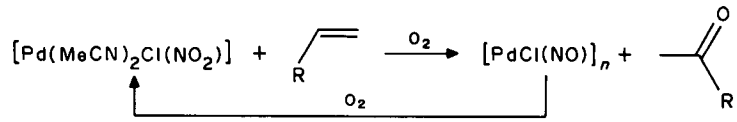
(93)

$$RCH{=}CH_2 + PPh_3 + O_2 \xrightarrow{[Rh]} RCOMe + Ph_3PO \tag{94}$$

The oxygen adducts $[Rh(PPh_3)_2(O_2)X](X = Cl, NCO, NCS)$ decompose in benzene solution in the presence of oct-1-ene to yield hexyl methyl ketone and Ph_3PO. This is a stoichiometric model reaction for the rhodium-catalysed hetero-co-oxygenation of terminal alkenes[337]. Oxidation of hex-1-ene to hexan-2-one by O_2 in *i*-PrOH as solvent is catalysed by $RhCl_3 \cdot 3H_2O$ or $[Rh_2(CO)_4Cl_2]$ as shown in equation 95[338]. $[Pd(MeCN)_2ClNO_2]$ also catalyses the oxidation of olefins to ketones. The catalytic cycle

is based on a nitro–nitrosyl redox couple[339] (equation 96).

$$CH_2{=}CHC_5H_{11} + O_2 + MeCHOHMe \longrightarrow MeCOC_5H_{11} + Me_2CO + H_2O \quad (95)$$



(96)

E. Acetylenes

The autoxidation of acetylenes has not been studied in much detail compared with the olefins. The propagation step involves competition between addition and hydrogen abstraction, the latter being favoured, giving α-acetylenic hydroperoxides as the primary products[340]. Straight-chain octynes are attacked at the C—H bond adjacent to the triple bond to yield ketones and acetylenic hydroperoxides in addition to α,β-unsaturated ketones through oxirene intermediates[341].

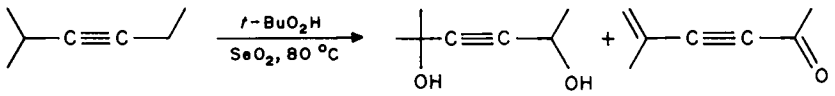
Terminal acetylenes undergo facile oxidative dimerization with dioxygen in pyridine at 30–40 °C catalysed by copper(I) chloride (equation 97)[342,343]. Similarly, the same reactions can be accomplished with copper(II) salts[344] for the preparation of a wide range of acetylenic compounds. The reaction involves deprotonation by amine to give a carbanion, which dimerizes to diacetylenes (equation 98). In the catalytic process the dioxygen reoxidizes copper(I) to copper(II).

$$RC{\equiv}CH \xrightarrow[\text{or } Cu^{II}\text{–py}]{\text{CuCl-py, } O_2} RC{\equiv}CC{\equiv}CR \quad (97)$$

$$RC{\equiv}CH \longrightarrow RC{\equiv}C^- \xrightarrow[Cu^{II}\text{–}Cu^{I}]{-e} RC{\equiv}C^{\bullet} \longrightarrow RC{\equiv}CC{\equiv}CR \quad (98)$$

Acetylenes undergo allylic oxidation by selenium dioxide (equation 99)[345]. These reactions can also be accomplished catalytically using selenium dioxide as the catalyst and *t*-BuO_2H as the primary oxidant[346]. Internal acetylenes undergo α,α′-dihidroxylation[346] showing a reactivity order of $CH_2 \simeq CH > CH_3$, allowing selective monohydroxylation by compounds having a methyl group. With acetylenes bearing a CH and a CH_2 substituent enynones are the major products (equation 100).

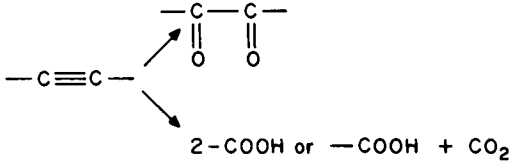
(99)



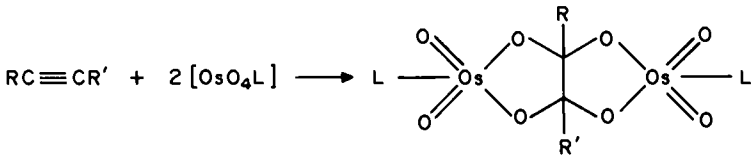
(100)

Acetylenes with no active CH and CH_2 groups undergo oxidation at the triple bond. The carbon–carbon triple bond is less accessible toward electrophilic attack than the double bond. Alkynes can easily be transformed to 1,2-dicarbonyl compounds (equation 101) either in stoichiometric reactions with SeO_2[345] or with oxometal reagents

such as RuO_4[347], $KMnO_4$[348,349], cetyltrimethylammonium permanganate[292], OsO_4[24], and $[(hmpa)MoO(O_2)_2]$[350]. More drastic conditions lead to the formation of cleavage products (equation 101). In these reactions cyclic esters are assumed to be intermediates. Cyclic osmate esters could be isolated from the reaction of $[OsO_4L]$ (L = quinuclidine) with acetylenes (equation 102)[351].

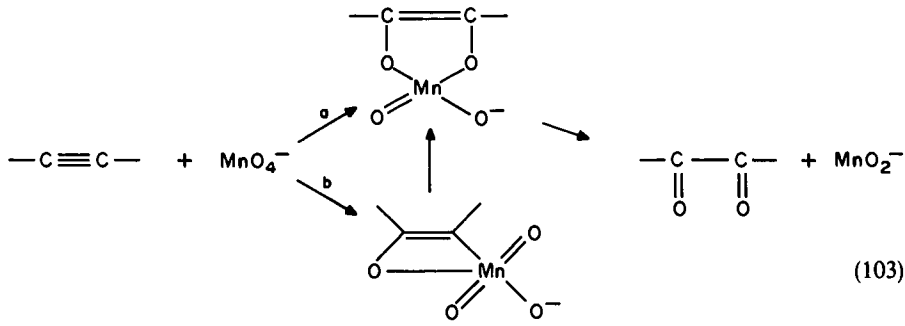


(101)



(102)

In the reaction of permanganate with acetylenes, nucleophilic[352] (path a) and electrophilic[353] (path b) attack of MnO_4^- on the triple bond (equation 103) have been suggested, the latter leading to the manganate(V) diester, via an organometallocycle, which decomposes to 1,2-dicarbonyls and manganese(III). The catalytic oxidation of acetylenes to 1,2-dicarbonyls by use of OsO_4 with H_2O_2[354], *t*-BuO_2H[292], *N*-methylmorpholine oxide[292], and $KClO_3$[355], or ruthenium(II) compounds with iodosylbenzene[356], and [Co(salpr)] with dioxygen[306] have been reported.



(103)

Terminal acetylenes undergo oxidative carbonylation catalysed by $PdCl_2$ in the presence of $CuCl_2$ (equation 104)[357]. This shows a close resemblance to the analogous reactions with olefins.

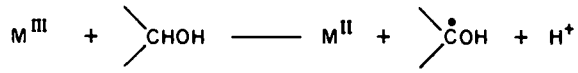
$$RC{\equiv}CH + CO + R'OH + 2CuCl_2 \longrightarrow RC{\equiv}CCO_2R' + 2CuCl + 2HCl \quad (104)$$

F. Heteroatom-containing Compounds

1. Alcohols

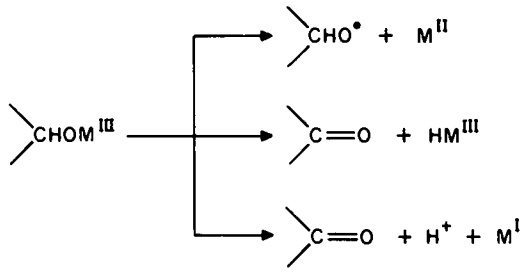
Transition metal ions act as either catalysts or inhibitors of alcohol oxidations. Low copper concentrations inhibit the autoxidation of cyclohexanol[358] whereas copper–

phenanthroline complexes catalyse the autoxidation of MeOH to HCOH[359]. Strong one-electron oxidants such as cobalt(III) and manganese(III) effect one-electron oxidation of the alcohol by M^{III} as shown in equation 105. This is the case in the oxidation of secondary alcohols to ketones by O_2 in the presence of cobalt(III)[360]. The overall result is reasonably explained by equation 105. There are, however, further possibilities for the formation of the alkoxy radical, e.g. the homolytic cleavage of the alkoxymetal intermediate, formed in equation 106, according to equations 107–109.



(105)

(106)



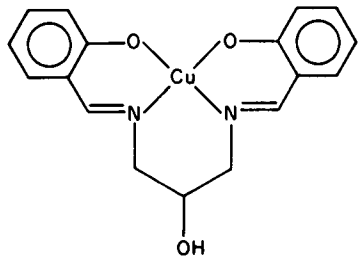
(107)

(108)

(109)

The oxidation of alcohols by palladium(II) and platinum(II) compounds often results in dehydrogenation products and metal hydrides through β-hydride elimination of the alkoxymetal species[361]. The regeneration of M^{II} proceeds by reaction of the metal hydride with dioxygen. A similar mechanism also operates in some hydrogen-transfer reactions, e.g. using $[RuCl_2(PPh_3)_3]$ as the catalyst[362]. Such a mechanism has been proposed for the ruthenium-catalysed oxidation of coordinated alcohols by dioxygen[363,364]. H_2O_2 is formed during the reaction utilizing a Ru^{II}–Ru^{IV} couple. For the galactose oxidase-catalysed oxidation of galactose an analogous mechanism with a Cu^{III}–Cu^{I} couple has been assumed[365].

The copper(II) complex **18** catalyses the oxidation of aliphatic alcohols to aldehydes by O_2 in the presence of KOH[366]. Benzoyl peroxide oxidizes primary and secondary alcohols to the corresponding carbonyl compounds in the presence of $NiBr_2$[367]. Primary alcohols are oxidized to aldehydes in good yields using $Pb(O_2CMe)_4$ in combination



(18)

with $Mn(OAc)_2$. The method is also suitable for the oxidation of olefinic and secondary alcohols[368]. $ZrO(OAc)_2$ catalyses the selective oxidation of primary alcohols with t-BuO_2H in aldehydes with very good yields without the formation of carboxylic acids. Allylic alcohols are transformed to α,β-unsaturated aldehydes[369]. Aromatic and α,β-unsaturated acyl cyanides can be prepared by the oxidation of cyanohydrins with t-BuO_2H in the presence of $[Ru(PPh_3)_3Cl_2]$ (equation 110)[370].

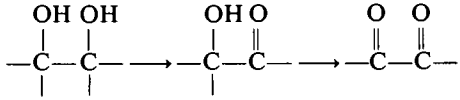
$$ArCH(OH)CN \longrightarrow ArCOCN \tag{110}$$

Oxometal reagents, such as oxochromium(VI)[21], oxovanadium[371] compounds are well suited for many stoichiometric alcohol oxidations. Furthermore, oxo complexes of ruthenium(IV) and ruthenium(VII) are used to oxidize organic compounds. RuO_4^{2-} and RuO_4^- oxidize primary alcohols to carboxylic acids and secondary alcohols to ketones. (Ph_4P) $[RuO_2Cl_3]$ and $[RuO_2(bpy)Cl_2]$ cleanly oxidize a wide range of alcohols to aldehydes and ketones without attack on the double bond[372]. Tetrabutylammonium ruthenate in an organic solvent is an efficient and selective oxidant for converting primary alcohols into aldehydes and secondary alcohols into ketones[373]. Primary alcohols are preferentially oxidized over secondary alcohols with OsO_4 in EtOH–py solution[374]. RuO_4 or RuO_4^{2-} can be used in catalytic amounts with NaOCl[375] or $K_2S_2O_8$[376] as the primary oxidants under phase-transfer conditions.

2. *Glycols*

Glycols can be transformed to ketones and aldehydes by oxidative C—C bond cleavage. Aldehydes may be oxidized further under the reaction conditions. $Pb(O_2CMe)_4$ and IO_4^- are generally used under mild conditions[377,378]. Glycols are selectively cleaved by molecular oxygen in the presence of cobalt(II) salts in aprotic solvents, resulting in aldehydes or carboxylic acids as the major products[379]. The complexes $[MoO_2L_2]$ and $[Mo_2O_3L_4]$ with sulphur-containing ligands (L = *S*-deprotonated cysteine ester or amides, Et_2NCS_2) catalyse the oxidation of benzoin to benzil by O_2 in dmf at 30 °C. Proton transfer from OH to MoO is followed by elimination of the methine proton to give the product[380]. Dezoxybenzoin is converted by Cu^{II}–py–Et_3N–MeOH–O_2 to benzil, bidesyl, PhCHO, and $PhCO_2H$. A product study comparing reactivities of benzil and bidesyl under identical conditions established 1) that the conversion of desoxybenzoin to bidesyl is effected by copper(II) alone, 2) that PhCHO is generated only from desoxybenzoin, in a reaction that requires both copper(II) and O_2, and 3) that benzil undergoes C—C bond cleavage only in the presence of H_2O, forming $PhCO_2H$ exclusively, in a reaction that requires copper(II) but not O_2[381].

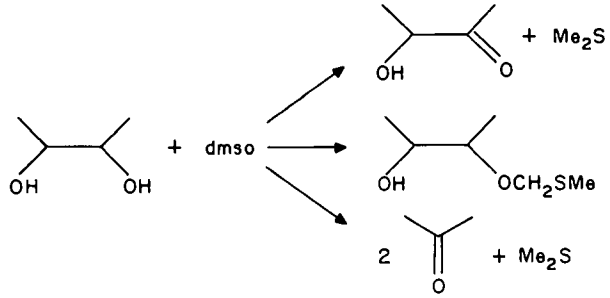
Glycols can be oxidized stepwise via α-ketols as intermediates to the corresponding 1,2-diketones (equation 111)[382]. Copper(II) salts oxidize α-ketols, for example benzoin is oxidized to benzil in the presence of a copper(II) catalyst and ammonium nitrate as the primary oxidant[383,384]. Acyloins are oxidized to 1,2-dicarbonyls by dioxygen using $[CuClpy]_n$ as catalyst in CH_2Cl_2 or $CHCl_3$[385]. Silver-catalysed oxidative cleavage of glycols by potassium peroxysulphate can be achieved[386,387]. Vanadium(V) catalysts can be used for the oxidation of cyclohexane-1,2-diol to adipic acid by nitric acid[387].



(111)

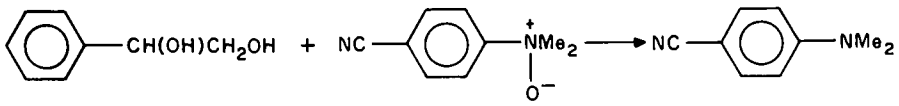
The molybdenum peroxide-catalysed oxidation of alcohols by dmso has been a useful route to 1,2-diols. Monooxidation, dioxidation with C—C bond cleavage, and the formation of 2-methylthiomethoxy-1-ols are observed (equation 112)[388]. Oxidation of

benzoin to benzyl by *p*-benzoquinone can be catalysed by $[Fe_4S_4(SR)_4]^{2-}$ complexes having cysteine-containing peptides or bulky thiolates as the RS group[389].



(112)

The oxidative cleavage of 1-phenylethane-1,2-diol into benzaldehyde by 4-cyano-*N*,*N*-dimethylaniline *N*-oxide (equation 113) is catalysed by [Cr(tpp)Cl]. In the stoichiometric reaction the intermediacy of [OCr(tpp)Cl] could be demonstrated[390]. Under irradiation the same reaction gives benzaldehyde and formaldehyde[391].



$$+ \text{PhCHO} + CH_2O + H_2O \qquad (113)$$

3. *Aldehydes and ketones*

Aldehydes are susceptible to autoxidation even at ambient temperatures. In the radical chain process organic peracids are formed, which oxidize the aldehyde.

Acetaldehyde oxidation is used for the production of peracetic acid[392], acetic anhydride[393], and acetic acid[394]. For the acetaldehyde oxidation batch autoxidation and a continuous process[395] have been developed using catalytic amounts of manganese(II) and cobalt(II) acetates. The metal catalyst initiates the oxidation through a one-electron transfer (equation 114) from the aldehyde to manganese(III), which is later regenerated. In the production of acetic anhydride[393], cobalt(II) and copper(II) acetates are used as catalysts. Copper(II) oxidizes the acyl radical (equation 115) and in a subsequent reaction (equation 116) acetic anhydride is formed. In the autoxidation of aldehydes the decarbonylation of the intermediate acyl radicals (equation 117) is a competing side-reaction, which is favoured at high temperatures and low oxygen concentration when the R group is branched at the α-position. Reaction 117 is also promoted in the presence of metal catalysts (cobalt and manganese).

$$MeCHO + Mn^{III} \longrightarrow Me\dot{C}O + Mn^{II} + H^+ \qquad (114)$$

$$Me\dot{C}O + Cu^{II} \longrightarrow Me\overset{+}{C}O + Cu^{I} \qquad (115)$$

$$Me\overset{+}{C}O + MeCO_2H \longrightarrow (MeCO)_2O + H^+ \qquad (116)$$

$$R\dot{C}O \longrightarrow R^{\cdot} + CO \qquad (117)$$

Aromatic aldehydes are also readily autoxidized to the corresponding benzoic acids. Cobalt(II) salts are often the catalysts of the reaction[396,397]. Acrolein can be selectively oxidized to acrylic acid using $[Co(acac)_3]$ as catalyst and acetaldehyde as promoter at 30–

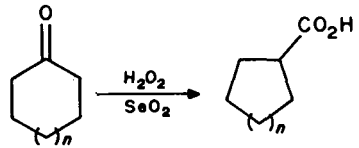
40 °C[398]. Methacrolein is converted to methacrylic acid in 96% yield using $Cu(OAc)_2$ catalyst in toluene or benzene solution at 30 °C and 14 bar oxygen pressure[399]. In the ammonoxidation of anisaldehyde with NH_3 and O_2 in the presence of NaOH, with $CuCl_2 \cdot 2H_2O$ as catalyst in MeOH at 30 °C, *p*-methoxybenzonitrile is obtained in 90% yield[400].

Aldehydes can be oxidized to the corresponding carboxylic acids using stoichiometric amounts of inorganic oxidants, such as chromium(VI) compounds, permanganate, and MnO_2. Aldehydes with protected hydroxy groups can be oxidized to the corresponding carboxylic acids with $KMnO_4$ in over 95% yields using a mixture of *t*-BuOH and aqueous NaH_2PO_4[401].

Ketones undergo facile metal-catalysed autoxidation with C—C bond cleavage to give carboxylic acids. In these reactions the direct oxidation of the ketone enolate by the metal oxidant is involved. The rate of oxidation of acetophenone in acetic acid and butyric acid at 130 °C catalysed by manganese(II) acetate is equal to the rate of enolization under the reaction conditions[402].

Ketones are oxidatively cleaved to carboxylic acids with stoichiometric amounts of MnO_4^- and chromium(VI) compounds. SeO_2 is the stoichiometric reagent for the oxidation of aldehydes and ketones to 1,2-dicarbonyl compounds (equation 118)[375,403–405]. Acetic acid and alcohol solvents are generally used at 80–100 °C. The SeO_2-catalysed oxidation of cyclic ketones with H_2O_2 in *t*-BuOH results in ring contraction (equation 119) with ca 30% yields[406,407]. The same reagent oxidizes acrolein to acrylic acid selectively[408].

$$RCOCH_2R' \xrightarrow{SeO_2} RCOCOR' \tag{118}$$



(119)

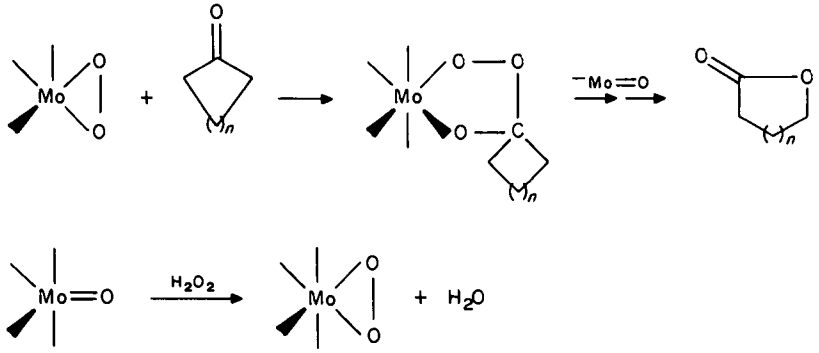
Catalytic Baeyer–Villiger oxidations using concentrated (90%) H_2O_2 have been reported (equation 120). Arsonated polystyrenes catalyse the oxidation of ketones with H_2O_2 to esters or lactones[409]. Biphasic and triphasic systems are used and the active oxidant is the polymer-bound peroxyarsonic acid. Peroxomolybdenum(VI) complexes stabilized by picolinato or pyridine-2,6-dicarboxylato ligands catalyse the Baeyer–Villiger oxidation of cyclic ketones with H_2O_2 (Scheme 12)[410].

$$RCOR' \xrightarrow{H_2O_2} RCOOR' \tag{120}$$

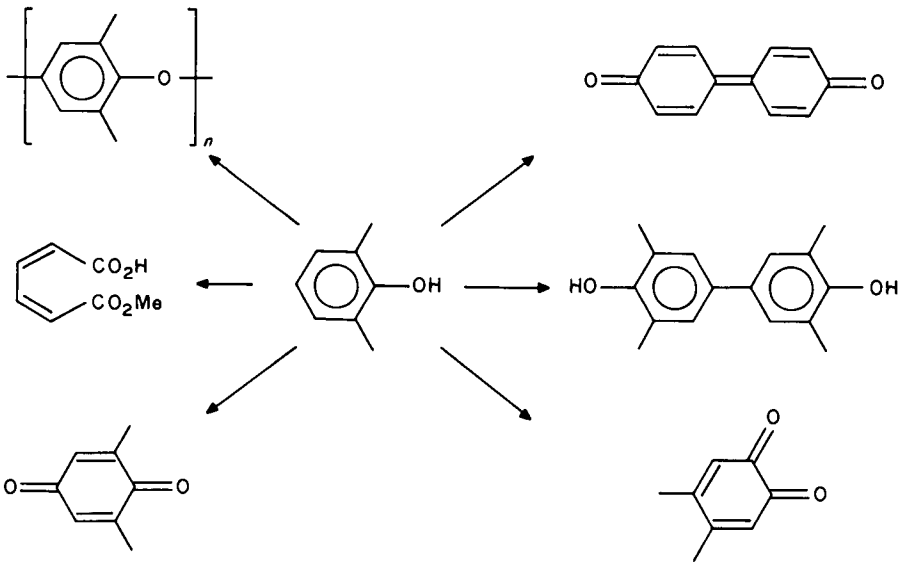
4. Phenols

Phenols are readily susceptible to oxidation with almost any oxidant. These oxidations are of synthetic importance and also implicated in many biogenetic reactions. Phenols are also used as inhibitors in free-radical autoxidations because of their facile reaction with alkylperoxy radicals. The key feature of metal-catalysed oxidative transformations of phenols is the oxidation of phenolate to the corresponding phenoxy radical (equation 121). Depending on the nature of the catalyst and the reaction conditions, phenols undergo a variety of oxidative transformations in the presence of metal compounds as shown in Scheme 13.

$$ArOM^{n+} \longrightarrow ArO^{\cdot} + M^{(n-1)+} \tag{121}$$

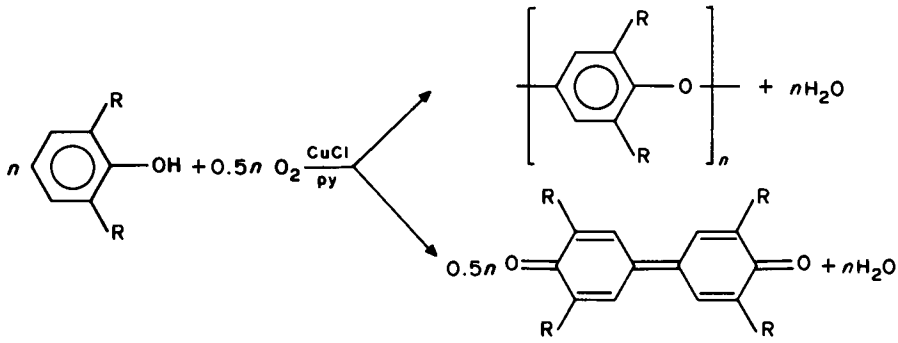


SCHEME 12



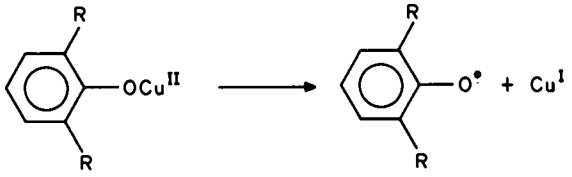
SCHEME 13

2,6-Disubstituted phenols are oxidized by O_2 at room temperature in the presence of copper(I) salts and a tertiary amine (usually CuCl–py) to give the corresponding polyphenylene ethers and/or diphenoquinones[411–415] (equation 122). The ratio of C—O and C—C coupling is mainly determined by the size of the group R, the molar ratio of the amine to copper(I), and the temperature. When R is bulky diphenoquinone is the sole product[411,412]. With small substituents, low catalyst concentrations, and/or low molar ratios of pyridine to copper(I), C—C coupling predominates[414,415]. Copper(II)–amine complexes are active catalysts only in the presence of strong bases such as KOH or NaOMe[412,413,416].

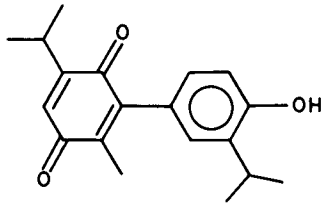


(122)

The key step in the oxidative coupling reaction is the formation of a phenoxy radical via one-electron oxidation of phenolate by copper(II) (equation 123). The phenoxy radical undergoes C—C or C—O coupling, depending on the reaction conditions. Anaerobic oxidation of 2,6-dimethylphenol by stoichiometric amounts of a copper(II)–phenylethylamine complex gives predominantly the dihydroxybiphenyl[417]. The oxidation of thymol with O_2 catalysed by $CuCl_2$ leads to **19**, which has both a *p*-quinoid structure and a phenyl ring. Novel coupling products can be achieved with other substrates[418]. Oxidation of 2,6-dimethylphenol by O_2 and catalysed by copper(II) complexes of 4-(*N*,*N*-dimethlyamino)pyridine gives diphenoquinone and polyether. Both mono- and dinuclear complexes are active, the most active species being $[Cu(dmap)_4Cl(OH)]$[419].



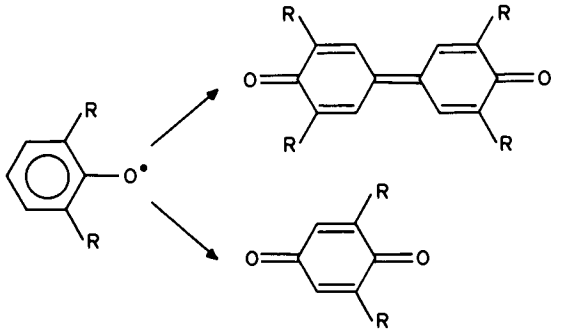
(123)



(19)

Autoxidation of phenols can give high yields of *p*-benzoquinones or diphenoquinones depending on the conditions (equation 124). The salen Co^{II}-catalysed autoxidation of phenols gives good yields of *p*-benzoquinones or diphenoquinones[420]. Phenol itself is selectively oxidized to 1,4-benzoquinone with O_2 at 70 bar in MeCN at 40 °C, and in the presence of catalytic amounts of CuCl or $CuCl_2$[421]. The oxidation of phenols by O_2 in the presence of $[Cu_4Cl_4O_2(MeCN)_4]$ gives oxidative coupling products selectively if the copper-to-phenol ratio is low, or *para*-hydroxylation products if this ratio is high. In the latter case phenols unsubstituted in the *para* position yield *p*-quinones whereas *p*-

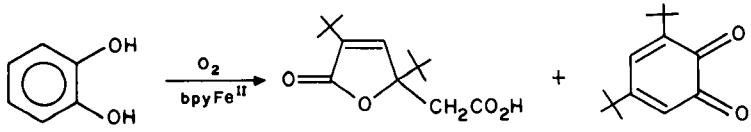
substituted phenols are transformed into *p*-quinols[422] (equation 125). 2,3,5-Trimethylphenol is oxidized to 2,3,5-trimethyl-1,4-benzoquinone with salen Co^{II} as catalyst in 94% selectivity at 94% conversion[423]. Phenols blocked in the *para* position, e.g. 2,4-di(*tert*-butyl)phenol, can be selectively oxidized to the corresponding *o*-benzoquinones in the presence of salen Co^{II}[13]. When both *ortho* and *para* positions are blocked in the phenol, *p*-quinols results[424]. 2,6-Dimethylphenol is oxygenated to the corresponding *p*-quinone catalysed by Schiff base complexes of cobalt. Initial rates and turnover numbers depend on the substitution of the Schiff base[425]. Oxidation of 2,6-di-(*tert*-butyl)phenol by O_2 in the presence of cobalt(II) chelates of several polyamines give the corresponding quinone and diphenoquinone[426]. Oxidation of phenols to quinones by cobalt–Schiff base complexes gives good yields in different solvents[427]. 2,4,6-Tri(*tert*-butyl)phenol reacts with O_2 and $[Co(dmg)_2py]$ to give an organic peroxo–metal complex, which on reaction with H^+ results in 2,6-di(*tert*-butyl)-*p*-benzoquinone[428]. $[CuClpy]_n$ catalyses the oxidation of 3,5-di(*tert*-butyl)catechol by O_2 to the corresponding quinone without ring cleavage. The formation of a dinuclear peroxo complex has been proposed for the rate-determining step[429]. The oxidation of phenol in the presence of morpholine and copper(II) produces dimorpholino-substituted *o*-benzoquinone[430].



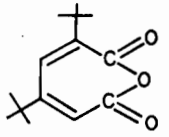
(124)

(125)

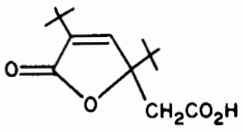
Many of the copper- and iron-catalysed oxygenations of phenols are reminescent of biochemical reactions mediated by copper- and iron-containing oxygenases. The oxidative ring cleavage of 3,5-di(*tert*-butyl)catechol by dioxygen is catalyzed by 2,2′-bipyridineiron(II)[431] (equation 126). Oxygenation of 3,5-di(*tert*-butyl)catechol in the presence of an Fe^{III}–bpy–py complex formed from $FeCl_3$ gives the products **20**, **21**, and **22**. The reaction proceeds by formation of a catecholate complex; the reaction with O_2 gives a peroxidic intermediate, which breaks down to the final products by ring scission[432].



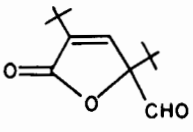
(126)



(20)



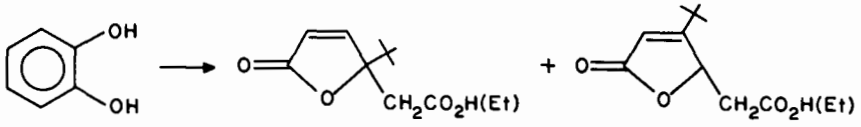
(21)



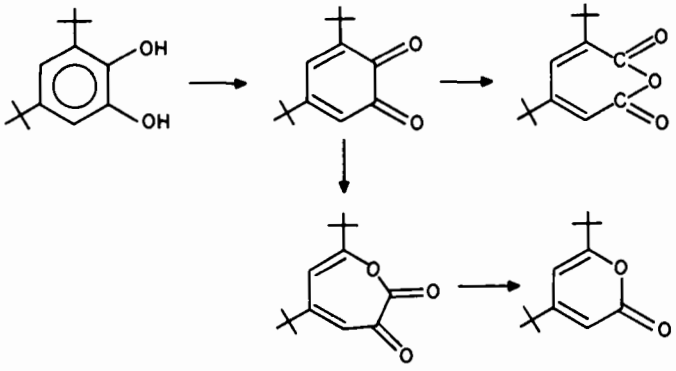
(22)

The oxidation of phenol catalysed by Cu^{I}–py in MeOH affords the monomethyl ester of *cis,cis*-muconic acid by oxidative C—C bond scission, involving catechol and *o*-benzoquinone as intermediates[432–437]. Similar ring cleavage of catechols and *o*-quinones can be achieved with $[CuCl(OMe)py_2]$[438] and the CuCl–py system[430]. The key steps in these reactions are believed to be oxidation of catechols to *o*-quinones and then nucleophilic attack of coordinated MeO^- or oxygen–copper complexes at the C=O carbon.

The iron(III)–nitrilotriacetate system is a good model for the active centre of non-haeme iron(III) dioxygenase. It catalyses the oxygenation of 4-*tert*-butylcatechol in $EtOH–H_2O$ to the lactones formed via oxidative ring cleavage (equation 127)[439]. Oxygenation of 3,5-di(*tert*-butyl)catechol to the corresponding muconic anhydride, 2-pyrone, and *o*-quinone (equation 128) is catalysed by vanadium(III) or vanadium(IV) complexes at 20 °C[440]. The quinone is not oxidized under these conditions. When $[Ru(PPh_3)_3Cl_2]$ is the catalyst the anhydride and pyrone are the products[441].



(127)



(128)

IV. REFERENCES

1. R. Landau and A. Saffer, *Chem. Eng. Prog.*, **64**, October, 20 (1968); P. H. Towle and R. H. Baldwin, *Hydrocarbon Process.*, **43**, November, 149 (1964).
2. R. Jira, W. Blau, and D. Grimm, *Hydrocarbon Process.*, March, 97 (1976); R. Jira, 'Manufacture of acetaldehyde directly from ethylene', in *Ethylene and Its Industrial Derivatives* (Ed. S. A. Miller), Ernest Benn, London, 1969, p. 650.

3. *Kirk-Othmer Encyclopedia of Chemical Technology*, Vol. 1, 3rd ed., Wiley–Interscience, New York, 1978, p. 130.
4. N. M. Emanuel (Ed.), *Oxidation of Hydrocarbons in the Liquid Phase*, Pergamon Press, Oxford, 1965.
5. N. M. Emanuel, E. T. Denisov, and Z. K. Maizus, *Liquid Phase Oxidation of Hydrocarbons*, Plenum Press, New York, 1967.
6. F. R. Mayo, *Acc. Chem. Res.*, **1**, 193 (1968).
7. P. George, *Oxidases and Related Redox Systems*, Wiley, New York, 1965, p. 3.
8. L. Vaska, *Acc. Chem. Res.*, **9**, 175 (1976).
9. H. Mimoun, *Rev. Inst. Fr. Pet.*, **33**, 259 (1978).
10. J. E. Lyons, in *Aspects Homogeneous Catalysis* (Ed. R. Ugo), Vol. 3, Reidel, Dordrecht, 1977, Ch. 1.
11. A. Nishinaga, H. Tomita, T. Shizumi, and T. Matsuura in *Fundamental Research in Homogeneous Catalysis* (Eds Y. Ishii and M. Tsutsui), Vol. 2, Plenum Press, New York, 1978, p. 241.
12. R. Ugo, G. M. Zanderighi, A. Fusi, and D. Carreri, *J. Am. Chem. Soc.*, **102**, 3745 (1980).
13. R. A. Sheldon and J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, 1981.
14. J. P. Shirmann and S. Y. Delavarenne, *Hydrogen Peroxide in Organic Chemistry*, Informations Chimie, Paris, 1979.
15. K. B. Sharpless and T. R. Verhoeven, *Aldrichim Acta*, **12**, 63 (1979).
16. R. H. Holm, *Chem. Rev.*, **87**, 1401 (1987).
17. C. D. Hodgman, R. C. West, and S. M. Selby (Eds), *Handbook of Chemistry and Physics*, Chemical Rubber Publishing Co., Cleveland, OH, 1958, p. 1733.
18. J. A. Connor and E. A. V. Ebsworth, *Adv. Inorg. Chem. Radiochem.*, **6**, 279 (1964).
19. H. Mimoun, *Angew. Chem.*, **94**, 750 (1982).
20. R. Stewart, in *Oxidation in Organic Chemistry, Part A* (Ed. K. B. Wiberg), Academic Press, New York, 1965, p. 2.
21. K. B. Wiberg, in *Oxidation in Organic Chemistry, Part A* (Ed. K. B. Wiberg), Academic Press, New York, 1965, p. 69.
22. H. H. Reich, in *Oxidation in Organic Chemistry, Part C* (Ed. W. S. Trahanovsky), Academic Press, New York, 1978, p. 1.
23. N. Rabjohn, *Org. React.*, **24**, 261 (1978).
24. M. Schroeder, *Chem. Rev.*, **80**, 187 (1980).
25. D. G. Lee and M. van der Engh, in *Oxidation in Organic Chemistry, Part B* (Ed. W. S. Trahanovsky), Academic Press, New York, 1978, Ch. 4.
26. A. J. Fatiadi, *Synthesis*, 65 (1976).
27. J. S. Pizey, *Synthetic Reagents*, Vol. 2, Wiley, New York, 1974, pp. 143–174.
28. K. B. Sharpless, A. Y. Teranishi, and J. E. Bäckwall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
29. B. Meunier, *Bull. Soc. Chim. Fr.*, 578 (1986).
30. J. K. Kochi, in *Free Radicals* (Ed. J. K. Kochi), Vol. 1, Wiley, New York, 1973, p. 591.
31. J. K. Kochi, *Acc. Chem. Res.*, **7**, 351 (1974).
32. J. K. Kochi, *Pure Appl. Chem.*, **4**, 377 (1971).
33. I. V. Berezin, E. T. Denisov, and N. M. Emanuel, *The Oxidation of Cyclohexane*, Pergamon Press, Oxford, 1966.
34. E. T. Denisov and N. M. Emanuel, *Russ. Chem. Rev.*, **29**, 645 (1960).
35. R. Hiatt and K. C. Irwin, *J. Org. Chem.*, **33**, 1436 (1968).
36. N. A. Milas and D. M. Surgenor, *J. Am. Chem. Soc.*, **68**, 205, 463 (1946).
37. R. Hiatt, K. C. Irwin, and C. W. Gould, *J. Org. Chem.*, **33**, 1430 (1968).
38. S. Ye, F. Han, S. Zhang, S. Qu, and S. Wu, *Ranliao Huaxue Xuebao*, **10**, 230 (1982); *Chem. Abstr.*, **98**, 34045 (1983).
39. M. U. Fedurtsa and S. S. Abadzhev, *Ukr. Khim. Zh.*, **48**, 266 (1982); *Chem. Abstr.*, **97**, 5747 (1982).
40. D. T. Woodbridge, *J. Chem. Soc., Perkin Trans. 2*, 50 (1966).
41. P. F. Wolf, J. E. McKeon, and D. W. Cannell, *J. Org. Chem.*, **40**, 1875 (1975).
42. H. Sakaguchi, Y. Kamiya, and N. Ohta, *Bull. Jpn. Pet. Inst.*, **14**, 71 (1972).
43. A. N. Bashkirov, V. V. Kamzolkin, K. M. Sokova, and T. P. Andreyeva, in *The Oxidation of Hydrocarbons in the Liquid Phase* (Ed. N. M. Emanuel), Pergamon Press Oxford, 1965, p. 183.
44. B. Ya. Ladygin and N. N. Fedyaeva, *Neftekhimiya*, **22**, 237 (1982).

45. L. G. Jodra, A. Romero, F. Garcia-Ochoa, and J. Querol, *Ing. Quim. (Madrid)*, **14**, 111 (1982); *Chem. Abstr.*, **98**, 36458 (1983).
46. T. S. Pekevich, L. V. Kolashko, N. A. Kovalenko, and N. I. Mitskevich, *Neftekhimiya*, **24**, 404 (1984).
47. S. A. Miller, *Chem. Process Eng. (London)*, **50**(6), 63 (1969).
48. J. W. M. Steeman, S. Kaarsemaker, and P. J. Hoftyzer, *Chem. Eng. Sci.*, **14**, 139 (1961).
49. M. Sittig, *Combine Hydrocarbons and Oxygen for Profit, Chem. Process. Rev.*, No. 11, Noyes Data Corp., Park Ridge, NJ, 1968, p. 185.
50. R. P. Lowry and A. Aguilo, *Hydrocarbon Process*, **53**, No. 11, 103 (1974).
51. A. Onopchenko and J. G. D. Schulz, *J. Org. Chem.*, **38**, 909 (1973).
52. A. Onopchenko and J. G. D. Schulz, *J. Org. Chem.*, **38**, 3729 (1973).
53. K. Tanaka, *Hydrocarbon Process.*, **53**, (11), 114 (1974).
54. J. G. D. Schulz and A. Onopchenho, *J. Org. Chem.*, **45**, 3716 (1980).
55. Y. Kamiya, *J. Catal.*, **33**, 480 (1974).
56. M. N. Gabdrakhmanov, Yu. V. Geletii, and I. V. Zakharov, *Neftekhimiya*, **24**, 496 (1984).
57. J. Hanotier, P. Camerman, H. Hanotier-Bridoux and P. de Radzitsky, *J. Chem. Soc., Perkin Trans. 2*, 2247 (1972).
58. S. R. Jones and J. M. Mellor, *J. Chem. Soc., Perkin Trans. 2*, 511 (1977).
59. R. A. Sheldon and J. K. Kochi, *Adv. Catal.*, **25**, 272 (1976).
60. G. A. Olah, *Chem. Br.*, **8**, 281 (1972).
61. G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, **12**, 173 (1973).
62. E. Bachiocchi, T. Del Giaccio, and G. V. Sebastiani, *Tetrahedron Lett.*, **28**, 1941 (1987).
63. T. Muto, C. Urano, T. Hayashi, T. Miura, and M. Kitamura, *Chem. Pharm. Bull.*, **31**, 1166 (1983).
64. H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer, and R. Weiss, *J. Am. Chem. Soc.*, **105**, 3101 (1983).
65. A. E. Shilov and A. A. Shteinman, *Coord. Chem. Rev.*, **24**, 97 (1977).
66. A. E. Shilov, in *Activation of Saturated Hydrocarbons by Transition Metal Complexes* (Eds R. Ugo and B. R. James), Reidel, Dordrecht, 1984, p. 185.
67. P. J. Davidson, M. F. Lappert, and R. Pierce, *Acc. Chem. Res.*, **7**, 209 (1974).
68. N. Z. Muradov, A. E. Shilov, and A. A. Shteinman, *Kinet. Katal. (Engl. Transl.)*, **13**, 1219 (1972).
69. I. S. Kolomnikov, V. P. Kukolev, and M. E. Volpin, *Russ. Chem. Rev.*, **43**, 399 (1974).
70. G. W. Parshall, *Homogeneous Catalysis*, Wiley, New York, 1980.
71. J. Rocek and F. Mares, *Collect. Czech. Chem. Commun.*, **24**, 2741 (1958).
72. K. B. Wieberg and G. Foster, *J. Am. Chem. Soc.*, **83**, 423 (1961).
73. R. Stewart and U. A. Spitzer, *Can. J. Chem.*, **56**, 1273 (1978).
74. E. S. Rudakov and L. K. Volkova, *Kinet. Katal.*, **24**, 542 (1983).
75. E. S. Rudakov and A. I. Lutsyk, *Neftekhimiya*, **20**, 163 (1980).
76. E. S. Rudakov, V. P. Tretyakov, L. A. Minko, and N. A. Tishchenko, *React. Kinet. Catal. Lett.*, **16**, 77 (1981).
77. C.-M. Che and W.-H. Leung, *J. Chem. Soc., Chem. Commun.*, 1376 (1987).
78. M. Faraj and C. L. Hill, *J. Chem. Soc., Chem. Commun.*, 1487 (1987).
79. B. Meunier, *Bull. Soc. Chim. Fr.*, 578 (1986).
80. J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, **105**, 6243 (1983).
81. J. R. Lindsay-Smith and P. R. Sleath, *J. Chem. Soc., Perkin Tans. 2*, 1165 (1983).
82. J. T. Groves, W. J. Kruper, and R. C. Haushaster, *J. Am. Chem. Soc.*, **102**, 6375 (1980).
83. L. C. Hill and B. C. Schardt, *J. Am. Chem. Soc.*, **102**, 6374 (1980).
84. D. Dolphin, B. R. James, and T. Leung, *Inorg. Chim. Acta*, **79**, 25 (1983).
85. R. Breslow and S. H. Gellman, *J. Chem. Soc., Chem. Commun.*, 1400 (1982).
86. B. De Poorter, M. Ricci, O. Bortolini, and B. Meunier, *J. Mol. Catal.*, **31**, 221 (1985).
87. C. L. Hill, J. A. Smegal, and T. J. Henly *J. Org. Chem.*, **48**, 3277 (1983).
88. I. Tabushi and Yazahi, *J. Am. Chem. Soc.*, **103**, 7371 (1981).
89. M. Fontecave and D. Mansuy, *Tetrahedron*, **40**, 4297 (1984).
90. A. M. Khenkin and A. A. Shteinman, *Ox. Com.*, **4**, 433 (1983).
91. A. M. Khenkin and A. A. Shteinman, *J. Chem. Soc., Chem. Commun.*, 1219 (1984).
92. B. De Poorter, M. Ricci, and B. Meunier, *Tetrahedron Lett.*, **26**, 4459 (1985).
93. K. S. Suslick, F. V. Acholla, and B. R. Cook, *J. Am. Chem. Soc.*, **109**, 2818 (1987).
94. A. S. Yakovlev, A. M. Syroezkho, A. A. Vikorev, and V. A. Proskuryakov, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*, **26**, 121 (1983); *Chem. Abstr.*, **98**, 142993 (1983).

95. A. M. Syroezhko, A. A. Vikhorev, and A. S. Yakovlev, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*, **29**, 103 (1986); *Chem. Abstr.*, **105**, 96861 (1986).
96. D. H. R. Barton, M. J. Gastiger, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 41 (1983).
97. D. H. R. Barton, R. S. Hay-Motherwell, and W. B. Motherwell, *Tetrahedron Lett.*, **24**, 1979 (1983).
98. D. H. R. Barton, M. J. Gastiger, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 731 (1983).
99. D. H. R. Barton, J. Boivin, N. Ozbalik, and K. M. Schwarzentruber, *Tetrahedron Lett.*, **25**, 4219 (1984).
100. D. H. R. Barton, J. Boivin, N. Ozbalik, K. M. Schwarzentruber, and K. Jankowski, *Tetrahedron Lett.*, **26**, 447 (1985).
101. G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, N. Ozbalik, and H. Riviére, *Tetrahedron Lett.*, **27**, 2849 (1986).
102. G. Balavoine, D. H, R. Barton, J. Boivin, A. Gref, N. Ozbalik, and H. Riviére, *J. Chem. Soc., Chem. Commun.*, 1727 (1986).
103. E. T. Karasevich, A. M. Khenkin, and A. E. Shilov, *J. Chem. Soc., Chem. Commun.*, 731 (1987).
104. P. Battiani, J. F. Bartoli, P. Leduc, M. Fontecave, and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 791 (1987).
105. N. F. Goldshleger, M. L. Khidekel, A. E. Shilov, and A. A. Shteinman, *Kinet. Katal.*, **15**, 261 (1974).
106. E. S. Rudakov and A. F. Lutsyk, *Neftekhimiya*, **20**, 163 (1980).
107. V. V. Eskova, A. E. Shilov, and A. A. Shteinman, *Kinet. Katal.*, **13**, 534 (1972).
108. N. F. Goldshleger, V. V. Eskova, A. E. Shilov, and A. A. Shteinman, *Zh. Fiz. Khim.*, **46**, 1353 (1972).
109. R. H. Crabtree, J. M. Mihelcic, and J. M. Quirk, *J. Am. Chem. Soc.*, **101**, 7738 (1979).
110. R. H. Crabtree, M. F. Mellea, J. M. Mihelcic, and J. M. Quirk, *J. Am. Chem. Soc.*, **104**, 107 (1982).
111. R. H. Crabtree, P. C. Demon, D. Eden, J. M. Mihelcic, C. P. Parnell, J. M. Quirk, and G. E. Morris, *J. Am. Chem. Soc.*, **104**, 6994 (1982).
112. D. Bandry, M. Ephritikine, and H. Felkin, *J. Chem. Soc., Chem. Commun.*, 1243 (1980).
113. D. Bandry, M. Ephritikine, and H. Felkin, *J. Chem. Soc., Chem. Commun.*, 606 (1982).
114. D. Bandry, M. Ephritikine, H. Felkin, and R. Holmes-Smith, *J. Chem. Soc., Chem. Commun.*, 788 (1983).
115. R. M. Cole, A. W. Fairbairn, and K. D. Detling, *Chem. Eng. Sci.*, **3**, Spec. Suppl., 67 (1954).
116. M. Hronec, Z. Cvengrosova, and J. Ilavsky, *Ind. Eng. Chem., Process Des. Dev.*, 24 (1985); *Chem. Abstr.*, **103**, 53545 (1985).
117. A. M. Ivanov and E. V. Shuran, *Kinet. Katal.*, **26**, 1078 (1985).
118. R. Landau and H. Saffer, *Chem. Eng. Prog.*, **64**, No. 10, 20 (1968).
119. D. E. Burney, G. H. Weisemann, and N. Fragen, *Pet. Refiner*, **38**, No. 6, 186 (1959).
120. P. H. Towle and R. H. Baldwin, *Hydrocarbon Process.*, **43**, No. 11, 149 (1964).
121. C. E. Somner and G. R. Steinmetz, *J. Am. Chem. Soc.*, **107**, 6124 (1985).
122. Y. Ichikawa and Y. Takeuchi, *Hydrocarbon Process.*, **51**, No. 11, 103 (1972).
123. A. S. Hay and H. S. Blanchard, *Can. J. Chem.*, **43**, 1306 (1965).
124. H. S. Bryant, C. A. Duval, L. E. McMakin, and J. I. Savoca, *Chem. Eng. Prog.*, **67**, No. 9, 69 (1971).
125. A. S. Hay, J. W. Eustance, and H. S. Blanchard, *J. Org. Chem.*, **25**, 616 (1960).
126. Y. Kamiya, *Adv. Chem. Ser. No.*, **76**, 192 (1968).
127. A. W. Chester, P. S. Landis, and E. J. Y. Scott, *ChemTech*, **8**, 366 (1978).
128. F. F. Shcherbina and T. V. Lysukho, *Kinet. Katal.*, **19**, 872 (1978).
129. M. Hronec and V. Vesely, *Collect. Czech. Chem. Commun.*, **40**, 2165 (1975).
130. M. Hronec and V. Vesely, *Collect. Czech. Chem. Commun.*, **42**, 1851 (1977).
131. E. I. Heiba, R. M. Dessau, and W. J. Koehl, *J. Am. Chem. Soc.*, **91**, 6830 (1969).
132. J. P. Fortuin, M. J. Waale, and R. P. van Oosten, *Pet. Refiner*, **38**, No. 6, 189 (1959).
133. H. J. den Hertog and E. C. Kooyman, *J. Catal.*, **6**, 357 (1966).
134. J. D. V. Hanotier and M. G. S. Hanotier-Bridoux, *Ger. Pat.*, 2242386 (1974).
135. Y. Sasson, G. D. Zappi and R. Neumann, *J. Org. Chem.*, **51**, 2880 (1986).
136. J. Imamura, M. Takehara, and K. Kizawa, *Ger. Pat.*, 2605678 (1976).

137. J. Hanotier, M. Hanotier-Bridoux, and P. de Radzitzky, *J. Chem. Soc., Perkin Trans. 2*, 381 (1973).
138. Y. Kamiya and M. Kashima, *Bull. Chem. Soc. Jpn.*, **46**, 905 (1973).
139. D. H. Beching, *US Pat.*, 3985809 (1976).
140. S. Lunák, M. Vasková, P. Lederer, and J. Veprek-Siska, *J. Mol. Catal.*, **34**, 321 (1986).
141. W. Sawodny, R. Grünes, and H. Reitzle, *Angew. Chem.*, **94**, 803 (1982).
142. J. Muzart, *Tetrahedron Lett.*, **27**, 3139 (1986).
143. A. J. Pearson and G. R. Han, *J. Org. Chem.*, **50**, 2791 (1985).
144. A. K. Bhattacharjee and M. K. Mahanti, *Bull. Soc. Chim. Fr.*, 270 (1983).
145. R. P. Kreh, R. M. Spotnitz, and J. T. Lundquist, *Tetrahedron Lett.*, **28**, 1067 (1987).
146. F. M. Hauser and S. R. Ellenberger, *Synthesis*, 723 (1987).
147. J. Muzart, *Tetrahedron Lett.*, **28**, 2131 (1987).
148. R. Rangarajan and E. J. Eisenbraun, *J. Org. Chem.*, **50**, 2435 (1985).
149. S. M. Gannon and J. G. Krause, *Synthesis*, 915 (1987).
150. D. R. Bryant, J. E. McKeon, and B. C. Ream, *J. Org. Chem.*, **33**, 4123 (1968).
151. E. Baccocchi, A. Dalla Cort, L. Eberson, L. Mandolini, and C. Rol, *J. Org. Chem.*, **51**, 4544 (1986).
152. K. Kurosawa, T. Takamura, Y. Ueno, J. F. N. McOmie, and N. D. Pearson, *Bull. Chem. Soc. Jpn.*, **57**, 1914 (1984).
153. I. V. Kozhevnikov, V. I. Kim, and E. P. Talzi, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2167 (1985).
154. A. B. Goel, *Inorg. Chim. Acta*, **90**, L15 (1984).
155. A. B. Goel, *Inorg. Chim. Acta*, **121**, L11 (1986).
156. A. B. Goel, P. E. Throckmorton, and R. A. Grimm, *Inorg. Chim. Acta*, **117**, L15 (1986).
157. A. Belli, C. Giordano, and A. Citterio, *Synthesis*, 477 (1980).
158. L. A. Deardurff, M. S. Alnajjar, and D. M. Camainoni, *J. Org. Chem.*, **51**, 3686 (1986).
159. J. K. Kochi, R. T. Tang, and T. Bernath, *J. Am. Chem. Soc.*, **95**, 7114 (1973).
160. T. Szymanska-Buzar and J. Ziolkowski, *J. Mol. Catal.*, **5**, 341 (1979).
161. J. R. Campbell, J. R. Kalman, J. T. Pinkey and S. Sternhell, *Tetrahedron Lett.*, **13**, 1763 (1972).
162. H. C. Bell, J. R. Kalman, J. T. Pinkey, and S. Sternhell, *Tetrahedron Lett.*, **15**, 853, 857 (1974).
163. J. M. Davidson and C. Triggs, *J. Chem. Soc. A*, 1324, 1331 (1968).
164. P. M. Henry, *J. Org. Chem.*, **36**, 1886 (1971).
165. L. Eberson and L. Gomez-Gonzales, *J. Chem. Soc., Chem. Commun.*, 263 (1971).
166. L. Eberson and L. Jönsson, *Acta Chem. Scand., Ser. B*, **28**, 597 (1974).
167. K. Nyberg and L. G. Wistrand, *J. Org. Chem.*, **43**, 2613 (1978).
168. C. Giordano, A. Belli, A. Citterio, and F. Minisai, *J. Org. Chem.*, 44, 2314 (1979).
169. T. Sugiyama, *Chem. Lett.*, 1013 (1987).
170. R. DiCosimo and H.-C. Szabo, *J. Org. Chem.*, **51**, 1365 (1986).
171. R. van Helden and G. Verberg, *Recl. Trav. Chim. Pays-Bas*, **84**, 1263 (1985).
172. F. R. S. Clark, R. O. C. Norman, C. B. Thomas, and J. S. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1289 (1974).
173. M. O. Unger and R. A. Fouty, *J. Org. Chem.*, **34**, 18 (1969).
174. A. McKillop, A. G. Turrell, D. W. Young, and E. C. Taylor, *J. Am. Chem. Soc.*, **102**, 6504 (1980).
175. Y. Landais, D. Rambault, and J. P. Robin, *Tetrahedron Lett.*, **28**, 543 (1987).
176. P. Palumbo, M. d'Ischia, O. Crescenzi, and G. Prota, *Tetrahedron Lett.*, **28**, 467 (1987).
177. S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.*, **208**, 731 (1954).
178. H. Mimoun and I. Sérée de Roch, *Tetrahedron*, **31**, 777 (1975).
179. R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc., London*, 138 (1962).
180. D. M. Jerina, J. W. Daly, W. Landis, B. Witkop, and S. Undenfriend, *J. Am. Chem. Soc.*, **89**, 3347 (1967).
181. K. Sasaki, S. Ito, Y. Saheki, T. Kinoshita, T. Yamasaki, and J. Harada, *Chem. Lett.*, 37 (1983).
182. T. Kinoshita, J. Harana, S. Ito, and K. Sazaki, *Angew. Chem.*, **95**, 504 (1983).
183. J. van Gent, A. A. Wismeijer, A. W. P. G. Peters Rit, and H. van Bekkum, *Tetrahedron Lett.*, **27**, 1059 (1986).
184. A. Kunai, S. Hata, S. Ito, and K. Sasaki, *J. Org. Chem.*, **51**, 3471 (1986).
185. I. Tabushi and K. Morimitsu, *Tetrahedron Lett.*, **27**, 51 (1986).
186. T. Shimidzu, T. Iyoda, and N. Kanda, *J. Chem. Soc., Chem. Commun.*, 1206 (1981).
187. K. D. Karlin, J. C. Hayes, Y. Gultneh, R. W. Cruse, J. W. McKown, J. P. Hutchinson, and J. Zubieta, *J. Am. Chem. Soc.*, **106**, 2121 (1984).

188. G. Sosnovsky, in *Organic Peroxides* (Ed. D. Swern), Vol. 2, Wiley–Interscience, New York, 1971, p. 269.
189. C. Walling, *Acc. Chem. Res.*, **8**, 125 (1975).
190. C. Walling, D. M. Camainoni, and S. S. Kim, *J. Am. Chem. Soc.*, **100**, 4814 (1978).
191. J. T. Groves and G. A. McClusky, *J. Am. Chem. Soc.*, **98**, 859 (1976).
192. A. Kunai, S. Hata, S. Ito, and K. Sasaki, *J. Am. Chem. Soc.*, **108**, 6012 (1986).
193. S. Tamagaki, K. Suzuki, H. Okamoto, and W. Tagaki, *Tetrahedron Lett.*, **24**, 4847 (1983).
194. K. Hotta, S. Tamagaki, Y. Suzuki, and W. Tagaki, *Chem. Lett.*, 789 (1981).
195. J. Koshitani, T. Kado, Y. Ueno, and T. Yoshida, *Bull. Chem. Soc. Jpn.*, **55**, 1931 (1982).
196. J. Koshitani, T. Kado, Y. Ueno, and T. Yoshida, *J. Org. Chem.*, **47**, 2879 (1982).
197. S. Yamaguchi, M. Inoue, and S. Enomoto, *Chem. Lett.*, 827 (1985).
198. P. Müller and C. Bobillier, *Tetrahedron Lett.*, **22**, 5157 (1981).
199. P. Müller and C. Bobillier, *Tetrahedron Lett.*, **24**, 5499 (1983).
200. J. E. Rice, E. J. LaVoie, D. J. McCaustland, D. L. Fischer, and J. C. Wiley, *J. Org. Chem.*, **51**, 2428 (1986).
201. E. V. Dehmlow and J. K. Makrandi, *J. Chem. Res. (S)*, 32 (1986).
202. U. A. Spitzer and D. G. Lee, *J. Org. Chem.*, **39**, 2468 (1974).
203. J. A. Caputo and R. Fuchs, *Tetrahedron Lett.*, **8**, 4729 (1967).
204. D. C. Ayres, *J. Chem. Soc., Chem. Commun.*, 440 (1975).
205. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
206. P. A. Kilty and W. M. H. Sachtler, *Catal. Rev.*, **10**, 1 (1974).
207. S. Ito, K. Inoue, and M. Matsumoto, *J. Am. Chem. Soc.*, **104**, 6450 (1982).
208. D. Mansuy, M. Fontecave, and J. F. Bartoli, *J. Chem. Soc., Chem. Commun.*, 253 (1983).
209. A. Heuman, F. Chauvet, and B. Waegell, *Tetrahedron Lett.*, **23**, 2767 (1982).
210. M. A. Andrews and C. W. F. Cheng, *J. Am. Chem. Soc.*, **104**, 4268 (1982).
211. R. A. Sheldon, in *Aspects of Homogeneous Catalysis* (Ed. R. Ugo), Vol. 4, Reidel, Dordrecht, 1981, p. 3.
212. Shell Development, *US Pat.*, 2833787 (1958).
213. Du Pont, *US Pat.*, 3156709 (1964).
214. G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1979).
215. Ugine Kuhlmann, *Ger. Pat.*, 2752626 (1978).
216. Ugine Kuhlmann, *Ger Pat.*, 2803757 (1977).
217. Ugine Kuhlmann, *Ger. Pat.*, 2803791 (1977).
218. J. Itakura, H. Tanaka, and H. Ito, *Bull. Chem. Soc. Jpn.*, **42**, 1604 (1969).
219. Sumimoto, *Fr. Pat.*, 2038948 (1971).
220. G. Strukul and R. A. Michelin, *J. Chem. Soc., Chem. Commun.*, 1538 (1984).
221. E. D. Talai, V. P. Babenko, V. A. Likholobov, V. M. Nehipelov, and V. D. Chikanov, *J. Chem. Soc., Chem. Commun.*, 1768 (1985).
222. H. Mimoun, I. Sérée de Roch, and L. Sajus, *Bull. Soc. Chim. Fr.*, 1481 (1969).
223. D. Westlake, R. Kergoat, and J. E. Guerchais, *C. R. Acad. Sci., Ser. C*, **280**, 113 (1975).
224. H. Mimoun, I. Sérée de Roch, and L. Sajus, *Tetrahedron*, **26**, 37 (1970).
225. K. B. Sharpless, J. M. Townsend, and D. R. Williams, *J. Am. Chem. Soc.*, **94**, 295 (1972).
226. C. Bocard, H. Mimoun, and I. Sérée de Roch, to Institut Français du Pétrole, *Fr. Pat.*, 2082811 (1974).
227. G. A. Tolstikov, V. P. Yurev, and U. M. Dzhemilev, *Russ. Chem. Rev.*, **44**, 319 (1975).
228. D. I. Melelitza, *Russ. Chem. Rev.*, **41**, 807 (1972).
229. R. Landau, *Hydrocarbon Process*, **46**, (4), 141 (1967).
230. N. Indictor and W. F. Brill, *J. Org. Chem.*, **30**, 2074 (1965).
231. British Petroleum, *Belg. Pat.*, 640202 (1964).
232. R. A. Sheldon, *J. Mol. Catal.*, **7**, 107 (1980).
233. M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970).
234. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
235. M. Kobayashi, S. Kurozumi, T. Toru, and S. Ishimoto, *Chem. Lett.*, 1341 (1979).
236. B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, **20**, 4733 (1979).
237. S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, *J. Am. Chem. Soc.*, **96**, 5254 (1974).
238. A. S. Narula, *Tetrahedron Lett.*, **23**, 5579 (1982).

239. K. B. Sharpless, *Chem. Br.*, **22**, 38 (1986).
240. K. Tani, M. Hanafusa, and S. Otsuka, *Tetrahedron Lett.*, **20**, 3017 (1979).
241. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
242. M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 5, Academic Press, New York, 1985, Ch. 8, p. 247.
243. F. Di Furia, H. Modena, R. Curci, S. J. Bachofer, J. O. Edwards, and M. Pomerantz, *J. Mol. Catal.*, **14**, 219 (1982).
244. P. Cheumette, H. Mimoun, L. Saussine, J. Fischer, and A. Mitschler, *J. Organomet. Chem.*, **250**, 291 (1983).
245. J. Kaloustian, L. Lena, and J. Metzgar, *Bull. Soc. Chim. Fr.*, 4411, 4415 (1971).
246. A. O. Chong and K. B. Sharpless, *J. Org. Chem.*, **42**, 1587 (1977).
247. H. J. Ledon, P. Durbut, and F. Varescon, *J. Am. Chem. Soc.*, **103**, 3601 (1981).
248. H. J. Ledon and F. Varescon, *Inorg. Chem.*, **23**, 2735 (1984).
249. J. T. Groves, T. E. Nemo, and R. S. Myers, *J. Am. Chem. Soc.*, **101**, 1032 (1979).
250. J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, **105**, 5786 (1983).
251. J. P. Collman, T. Kodadek, S. A. Raybuck, J. I. Brauman, and L. M. Papazian, *J. Am. Chem. Soc.*, **107**, 4343 (1985).
252. T. G. Traylor, J. C. Marsters, Jr., T. Nakano, and B. E. Dunlap, *J. Am. Chem. Soc.*, **107**, 5537 (1985).
253. T. Mashiko, D. Dolphin, T. Nakano, and T. G. Traylor, *J. Am. Chem. Soc.*, **107**, 3735 (1985).
254. D. Mansuy, L. Devocelle, I. Artaud, and J. P. Battioni, *Nouv. J. Chim.*, **9**, 711 (1985).
255. J. T. Groves and R. S. Myers, *J. Am. Chem. Soc.*, **105**, 5791 (1983).
256. J. T. Groves, W. J. Kruper, and R. C. Haushalter, *J. Am. Chem. Soc.*, **102**, 6375 (1980).
257. M. Girardet and B. Meunier, *Tetrahedron Lett.*, **28**, 2955 (1987).
258. E. Guelmet and B. Meunier, *Tetrahedron Lett.*, **21**, 4449 (1980).
259. B. Meunier, E. Guilmet, M. E. De Carvalho, and R. Poilblanc, *J. Am. Chem. Soc.*, **106**, 6668 (1984).
260. C. C. Franklin, R. B. VanAtta, A. F. Tai, and J. S. Valentine, *J. Am. Chem. Soc.*, **106**, 814 (1984).
261. A. F. Tai, L. D. Margerum, and J. S. Valentine, *J. Am. Chem. Soc.*, **108**, 5006 (1986).
262. M. Fontecave and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 879 (1984).
263. G. Balavoine, C. Eskenazi, F. Meunier, and H. Riviere, *Tetrahedron Lett.*, **25**, 3187 (1984).
264. T. J. Collins, S. Ozaki, and T. G. Richmond, *J. Chem. Soc., Chem. Commun.*, 803 (1987).
265. T. Dumas and W. Bulani, *Oxidation of Petrochemicals: Chemistry and Technology*, Applied Science, London, 1974.
266. D. J. Hucknall, *Selective Oxidation of Hydrocarbons*, Academic Press, London, 1974.
267. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).
268. A. J. Pearson, Y.-S. Chen, S.-Y. Hsu, and T. Ray, *Tetrahedron Lett.*, **25**, 1235 (1984).
269. S. Uemura and S. R. Patil, *Tetrahedron Lett.*, **23**, 4353 (1982).
270. S. Uemura, S. Fukuzawa, A. Toshimitsu, and M. Okano, *Tetrahedron Lett.*, **23**, 87 (1982).
271. C. Walling and A. Zavidzas, *J. Am. Chem. Soc.*, **85**, 2084 (1963).
272. G. Sosnovsky, *Tetrahedron*, **21**, 871 (1965).
273. D. J. Rawlison and G. Sosnovsky, *Synthesis*, 1 (1972).
274. J. E. McMurry and P. Kocovsky, *Tetrahedron Lett.*, **25**, 4187 (1984).
275. D. J. Rawlison and G. Sosnovsky, *Synthesis*, 567 (1973).
276. M. A. Andrews, T. C.-T. Chang, C.-W. F. Cheng, and K. P. Kelly, *Organometallics*, **3**, 1777 (1984).
277. V. J. Freer and P. Yates, *Chem. Lett.*, 2031 (1984).
278. A. Morvillo and M. Bressau, *J. Mol. Catal.*, **37**, 63 (1986).
279. H. Hatekayama, Y. Matsui, M. Suzuki, K. Sakurai, and S. Takano, *Tetrahedron Lett.*, **26**, 6485 (1985).
280. A. Byers and W. J. Hichinbottom, *J. Chem. Soc.*, 286 (1948).
281. K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976).
282. K. A. Hofman, *Ber. Dtsch. Chem. Ges.*, **45**, 3329 (1912).
283. T. A. Foglia, P. A. Barr, A. J. Malloy, and M. J. Constanzo, *J. Am. Oil. Chem. Soc.*, **54**, 870A (1977).
284. V. van Rheenen, R. C. Kelly, and D. F. Cha, *Tetrahedron Lett.*, **17**, 1973 (1976).
285. A. G. Abatjoglou and D. R. Bryant, *Tetrahedron Lett.*, **22**, 2051 (1981).
286. F. Mares, S. E. Diamond, F. J. Regina, and J. P. Solar, *J. Am. Chem. Soc.*, **107**, 3545 (1985).
287. J.-E. Bäckwall and A. Heuman, *J. Am. Chem. Soc.*, **108**, 7107 (1986).

288. P. S. Traylor, D. Dolphin, and T. Traylor, *J. Chem. Soc., Chem. Commun.*, 279 (1984).
289. J. E. Taylor, D. Williams, K. Edwards, D. Otonnaa, and D. Samanich, *Can. J. Chem.*, **62**, 11 (1984).
290. M. Hönel and H. S. Mosher, *J. Org. Chem.*, **50**, 4386 (1985).
291. T. Mukaiyama, F. Tabusa, and K. Suzuki, *Chem. Lett.*, 173 (1983).
292. V. Bushan, R. Rathore, and C. Chandrasekavan, *Synthesis*, 431 (1984).
293. N. I. Kuznetsova, M. A. Fedotov, V. A. Likholobov, and Yu. I. Yermakov, *J. Mol. Catal.*, **38**, 263 (1986).
294. N. I. Kuznetsova, V. A. Likholobov, and Yu. I. Yermakov, *React. Kinet. Catal. Lett.*, **22**, 139 (1983).
295. M. G. Volkonskii, V. A. Likholobov, and Yu. I. Yermakov, *Kinet. Katal.*, **24**, 578 (1983).
296. M. Hirano and T. Morimoto, *J. Chem. Soc., Perkin Trans. 2*, 1033 (1984).
297. E. V. Gusevskaya, V. A. Likholobov, E. P. Talzi, and Yu. I. Yermakov, *Kinet. Katal.*, **24**, 53 (1983).
298. E. V. Gusevskaya, V. A. Likholobov, and Yu. I. Yermakov, *Kinet. Katal.*, **24**, 61 (1983).
299. D. H. Olson, *Tetrahedron Lett.*, 7, 2053 (1966).
300. K. A. Javiad, N. Sonoda and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **42**, 2056 (1969).
301. P. Viski, Z. Szeverényi, and L. T. Simándi, *J. Org. Chem.*, **51**, 3213 (1986).
302. F. Freeman, and I. Y. Chang, *J. Am. Chem. Soc.*, **108**, 4504 (1986).
303. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
304. S. Torii, T. Inokuchi, and K. Kondo, *J. Org. Chem.*, **50**, 4980 (1985).
305. J. P. Marino and J. C. Jean, *Synth. Commun.*, **13**, 1057 (1983).
306. A. Nishinaga, H. Iwasaki, T. Shimizu, Y. Toyoda, and T. Matsuura, *J. Org. Chem.*, **51**, 2257 (1986).
307. H. Bönnemann, W. Nunez, and D. M. M. Rohe, *Helv. Chim. Acta*, **66**, 177 (1983).
308. S. Uemura and S. R. Patil, *Chem. Lett.*, 1743 (1982).
309. A. U. Bhattacharjee and M. K. Mahanti, *Gazz. Chim. Ital.*, **114**, 337 (1984).
310. Ethyl Corporation, *US Pat.*, 3409649 (1968).
311. S. Wolfe, S. K. Hasan, and J. R. Campbell, *J. Chem. Soc., Chem. Commun.*, 1420 (1970).
312. H. Orita, T. Hayakawa, and K. Tahehira, *Bull. Chem. Soc. Jpn.*, **59**, 2637 (1986).
313. Y. Ogata, in *Oxidation in Organic Chemistry, Part C* (Ed. W. S. Trahanovsky), Academic Press, New York, 1978, p. 295.
314. Du Pont, *US Pat.*, 3961160 (1969).
315. J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Ruttinger, and H. Kojer, *Angew. Chem.*, **71**, 176 (1959).
316. J. Smidt, *Chem. Ind. (London)*, 54 (1962).
317. W. Hafner, R. Jira, J. Sedlmeier, J. Smidt, P. Fliegel, W. Friedrick, and A. Trommett, *Chem. Ber.*, **95**, 1575 (1962).
318. R. Jira, J. Sedlmeier, and J. Smidt, *Justus Liebigs Ann. Chem.*, **693**, 99 (1966).
319. G. Szönyi, *Adv. Chem. Ser.*, No. 70, 53 (1968).
320. R. Jira and W. Freiesleben, *Organomet. React.*, **3**, 1 (1972).
321. P. M. Henry, *J. Am. Chem. Soc.*, **88**, 1595 (1966).
322. *Russ. Pat.*, 189415 (1966).
323. W. G. Lloyd and B. J. Luberoff, *J. Org. Chem.*, **34**, 3949 (1969).
324. W. H. Clement and C. M. Selwitz, *J. Org. Chem.*, **29**, 241 (1964).
325. D. R. Fahey and A. E. Zuech, *J. Org. Chem.*, **39**, 3276 (1974).
326. J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, **17**, 2975 (1976).
327. J. E. Bäckwall, B. Åkermark, and S. O. Ljunggren, *J. Chem. Soc., Chem. Commun.*, 264 (1977); *J. Am. Chem. Soc.*, **101**, 2411 (1979).
328. J. K. Stille and R. Divakaruni, *J. Organomet. Chem.*, **169**, 239 (1979); *J. Am. Chem. Soc.*, **100**, 1303 (1978).
329. B. Åkermark, B. C. Söderberg, and S. S. Hall, *Organometallics*, **6**, 2608 (1987).
330. P. M. Henry, *J. Am. Chem. Soc.*, **86**, 3246 (1964).
331. R. Hamilton, T. R. B. Mitchell, J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 456 (1981).
332. K. Januszkiewicz and H. Alper, *Tetrahedron Lett.*, **24**, 5159 (1983).
333. M. Perrèe-Fauyet and A. Gaudemer, *J. Chem. Soc., Chem. Commun.*, 874 (1981).
334. M. T. Atlay, M. Preece, G. Strukul, and B. R. James, *J. Chem. Soc., Chem. Commun.*, 406 (1982).
335. L. Carlton, G. Read, and M. Urgelles, *J. Chem. Soc., Chem. Commun.*, 586 (1983).

336. L. Carlton and G. Read, *J. Mol. Catal.*, **10**, 133 (1981).
337. M. T. Atlay, L. Carlton, and G. Read, *J. Mol. Catal.*, **19**, 57 (1983).
338. R. S. Drago, A. Zuzick, and E. D. Nyberg, *J. Am. Chem. Soc.*, **107**, 2898 (1985).
339. M. A. Andrews and K. P. Kelly, *J. Am. Chem. Soc.*, **103**, 2894 (1981).
340. S. Korcek, J. H. B. Chenier, J. A. Howard, and K. U. Ingold, *Can. J. Chem.*, **50**, 2285 (1972).
341. W. Pritzkow, R. Radeglia, and W. Schmidt-Renner, *Neftekhimiya*, **19**, 885 (1979).
342. A. S. Hay, *J. Org. Chem.*, **25**, 1275 (1960).
343. G. Eglinton and A. R. Galbraith, *J. Chem. Soc.*, 889 (1959).
344. G. Eglinton and W. McCrae, *Adv. Org. Chem.*, **4**, 225 (1963).
345. N. Rabjohn, *Org. React.*, **5**, 331 (1939).
346. B. Chabaud and K. B. Sharpless, *J. Org. Chem.*, **44**, 4202 (1979).
347. H. Gopal and A. J. Gordon, *Tetrahedron Lett.*, **12**, 2941 (1971).
348. N. A. Khan and M. S. Newman, *J. Org. Chem.*, **17**, 1063 (1952).
349. R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, Academic Press, New York, 1955, p. 31.
350. F. P. Ballistreri, S. Failla, G. A. Tomaselli, and R. Curci, *Tetrahedron Lett.*, **27**, 5139 (1986).
351. M. Schroder, A. J. Nielson, and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1607 (1979).
352. L. T. Simándi, in *The Chemistry of Functional Groups, Supplement C* (Eds S. Patai and Z. Rappoport), Wiley, Chichester, 1983, p. 547.
353. D. G. Lee, E. J. Lee, and W. D. Chandler, *J. Org. Chem.*, **50**, 4306 (1985).
354. N. A. Milas, *US Pat.*, 2347358 (1944).
355. L. Bassignani, A. Brandt, V. Caciagli, and L. Re, *J. Org. Chem.*, **43**, 4245 (1978).
356. P. Müller and J. Godoy, *Helv. Chim. Acta*, **64**, 2531 (1981).
357. J. Tsuji, M. Takahashi, and T. Takahashi, *Tetrahedron Lett.*, **21**, 849 (1980).
358. A. L. Alexandrov and E. T. Denisov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8**, 1652 (1969).
359. W. Brackman and C. J. Gaasbeek, *Recl. Trav. Chim. Pays-Bas*, **85**, 242 (1966).
360. P. J. A. C. Camerman and J. D. V. Hanotier, *Br. Pat.*, 1275699 (1972).
361. T. F. Blackburn and J. Schwartz, *J. Chem. Soc., Chem. Commun.*, 157 (1977).
362. G. Speier and L. Markó, *J. Organomet. Chem.*, **210**, 253 (1981).
363. B. S. Tovrog, S. E. Diamond, and F. Mares, *J. Am. Chem. Soc.*, **101**, 5067 (1979).
364. R. Tang, S. E. Diamond, N. Neary, and F. Mares, *J. Chem. Soc., Chem. Commun.*, 562 (1978).
365. G. A. Hamilton, P. U. Adolf, J. de Jersey, G. C. Dubois, G. A. Dyrkacz, and R. D. Libby, *J. Am. Chem. Soc.*, **100**, 1899 (1978).
366. N. Kitajima, U. Whang, Y. Moro-Oka, A. Uchida, and Y. Sasada, *J. Chem. Soc., Chem. Commun.*, 1504 (1986).
367. M. P. Doyle, U. J. Patrie, and S. B. Williams, *J. Org. Chem.*, **44**, 2955 (1979).
368. M. Li. Mihailovic, S. Konstantinovic, and R. Vukicevic, *Tetrahedron Lett.*, **27**, 2287 (1986).
369. K. Kaneda, Y. Kawaniski, and S. Teranishi, *Chem. Lett.*, 1481 (1984).
370. S.-I. Mirahashi, T. Naota, and N. Nahajima, *Tetrahedron Lett.*, **26**, 925 (1985).
371. W. A. Waters and J. S. Littler, in *Oxidation in Organic Chemistry, Part A* (Ed. K. B. Wiberg), Academic Press, New York, 1965, p. 186.
372. G. Green, W. P. Griffith, D. M. Hollinshead, S. V. Ley, and M. Schroder, *J. Chem. Soc., Perkin Trans. 1*, 681 (1984).
373. A. C. Denyel, R. A. Hudorn, and W. P. Griffith, *Transition Met. Chem.*, **10**, 98 (1985).
374. A. M. Maione and A. Romes, *Synthesis*, 955 (1984).
375. K. V. Uma and S. M. Mayanna, *J. Catal.*, **61**, 165 (1980).
376. K. S. Kim, S. J. Kim, Y. H. Song, C. S. Hahn, *Synthesis*, 1017 (1987).
377. A. S. Perlin, in *Oxidation* (Ed. R. L. Augustine), Vol. 1, Marcel Dekker, New York, 1969, p. 189.
378. C. A. Bunton, in *Oxidation in Organic Chemistry, Part 1* (Ed. K. B. Wiberg), Academic Press, New York, 1965, p. 367.
379. G. de Vries and A. Schors, *Tetrahedron Lett.*, **9**, 5689 (1968).
380. N. Ueyama, K. Kamabuchi, and A. Nakamura, *J. Chem. Soc., Dalton Trans.*, 635 (1985).
381. L. M. Sayre and S.-J. Jin, *J. Org. Chem.*, **49**, 3498 (1984).
382. W. G. Nigh, in *Oxidation in Organic Chemistry, Part B* (Ed. W. J. Trahanovsky), Academic Press, New York, 1973, p. 1.
383. H. T. Clarke and E. E. Dreger, *Org. Synth., Collect. Vol.*, **1**, 87 (1932).
384. A. T. Blomquist and A. Goldstein, *Org. Synth.*, **36**, 77 (1956).
385. G. Speier, *Acta Chim. Hung.*, **124**, 155 (1987).

386. F. P. Greenspan and H. M. Woodburn, *J. Am. Chem. Soc.*, **76**, 6345 (1972).
387. G. Gut, R. V. Falkenstein, and A. Guyer, *Chimia*, **19**, 581 (1965).
388. Y. Masuyama, M. Usukura, and Y. Kurusu, *Chem. Lett.*, 1951 (1982).
389. N. Ueyama, T. Sugawara, A. Kajiwara, and A. Nakamura, *J. Chem. Soc., Chem. Commun.*, 434 (1986).
390. R. I. Murray and S. G. Sligar, *J. Am. Chem. Soc.*, **107**, 2186 (1985).
391. L.-C. Yuan, T. C. Calderwood, and T. C. Bruice, *J. Am. Chem. Soc.*, **107**, 8273 (1985).
392. J. A. John and F. J. Weymonth, *Chem. Ind. (London)*, 62 (1962).
393. G. Benson, *Chem. Metall. Eng.*, **47**, No. 3, 150 (1940).
394. G. C. Allen and A. Augilo, *Adv. Chem. Ser.*, No. 76, 363 (1968).
395. A. S. Hester and K. Kimmler, *Ind. Eng. Chem.*, **51**, 1424 (1959).
396. C. E. H. Bawn and J. E. Jolley, *Proc. R. Soc. London, Ser. A*, **236**, 297 (1956).
397. F. Márta, E. Boga, and M. Matic, *Discuss. Faraday Soc.*, **46**, 173 (1968).
398. M. Zawadzki and J. J. Ziolkowski, *React. Kinet. Catal. Lett.*, **10**, 119 (1979).
399. J. M. Church and L. Lynn, *Ind. Eng. Chem.*, **42**, 768 (1950).
400. W. Brackman and P. J. Smit, *Recl. Trav. Chim. Pays-Bas*, **82**, 757 (1963).
401. A. Abiko, J. C. Roberts, T. Takemasa, and S. Masamune, *Tetrahedron Lett.*, **27**, 4537 (1986).
402. H. J. den Hertog and E. C. Kooyman, *J. Catal.*, **6**, 357 (1966).
403. E. N. Trachtenberg, in *Oxidation* (Ed. R. L. Augustine), Vol. 1, Marcel Dekker, New York, 1969, p. 119.
404. H. L. Riley, J. F. Morley, and N. A. C. Friend, *J. Chem. Soc.*, 1875 (1932).
405. H. A. Riley and A. R. Gray, *Org. Synth., Collect. Vol.*, **2**, 509 (1943).
406. G. B. Payne and C. W. Smith, *J. Org. Chem.*, **22**, 1680 (1957).
407. W. D. Dittmann, W. Kirchoff, and W. Stumpf, *Justus Liebigs Ann. Chem.*, **681**, 30 (1965).
408. C. W. Smith and R. T. Holm, *J. Org. Chem.*, **22**, 746 (1957).
409. S. E. Jacobson, F. Mares, and P. M. Zambri, *J. Am. Chem. Soc.*, **101**, 6938 (1979).
410. S. E. Jacobson, R. Tang, and F. Mares, *J. Chem. Soc., Chem. Commun.*, 888 (1978).
411. A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Am. Chem. Soc.*, **81**, 6335 (1959).
412. A. S. Hay, *J. Polym. Sci.*, **58**, 581 (1962).
413. A. S. Hay, *Adv. Polym. Sci.*, **4**, 496 (1967).
414. H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966).
415. G. F. Endres, A. S. Hay, and J. W. Eustance, *J. Org. Chem.*, **28**, 1300 (1963).
416. S. Tsuruya, T. Shirai, T. Kawamura, and T. Yonezawa, *Makromol. Chem.*, **132**, 57 (1970).
417. B. Feringa and H. Wynberg, *Tetrahedron Lett.*, **18**, 4447 (1977).
418. Y. Takizawa, T. Munakata, Y. Iwasa, T. Suzuki, and T. Mitsuhashi, *J. Org. Chem.*, **50**, 4383 (1985).
419. C. E. Koning, G. Challa, F. B. Hulsbergen, and J. Reedijk, *J. Mol. Catal.*, **34**, 355 (1986).
420. L. H. Vogt, J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).
421. E. L. Reilly, to DuPont, *Br. Pat.*, 1 511 813 (1978).
422. P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, **24**, 5611 (1983).
423. A. J. de Jong and R. van Helden, to Shell, *Ger. Pat.*, 2 460 665 and 2 517 870 (1975).
424. A. Nishinaga, K. Watanabe, and T. Matsuura, *Tetrahedron Lett.*, **15**, 1291 (1974).
425. B. B. Corden, R. S. Drago, and R. P. Perito, *J. Am. Chem. Soc.*, **107**, 2903 (1985).
426. S. A. Bedell and A. E. Martell, *J. Am. Chem. Soc.*, **107**, 7909 (1985).
427. A. Gaudemer, K. Nguyen-Van-Duong, N. Shahkarami, S. S. Achi, M. Frostin-Rio, and D. Pujol, *Tetrahedron*, **41**, 4035 (1985).
428. M. Frostin-Rio, D. Pujol, C. Bied-Charreton, M. Perree-Fauvet, and A. Gaudemer, *J. Chem. Soc., Perkin Trans. 1*, 1971 (1984).
429. G. Speier, *J. Mol. Catal.*, **37**, 259 (1986).
430. W. Brackman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **74**, 937, 1021, 1070, 1100, 1107 (1955).
431. T. Funabiki and H. Sakamoto, *J. Chem. Soc., Chem. Commun.*, 754 (1979).
432. T. Funabiki, A. Mizoguchi, T. Sugimoto, S. Tada, M. Tsuji, H. Sakamoto, and S. Yoshida, *J. Am. Chem. Soc.*, **108**, 2921 (1986).
433. J. Tsuji and H. Takayanagi, *J. Am. Chem. Soc.*, **96**, 7349 (1974).
434. J. Tsuji, H. Takayanagi, and I. Sakai, *Tetrahedron Lett.*, **16**, 1245 (1975).
435. J. Tsuji and H. Takayanagi, *Tetrahedron Lett.*, **17**, 1365 (1976).
436. M. M. Rogic, T. R. Demmin, and W. B. Hammond, *J. Am. Chem. Soc.*, **98**, 7441 (1976).

437. M. M. Rogic and T. R. Demmin, *J. Am. Chem. Soc.*, **100**, 5472 (1978).
438. G. Speier and Z. Tyeklár, *J. Chem. Soc., Dalton Trans.*, 1995 (1983).
439. M. C. Weller and U. Weser, *Inorg. Chim. Acta*, **107**, 243 (1985).
440. Y. Tatsuno, M. Tatsuda, and S. Otsuka, *J. Chem. Soc., Chem. Commun.*, 1100 (1982).
441. M. Matsumoto and K. Kuroda, *J. Am. Chem. Soc.*, **104**, 1433 (1982).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited By F. R. Hartley

CHAPTER 6

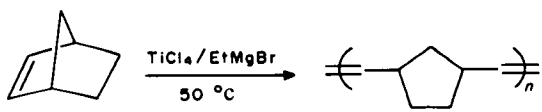
Olefin metathesis

W. JAMES FEAST and VERNON C. GIBSON

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK

I. INTRODUCTION

Olefin metathesis is a relatively new addition to the armoury of transition metal-mediated reactions available to the synthetic organic chemist. It is generally agreed that the first example of the reaction, which was identified as such with the wisdom of hindsight, was the ring-opening polymerization of bicyclo[2.2.1]hept-2-ene (equation 1) described in a DuPont Patent as recently as 1955[1]. Shortly after this a series of patents relating to the



(1)

catalysed exchange or disproportionation reactions of acyclic olefins appeared (equation 2).

$$2RCH{=}CHR' \rightleftharpoons RCH{=}CHR + R'CH{=}CHR' \qquad (2)$$

The term 'olefin metathesis' which is now in general use was not introduced in the literature until 1967, when it appeared in an unattributed news item describing the work of a Goodyear research group led by Calderon[2]. The word metathesis is in common use in chemistry, carrying the implication that during a metathesis reaction two units which individually comprise part of a larger entity are interchanged between pairs of such larger entities. In the case of 'olefin metathesis' it is alkylidene units, pairs of which constitute an olefin, which are exchanged. Calderon is credited with introducing the term and with the more important realization that the ring-opening polymerization of cycloalkenes and the olefin exchange or disproportionation reactions of acyclic olefins are, in fact, examples of the same general reaction type.

In this chapter we describe the mechanism of the reaction, the types of catalyst or initiator systems which can be used, the range of substrates which are susceptible, and the applications of the reaction which have been established both in academic research and in commercial industrial practice. The subject is vast and at the time this chapter was in preparation some parts of it were expanding rapidly; inevitably, in these circumstances, the view presented here is selective rather than comprehensive, with emphasis on more recent results. More detailed reviews of particular aspects of the subject are referenced at appropriate points in the text, and Ivin's book[3] provides an authoritative and comprehensive review of the literature through to the end of 1982.

Readers resorting to the original literature should be wary in their evaluation of some of the early experimental reports and the mechanistic rationalizations which have been published. Some aspects of the experimental work appear to have suffered from an element of irreproducibility, and some unsustainable mechanistic rationalizations were espoused long after their experimental refutation. These problems are by no means unique to the field of olefin metathesis, of course.

In this chapter we deal exclusively with the metathesis of carbon—carbon double bonds; other multiple bonds undergo metathesis and their chemistries are covered elsewhere[4].

II. THE MECHANISM

The generally accepted mechanism for the olefin metathesis reaction is shown in equation 3. First proposed by Herisson and Chauvin in 1970[5], it involves a reversible [2 + 2] cycloaddition of a carbon—carbon double bond to a metal carbene with the formation of a metallacyclobutane intermediate **1**.

$$\begin{array}{l} CHR \\ \| \\ [M] \end{array} + \begin{array}{l} CHR^1 \\ \| \\ CHR^2 \end{array} \rightleftharpoons \left[\begin{array}{c} RHC{-}CHR^1 \\ \quad | \quad | \\ [M]{-}CHR^2 \end{array}\right] \rightleftharpoons \begin{array}{l} RHC{=}CHR^1 \\ \quad + \\ [M]{=}CHR^2 \end{array} \qquad (3)$$

(1)

Fragmentation of **1** can then either regenerate the starting olefin and carbene or lead to a new carbene complex and olefin. The latter is termed *productive metathesis*, which is readily distinguishable by the observation of new olefinic species. A second commonly occurring process is one in which an identical olefin is generated. Such a process is called *degenerate metathesis* and can only be detected by isotope labelling (equation 4). *Degenerate metathesis* is particularly prevalent for terminal olefins which consequently appear to undergo metathesis at a much slower rate than internal olefins. Observations of

the chain carrying alkylidene species[6,7] and labelling studies[8] suggest that the substituted alkylidenes formed during the process are more stable than their methylidene counterparts, favouring addition in the direction shown in equation 5, i.e. with the substituted carbon adjacent to the metal centre.

$$\begin{array}{c} RHC \quad CD_2 \\ \| \; + \; | \\ H_2C \quad CHR^1 \end{array} \rightleftharpoons \begin{array}{c} RHC{=}CD_2 \\ + \\ H_2C{=}CHR^1 \end{array} \tag{4}$$

$$\begin{array}{c} RHC{=}CD_2 \\ + \\ [M]{=}CHR \end{array} \rightleftharpoons \left[\begin{array}{c} RHC{-}CD_2 \\ | \quad | \\ [M]{-}CHR \end{array}\right] \rightleftharpoons \begin{array}{c} RHC \quad CD_2 \\ \| \; + \; | \\ [M] \quad CHR \end{array} \tag{5}$$

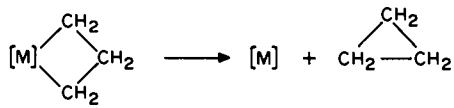
Another commonly encountered metathesis process is *self-metathesis*, which arises when two identical unsymmetric olefins undergo metathesis to yield a pair of symmetric olefins (equation 6).

$$\begin{array}{c} R'CH{=}CHR'' \\ + \\ R'CH{=}CHR'' \end{array} \rightleftharpoons \begin{array}{c} R'CH \quad CHR'' \\ \| \; + \; | \\ R'CH \quad CHR'' \end{array} \tag{6}$$

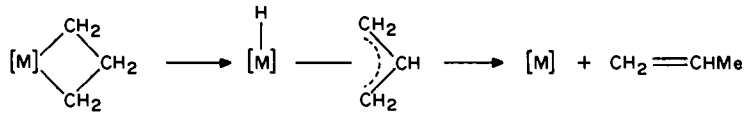
As the metathesis process is essentially thermoneutral for acyclic olefins, a statistical distribution of all the olefin alkylidene fragments eventually results. Furthermore, metathesis catalysts also often promote isomerization of the olefin substrates and so, for a mixture of two olefins in which all the alkylidene end-groups possess different substituents, an extremely complex mixture of product olefins could be formed. In practice, for simple olefins such a mixture is avoided since the number of possible combinations is limited, and for terminal olefins the situation may be simplified further by removal of the volatile ethylene component to drive the equilibrium of equation 7 to the right.

$$2RCH{=}CH_2 \rightleftharpoons RCH{=}CHR + CH_2{=}CH_2 \tag{7}$$

The two most commonly occurring side-reactions of the metathesis process arise owing to alternative decomposition pathways for the intermediate metallacycle. In one case, reductive elimination of the metallacycle C_3 fragment (equation 8) affords three-membered rings (*cyclopropanation*). In the other, rearrangement of the metallacycle occurs to give a homologated olefin (equation 9). The mechanism of the latter is not well understood but is believed to proceed via β-hydrogen elimination from the metallacycle followed by hydrogen transfer to what is most likely to be a transient allyl intermediate. The stability of the metallacycle to such side-reactions can be controlled, and so generally they do not prove troublesome in metathesis reactions.

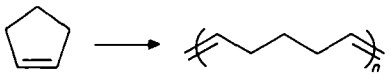


(8)

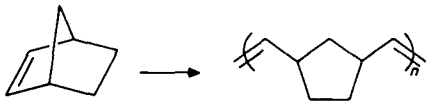


(9)

If the carbon—carbon double bond is contained within a ring then, depending on the 'polymerizability' of the ring system, a polymer containing unsaturated C=C linkages will result. The first ring-opening polymerizations of this type to be clearly documented were the conversion of cyclopentene to polypentenamer (equation 10), a finely balanced equilibrium process, and the more thermodynamically favourable ring opening of bicyclo[2.2.1]hept-2-ene (norbornene) derivatives to polynorbornenes (equation 11)[1,9–11]. Only the second of these reaction has so far been commercialized[12], although several companies have also developed the ring-opening polymerization of cyclopentene to the pilot plant stage. The product, polypentenamer, is a good general-purpose elastomer but, as yet, economic conditions have not justified the investment necessary for its production.

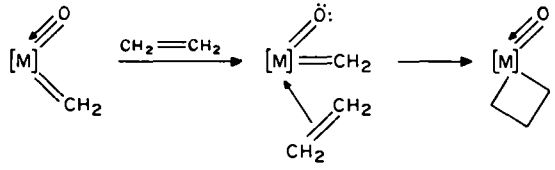


(10)



(11)

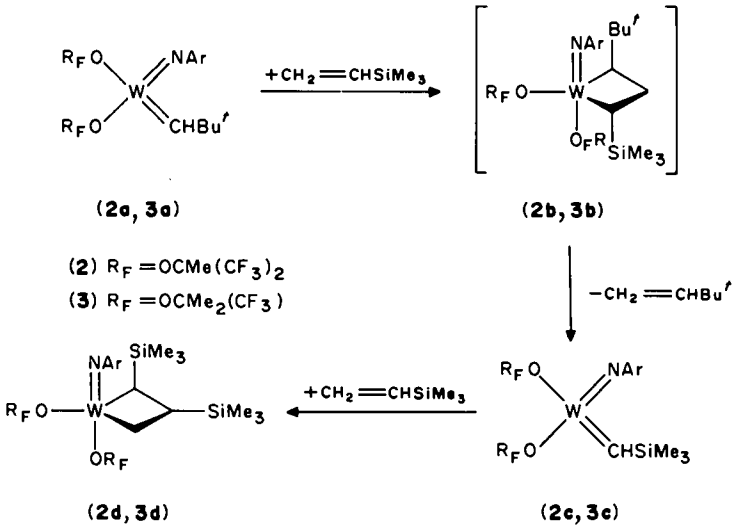
For efficient metathesis, the metallacycle and carbene–olefin complex should be close in energy with a low energy barrier between them. Experimentally determined rates indicate activation barriers in the range 30–60 kJ mol^{-1} [13–18], and the process also appears to be favoured by the presence of π-donor ligands such as oxo or imido[6,7,19]. *Ab initio* calculations by Rappé and Goddard[20] on the addition of C_2H_4 to a $Mo{=}CH_2$ fragment in the presence of a 'spectator oxo' ligand show that the process is considerably more favourable than when the oxo ligand is absent, an effect which has been attributed to the ability of π-donor ligands such as oxo or imido to form pseudo-triple bonds and thus stabilize the more oxidized metallacycle form (equation 12). The oxo ligand is effectively acting to reduce the barrier between carbene and metallacycle form and provides a rationale for the beneficial effect of trace amounts of oxygen in classical catalyst formulations. Indeed, some of the most active well defined carbene catalysts possess ancilliary oxo[6,7] and imido ligands[19,21].



(12)

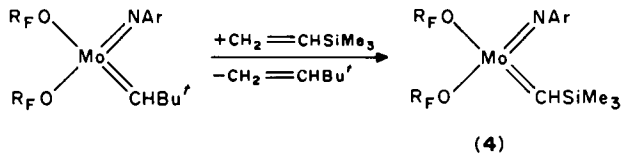
It is only in relatively recent years that both discrete carbene and metallacyclobutane complexes have been synthesized and shown to be active in olefin metathesis. However, studies of their reactivity have reinforced many of the previously held beliefs concerning the involvement of carbenes and metallacycle intermediates in classical formulations. Studies on the carbene catalysts $[M(CHBu^t)(NAr)(OR)_2]$ (M=Mo, W) have shown that the difference in energy between the carbene and metallacycle may indeed be very small and strongly influenced by the nature of the metal and attendant ligands. Thus, the

tungsten metathesis catalyst **2a** containing $OCMe(CF_3)_2$ ligands reacts with excess vinyltrimethylsilane to give the tungstacyclobutane complex **2d** containing α- and β-trimethylsilyl groups[19] (equation 13).



(13)

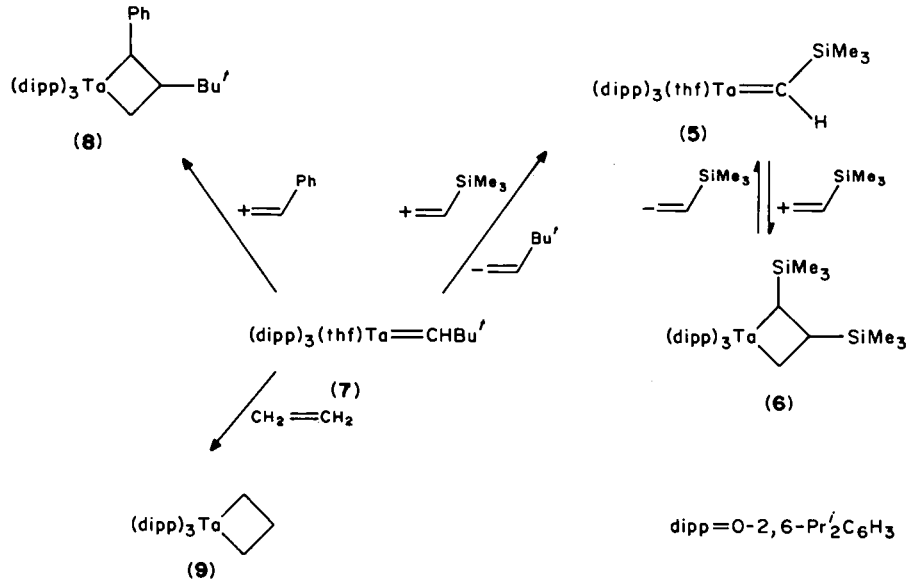
Neohexane is the only metathesis product observed at 25 °C, suggesting that the initial WC_3 ring containing α-Bu^t and α-$SiMe_3$ groups (**2b**) is unstable to loss of neohexene. However, if the alkoxide ligands are exchanged for the less electron-withdrawing $OCMe_2(CF_3)$, the trimethylsilylcarbene complex **3c** is favoured over the metallacycle form **3d**; hence the stability of the metallacycle correlates well with the electrophilicity of the metal centre. A similar effect is seen on changing the metal to molybdenum, where the trimethylsilyl carbene **4** (equation 14) forms in preference to the metallacyclobutane.



(14)

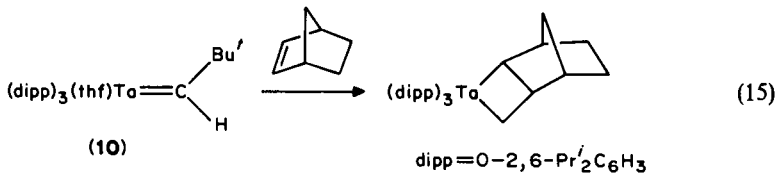
These observations suggest that olefin is lost more readily from the molybdacyclobutane than the tungstacyclobutane[21], consistent with the decreased electrophilicity of molybdenum.

There is some evidence for an equilibrium between the carbene **3c** and metallacycle **3d** in the presence of excess vinyltrimethylsilane. Such an equilibrium is observed readily in a related tantalum system, where the carbene **5** is observed to be in equilibrium with the metallacyclobutane complex **6**[22] (Scheme 1). In contrast, styrene reacts with **7** to give **8**, and no carbene is observed in this case, or in the reaction with C_2H_4 to give the tantalacyclobutane **9**.

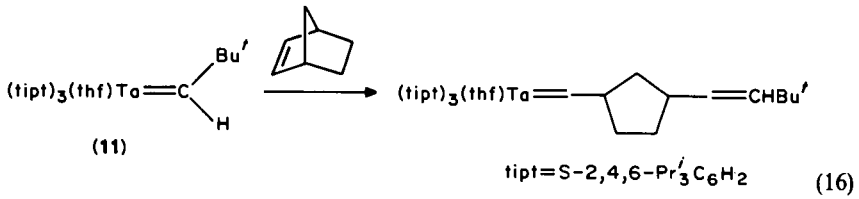


SCHEME 1

Dramatic effects on carbene and metallacycle stability have also been seen on changing from O- to S-based ancillary ligands. The tantalum complexes **10** and **11** will both initiate the ring-opening polymerization of norbornene. However, a metallacycle chain-propagating species prevails in the case of **10** (equation 15) whereas a carbene propagating species is found for **11**[22] (equation 16). This may be attributed to the reduced electrophilicity of the metal centre in the presence of the soft phenyl thiolate ligands.



(15)



(16)

The simultaneous presence and co-existence of carbene and metallacyclobutane complexes has recently been observed in a catalytic olefin metathesis reaction. On reaction

of $[W(CHBu^t)(OCH_2Bu^t)_2Br_2]$ with norbornene in the presence of $GaBr_3$, n.m.r. signals attributable both to chain-propagating carbene and metallacycle species were observed[23,24].

III. THE CATALYSTS

A wide variety of homogeneous and heterogeneous formulations will catalyse the olefin metathesis reaction. The most commonly used catalysts are based on molybdenum, tungsten, and rhenium, although metals from Groups 4, 5, 8, and 9 of the transition series have also been shown to be active.

A. Classical Catalyst Systems

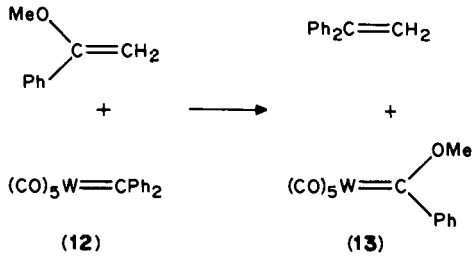
These catalysts were the first to be established and typically involve two or more components (often a Lewis acid and an alkyltin co-catalyst). They can be divided into heterogeneous and homogeneous systems, although the distinction between truly homogeneous systems and those involving fine particulate suspensions has not always been easy to discern. Heterogeneous formulations include those based on mixed metal oxides such as Re_2O_7–Al_2O_3[25–28], MoO_3–CoO–Al_2O_3[29,30], and WO_3–SiO_2[31–33] and supported systems obtained by treatment of SiO_2 or Al_2O_3 with soluble organometallic precursors such as $[(\eta^3\text{-}C_3H_5)_4M]$ (M = Mo[34–39], W[40]) or $[M(CO)_6]$ (M = Mo[41–44], W[41]). Many more complex multi-component formulations have also been investigated with a view to controlling selectivity, and the reader is referred to Ivin's book[3] for further details. Examples of homogeneous catalyst formulations are $[Mo(NO)_2(L)_2Cl_2]$–$[R_3Al_2Cl_3]$[45–48] (L = py, PPh_3; R = Me, Et), WCl_6–$EtAlCl_2$–EtOH[49,50], $WOCl_4$–$SnMe_4$[51], $MeReO_3$–$AlCl_3$[52], and $[Re(CO)_5Cl]$–$EtAlCl_2$[53]. Many of these and closely related species have also been supported on polymer resins[54–57].

Most of our early understanding of the metathesis reaction relied on empirical findings using classical catalyst formulations. Unfortunately, the activity of a given formulation was often found to be dependent on a number of factors, including its chemical, thermal, and mechanical history, and the order and rate of mixing of catalyst, olefin, and co-catalyst. This consequently nurtured the development of something approaching 'black art' in the preparation of such catalysts and contributed to the early difficulties associated with studying the intricacies of the olefin metathesis process. It is therefore to the credit of the many dedicated workers in this field that the essential details of the metathesis process were elucidated against these odds, and many of the early conclusions are now being confirmed by studies on well defined initiator systems.

B. Carbene Catalysts

Since the discovery of metal carbenes in 1964[58], a wide variety have been isolated and many have been shown to be reactive in olefin metathesis, although not usually at rates approaching classical formulations. The first carbenes to be isolated, the heteroatom-stabilized Fischer carbenes of the type $[(CO)_5M{=}C(OR)R']$ (M = Cr, W; R = Me; R' = Ph) showed disappointing activity as olefin metathesis catalysts, reacting only with strained cyclic olefins such as cyclobutenes and norbornenes[59]. Their activity may be increased considerably by addition of a Lewis acid co-catalyst, but the role and fate of the carbene ligand are no longer certain.

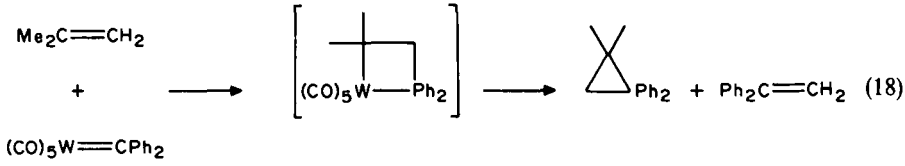
The diphenylcarbene complex **12**, first reported by Casey and Burkhardt[60] in 1973, is considerably more active. It will initiate the ring-opening polymerization of a range of cyclic olefins and catalyse the metathesis of enol ethers cleanly (equation 17) to give the methoxycarbene **13**[61].



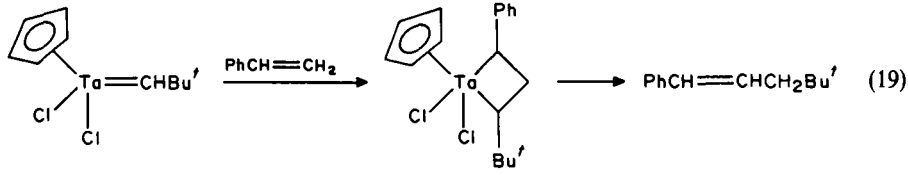
(12) (13) (17)

A clean metathesis appears to be favoured by the formation of the energetically favoured heteroatom-stabilized carbene **13**. When the reaction is carried out with isobutene, cyclopropanation becomes competitive[61] (equation 18).

The second type of transition metal complex containing metal—carbon double bonds, the high-valent nucleophilic carbenes (or alkylidenes), were discovered by Schrock[62] in 1974, the first example being $[Ta(CHCMe_3)(CH_2CMe_3)_3]$. Many are now known for the metals Ta, Nb, W, and Ti[63] containing a variety of ancillary ligands, but again, most show disappointing activity as metathesis catalysts. Nevertheless, together with their heteroatom-stabilized counterparts, much has been learnt about the metathesis reaction from a study of these first carbene complexes. Most of the niobium and tantalum alkylidene complexes were found to react with olefins, but metathesis was not observed; instead, homologated products were formed as a result of rearrangement of intermediate metallacyclobutanes. An example is the reaction of $[CpTa(CHBu^t)Cl_2]$ (**14**) with styrene to give a stable metallacyclobutane (**15**), which then rearranges via β-hydrogen abstraction to the homologated olefin[64] (equation 19).



(18)



(14) (15) (19)

The complexes $[M(CHR)L_2X_3]$ (M = Nb, Ta; R = Bu^t, Ph; L = phosphine; X = Cl, Br) were found to react similarly[65]. However, by changing two of the halide ligands for *tert*-butoxide, the rearrangement of the intermediate metallacyclobutane is slowed sufficiently to allow clean metathesis to give the new olefin and alkylidene complex **16** (equation 20).

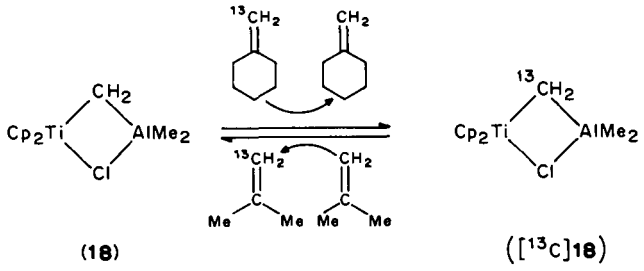
$$[Ta(CHBu^t)(OBu^t)_2Cl(PMe_3)] + PhCH{=}CH_2 \longrightarrow [Ta(CHPh)(OBu^t)_2Cl(PMe_3)]_x$$
(16)

$$\downarrow PMe_3$$

$$CH_2{=}CHBu^t + Bu^tCH{=}CHPh + [Ta(CHPh)(OBu^t)_2Cl(PMe_3)_2]$$
(17) (20)

The benzylidene complex **17** may be isolated by addition of PMe_3 but the tantalum–methylidene species did not prove sufficiently stable for isolation. This system demonstrates well the influence of ancillary ligands on metathetical activity, since exchanging just one of the halide ligands for a *tert*-butoxide gives a mixture of metathesis and rearrangement products.

The first example of a well defined carbene complex in which olefin incorporation could be observed in n.m.r. was reported by Tebbe *et al.*[66] in 1979. They reacted the methylene-bridged titanium–aluminium complex **18** (Tebbe reagent) with ^{13}C-labelled 1,1-disubstituted olefins and showed that the ^{13}C label of the olefin methylidene unit exchanges, albeit slowly, into the bridging methylene site of the complex (equation 21).



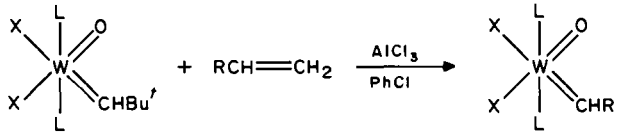
(18) **([^{13}C]18)** (21)

In the same year, Schrock *et al.*[67] isolated a far more active catalyst from the transfer of a neopentylidene group from tantalum to tungsten, resulting in the oxo neopentylidene complex **19** (equation 22).

$$[Ta(CHBu^t)X_3L_2] + [W(O)(OBu^t)_4] \longrightarrow [Ta(OBu^t)_4X] + [W(O)(CHBu^t)X_2L_2]$$
(19) (22)

$$L = PMe_3, PEt_3;\ X = Cl, Br$$

In the presence of $AlCl_3$ co-catalyst, **19** will metathesize terminal olefins (equation 23) and *cis*-pent-2-ene[7].



(19) R = H, Et, Ph (23)

All of the new alkylidenes including methylidene are observable by n.m.r. The role of the Lewis acid co-catalyst is believed to involve removal of either halide or phosphine, resulting in cationic or neutral 5-coordinate species, respectively. There is evidence for the existence of both of these types of species[7], and the cationic complexes have been shown to be productive in the metathesis of *cis*-pent-2-ene[63]. The oxo ligand of **19** is thought to have an important influence on the reactivity of the alkylidene ligand and the stability of the intermediate metallacycles. Thus, whereas the electron-deficient tantalum–neopentylidene complexes give rise to metallacycle rearrangement, the good π-donating ability of the oxo ligand, potentially acting as a 4-electron donor, may stabilize an 18-electron-metallacycle complex and disfavour rearrangement pathways. It has also been noted from these studies that the presence of ancillary phosphine ligands may not be particularly advantageous for metathesis since there is some indication of their involvement in termination[63] (equation 24).

$$[W(O)(CH_2)(PEt_3)_2Cl_2] + C_2H_4 \longrightarrow [W(O)(C_2H_4)(CH_2PEt_3)(PEt_3)Cl_2] \quad (24)$$

Tungsten–neopentylidene complexes (**22**) without phosphine ligands have recently been prepared[68] according to equation 25.

$$\underset{(\mathbf{20})}{[W(O)(OCH_2Bu^t)_2(CH_2Bu^t)_2]} + AlX_3 \longrightarrow \underset{(\mathbf{21})}{[W(OAlX_3)(OCH_2Bu^t)_2(CH_2Bu^t)_2]} \quad (25)$$

$$\downarrow$$

$$[W(CHBu^t)(OCH_2Bu^t)_2X_2]$$
$$(\mathbf{22})\ X = Cl, Br$$

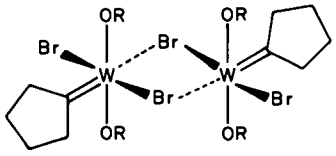
Aluminium halides bind to the terminal oxo ligand of **20** to give the intermediate **21** before rearrangement occurs to the neopentylidene species **22**. In the presence of MX_3 (M = Ga, Al; X = Cl, Br), these are found to be extraordinarily active metathesis catalysts. It has been suggested that the equilibria shown in equation 26 are set up in solution[69,70], with the tetracoordinate cationic complex **24** being the most active species.

$$\underset{(\mathbf{22})}{[W(CHBu^t)(OCH_2Bu^t)_2X_2]} + GaBr_3 \rightleftharpoons \underset{(\mathbf{23})}{[W(CHBu^t)(OCH_2Bu^t)_2X_2].GaBr_3} \quad (26)$$

$$\rightleftharpoons$$

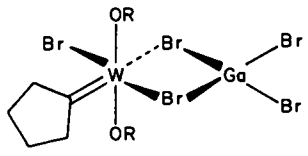
$$\underset{(\mathbf{24})}{[W(CHBu^t)(OCH_2Bu^t)_2Br]^+[GaBr_4]^-}$$

An X-ray structural study on a cyclopentylidene analogue[71] of **22** revealed two weakly associated pentacoordinate tungsten units with weak tungsten—bromine bridges (**25**). N.m.r. studies indicate that the molecule is dissociated in solution.



$R = CH_2Bu^t$

(**25**)



(**26**)

An analogous structure prevails in the presence of $GaBr_3$ (**26**), where one of the tungsten units is effectively replaced by the tricoordinate $GaBr_3$. However, a much stronger

interaction of Ga with the Br of the tungsten unit is apparent, consistent with previous suggestions that it readily dissociates into $GaBr_4^-$ and the highly reactive 4-coordinate cationic complex. The structures of these species offer some useful insight into the nature of the catalyst–co-catalyst interactions in classical multi-component formulations.

Basset and coworkers[72,73] have reported the related phenoxide complexes $[W(OAr)_2Cl_2(CHBu^t)(OEt_2)]$ and $[W(OAr)_2Cl(CHBu^t)(CH_2Bu^t)(OEt_2)]$ (Ar = 2,6-$Me_2C_6H_3$, 2,6-$Ph_2C_6H_3$, 2,6-$X_2C_6H_3$; X = Cl, Br) from reactions of $[W(OAr)_2Cl_4]$ with $Mg(CH_2Bu^t)_2$(dioxane) in diethyl ether and found that their stability in the presence of various co-catalysts is dependent on the nature of the *ortho* phenoxide substituents (activity decreases in the order Br > Cl > F > Ph > Me).

In 1986, neutral four coordinate alkylidene complexes of tungsten were isolated which are highly active olefin metathesis catalysts even in the absence of Lewis acids[74]. The complexes are of the general type $[W(CHBu^t)(NAr)(OR)_2]$, possessing the bulky imido ligand *N*-2,6-$Pr^i_2C_6H_3$ and alkoxide groups varying from the relatively electron-donating *tert*-butoxide to the highly electron-withdrawing $OC(CF_3)_2(CF_2CF_2CF_3)$. The benzylidene analogue, $[W(CHPh)(NAr)\{OCMe(CF_3)_2\}]$ has been shown to possess a peseudo-tetrahedral geometry[19].

The ligand orientations appear to be dominated primarily by steric interactions between the bulky imido and alkoxide ligands. However, the substituents on the alkylidene carbon lie in the same plane as the tungsten, alkylidene carbon, and imido nitrogen in order to avoid competition between W=C and the W≡N pseudo-triple bond for dπ orbitals. The W=C and W≡N distances are also relatively short, possibly owing to the low coordination number or the influence of the electron-withdrawing alkoxide ligands.

Closely related molybdenum complexes have recently been prepared by a similar method and n.m.r. data suggest that they are essentially analogous to their tungsten counterparts[21]. They are also active metathesis catalysts for a variety of olefins, although less active than their tungsten analogues, consistent with the reduced electrophilicity of the metal centre.

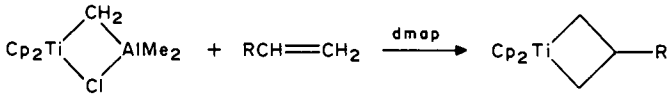
Surprisingly, neutral 4-coordinate rhenium alkylidenes of the type $[Re(NBu^t)_2(CHBu^t)(CH_2Bu^t)]$[75] and $[Re(CHBu^t)(NAr)_2(OR)]$[76] have been found to be unreactive towards ordinary and strained cyclic olefins. Here, it is believed that the rhenium centre is not sufficiently electrophilic in these neutral complexes and that cationic derivatives may be required for this metal.

C. Metallacyclobutane Catalysts

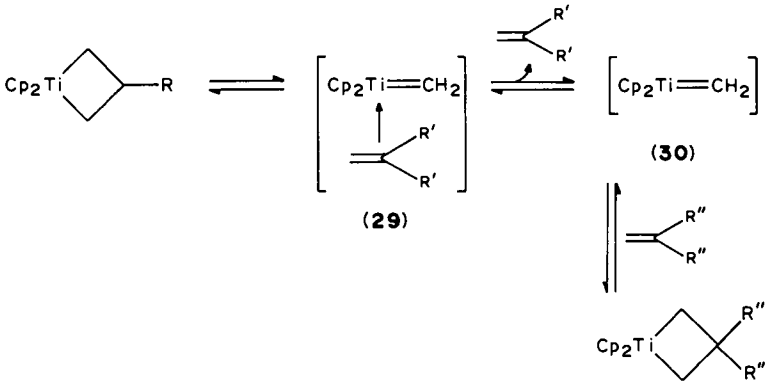
Although numerous methods now exist for preparing metallacyclobutane complexes, it is only relatively recently that these important intermediates of the olefin metathesis reaction have been observed in active metathesis systems. Consequently, it was thought that metallacyclobutanes were formed only as transient intermediates in olefin metathesis transformations. We now know that metal carbenes and metallacyclobutanes are very close in energy and may, in at least one case, even be observed simultaneously in metathesis reactions, and the metallacycle form may be the resting state of the catalyst.

The first metallacycle complexes to be isolated which are active metathesis catalysts were prepared by Grubbs and coworkers. The reaction of Tebbe reagent **27** with various olefins in the presence of nitrogen bases resulted in titanacyclobutane complexes[77,78] (equation 27).

The titanacycles **28** readily exchange with added olefins[79] via rate-determining loss of olefin from the titanacyclobutane ring to generate the transient methylidene species $Cp_2Ti{=}CH_2$ (**30**). This is in broad agreement with the results of general valence bond calculations by Upton and Rappé[80], although recent kinetic investigations have also



(27) (28) (27)



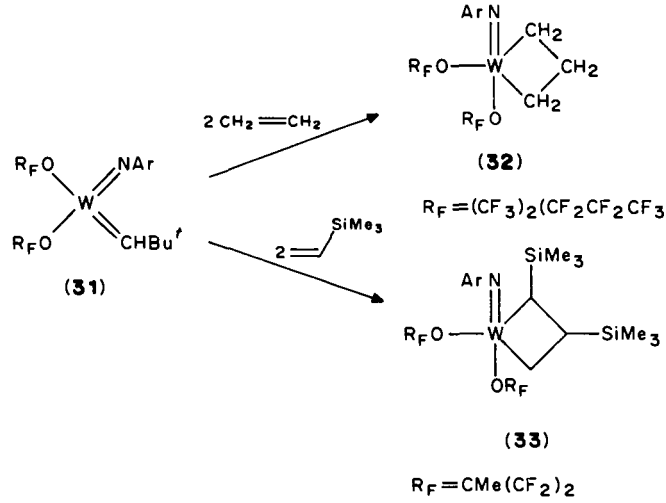
(28)

shown that an energy well exists for the olefin–titanocene methylidene adduct **29**[81] (equation 28), which was not predicted by calculation.

Grubbs and coworkers have also probed the relative energetics of the metallacycle and methylidene form through studies on the rate of metallacycle cleavage as a function of metallacycle and cyclopentadienyl ring substitution[82]. Both steric and electronic effects are found to play a role, although the electronic component appears dominant. For example, substituting electron-donating groups on to the Cp ring leads to destabilization of the metallacycle due to a build-up of electron density on the metal centre, which destabilizes the transition state in the pseudo-reductive transformation of the metallacycle to carbene–olefin form. Significant steric interactions are found between the cyclopentadienyl rings and β-carbon substituents, which will also tend to destabilize the metallacycle. The strain is partially relieved by 'rocking' of the β-carbon fragment rather than ring puckering as shown by the X-ray structures of $[Cp_2TiCH_2CH(Bu^t)CH_2]$ and $[Cp_2TiCH_2CH(Ph)CH_2]$[83]. The structures also reveal planar, symmetrical TiC_3 rings, suggesting that the metallacycle is not distorted towards the carbene–olefin form.

Metallacycle complexes have recently been isolated by Schrock *et al.*[19] from the neutral 4-coordinate carbene catalysts **31**. The tungstacyclobutane **32**, formed on treatment of $[\{(CF_3CF_2CF_2)(CF_3)_2CO\}_2W(NAr)(CHBu^t)]$ with slightly in excess of 2 equivalents of ethylene gives a flat WC_3 ring (equation 29).

A small bending of the ring is observed in the X-ray structure of **33**[19]; it is presumably due to an unfavourable steric interaction between the β-$SiMe_3$ group and the imido ligand. These tungsten complexes are close to trigonal bipyramidal, a geometry which is thought to be particularly suited to the stabilization of metallacycles in these systems[84]. The stability of the metallacycle also appears to be dependent on the electron withdrawing nature of the attendant ligands: the greater the electron-withdrawing capacity, the more electrophilic is the metal centre and consequently the less inclined it is to release olefin from the metallacycle. This is supported by the observation that changing the attendant

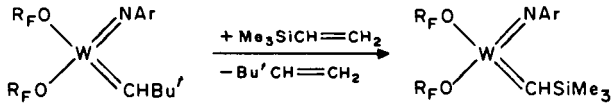


$R_F = (CF_3)_2(CF_2CF_2CF_3)$ (29)

$R_F = CMe(CF_2)_2$

fluoroalkoxide ligand from $C(CF_3)_2(CF_2CF_2CF_3)$ to $CMe(CF_3)_2$ in **31** does not give a stable metallacycle, but rather the trimethylsilyl carbene **34**[19] (equation 30).

The degree of substitution of the metallacycle ring also has an important influence on stability, which decreases in the order unsubstituted > β-substituted > α,β-substitute > trisubstituted, and pseudo-equatorial substitution appears to be preferred, certainly on the α-carbon and probably also on the β-carbon. Similar conclusions have been drawn from analysis of the product distribution arising from metathesis of (*Z*)-prop-1-ene-*d* by the heterogeneous catalyst system MoO_3/TiO_2–$SnMe_4$[85].



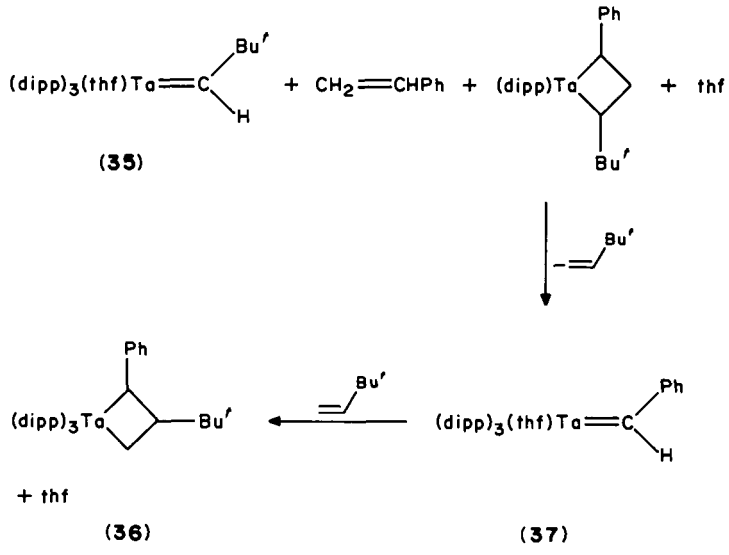
(30)

$R_F = (CF_3)_2(CH_3)C$—

The closely related neutral 4-coordinate tantalum carbene **35** reacts with styrene to give the tantalacyclobutane complex **36** via the benzylidene species **37**[22] (equation 31).

An X-ray structure of **36** revealed a slightly bent TaC_3 ring with the metallacycle elongated in the Ta—C_β direction. The overall geometry, somewhere between trigonal bipyramidal and square pyramidal, is believed to be strongly influenced by crystal packing forces.

The flow of structural and mechanistic information on metallacyclobutane complexes has increased considerably in recent years, and it should not be long before the influence of ring geometry and substitution on metallacycle stability and stereochemistry of the metathesis reaction is closely understood.



D. Ligand–Activity Relationships

The availability of well defined metathesis catalysts has offered an opportunity to correlate activity with the electronic and steric influences of various attendant ligands. Although these studies are at an early stage, trends are already becoming apparent. Not surprisingly, significant differences have already been found between comparable systems with different metals. In general, the tungsten complexes of the type $[W(CHBu^t)(NAr)(OR)_2]$ tend to be more electrophilic than analogous molybdenum species, leading to rates for metathesis by the tungsten complexes approximately an order of magnitude greater than those for their molybdenum counterparts[19,21]. Surprisingly, the 4-coordinate rhenium complex $[Re(CHBu^t)(NAr)_2(OR)]$[76] is inactive as a metathesis catalyst, owing, it is believed, to an insufficiently electrophilic metal centre.

Comparing the effect of ancillary alkoxide ligands in $[M(CHBu^t)(NAr)(OR)_2]$ complexes, metathesis activity is found to decrease in the order $R = C(CF_3)_2Me > C(CF_3)Me_2 > CMe_3$. Thus, whereas $[W(CHBu^t)(NAr)\{OCMe(CF_3)_2\}_2]$ will metathesize *cis*-pent-2-ene at a rate of 10^3 turnovers min^{-1}, $[W(CHBu^t)(NAr)(OBu^t)_2]$ is inactive as a metathesis catalyst for ordinary olefins. Complexes with $C(CF_3)Me_2$ ligands are usually found to have an activity intermediate between these two. The trend correlates well with the electron-withdrawing ability of the alkoxide ligand, $C(CF_3)_2Me$ being the most electron-withdrawing, leading to a more electrophilic metal centre. Steric influences appear to be overshadowed in these complexes as the Bu^tO would be expected to be the least crowded yet displays negligible metathesis activity. However, steric effects can become the more dominant factor since when $R = OC(CF_3)_2(CF_2CF_2CF_3)$, the activity is reduced dramatically and limited to ethylene and pent-1-ene.

The activity of the phenoxide systems $[W(OAr)_2Cl_4]$–$PbBu^n_4$, varies according to the nature of the *ortho* substituents of the phenoxide ligands[72,73]. Activity is found to increase in the order $CH_3 < Ph < F < Cl < Br$, which correlates fairly well with the Brønsted acidity or electron-withdrawing nature of the corresponding phenol.

Changing from O- to S-based ligands also has a dramatic effect. Thus, whereas $[(dipp)_3(thf)Ta{=}CHBu^t]$ will metathesize *cis*-pent-2-ene rapidly, $[(tipt)_3(thf)Ta{=}$

CHBu^t] is inactive towards ordinary olefins[22]. With bulky phenyl thiolates, the metal centre is no longer electrophilic enough to react with ordinary olefins. Similar observations have been made for alkylidyne acetylene metathesis catalysts[84] and, in general, it appears that electron-donating ligands can deactivate the metal towards reaction with carbon—carbon multiple bonds and possibly destabilize the metallacycle intermediates.

Controlling the metathetical activity of a given complex towards ordinary or cyclic olefins has proved to be immensely beneficial for ring-opening metathesis polymerizsation of strained cyclic olefins where a complex is required to be reactive towards the double bond of the cyclic olefin but not the ordinary double bonds of the growing polymer.

The review of the olefin metathesis reaction presented above has necessarily been selective rather than comprehensive and we have attempted to focus primarily on recent developments. There have been several other reviews of this subject from which more detailed information can be extracted concerning particular aspects of the subject[3,13,16,86,87].

IV. APPLICATIONS OF THE OLEFIN METATHESIS REACTION

The discovery and development of the olefin metathesis reaction opened up new routes to industrially important products such as ethylene, propylene, butenes and others associated with the traditional petrochemical industry. Most large-scale industrial applications involve heterogeneous catalyst systems[12,88], although homogeneous systems are beginning to find applications in the production of smaller volume, high-value chemicals for use in the pharmaceutical, agrochemical and perfume industries. Advances continue to be made in the metathesis of functionalized olefins using formulations of relatively low Lewis acidity such as WCl_6–Me_4Sn and Re_2O_7–Al_2O_3–Me_4Sn[89,90]. Commercialization possibilities, however, remain limited owing to the slow reaction rates for the metathesis of functionalized olefins. The metathesis polymerization of cyclic olefins has seen the development of industrial processes for the preparation of polynorbornene (Norsorex, CdF Chimie), polycyclooctene (Vestenamer, Chemische Werke Hüls), and polydicyclopentadiene (Metton RIM process, Hercules) and industrial processes based on the metathesis of functionalized cyclic olefins appear to be significantly more promising.

A. Acyclic Olefins

The first industrial-scale process exploiting the olefin metathesis reaction came on stream in 1966. The Phillips Triolefin Process[91] was used to produce high-purity ethylene and but-2-ene from propene (equation 32).

$$\begin{array}{ccc} CH_2{=}CHMe & & CH_2 \quad CHMe \\ + & \rightleftharpoons & \| \quad + \| \\ CH_2{=}CHMe & & CH_2 \quad CHMe \end{array} \qquad (32)$$

The plant was operated for 6 years, until the increased value of propene no longer made the process economically viable. However, the versatility of the equilibrium olefin metathesis reaction also allowed the process to be operated in the reverse direction to give propene, by employing excess ethylene, if market prices dictated.

Shifting the metathesis equilibrium by controlling the concentration of a volatile component such as ethylene has been exploited in a number of other processes. For example, a process operated by Phillips[92,93] uses excess ethylene to cleave 2,4,4-trimethylbut-2-ene to isobutene and neohexene (equation 33), an important intermediate in the perfume industry.

$$Bu^tCH{=}CMe_2 + CH_2{=}CH_2 \rightleftharpoons Bu^tCH{=}CH_2 + CH_2CMe_2 \qquad (33)$$

A related process, developed by Monsanto[94], converts stilbene to styrene (equation 34) in 99% yield.

$$PhCH{=}CHPh + CH_2{=}CH_2 \longrightarrow 2PhCH{=}CH_2 \quad (34)$$

$$2Me(CH_2)_5CH{=}CH_2 \longrightarrow Me(CH_2)_5CH{=}CH(CH_2)_5Me + CH_2{=}CH_2 \quad (35)$$

Alternatively, removal of a volatile component such as ethylene has been used to prepare long-chain internal olefins such as tetradec-7-ene from oct-1-ene (equation 35), and offers scope for the preparation of high-octane fuel components such as isopentene (equations 36 and 37) from abundant C_4 olefins such as isobutene and but-2-ene produced by steam cracking of petroleum[95].

$$Me_2C{=}CH_2 + MeCH{=}CHMe \rightleftharpoons Me_2C{=}CHMe + MeCH{=}CH_2 \quad (36)$$

$$Me_2C{=}CH_2 + MeCH{=}CH_2 \rightleftharpoons Me_2C{=}CHMe + CH_2{=}CH_2 \quad (37)$$

Combining the olefin metathesis reaction with other transition metal-catalysed reactions has proved particularly successful. In the Shell Higher Olefin Process (SHOP)[96], ethylene is first oligomerized to a mixture of pure, linear α-olefins using a nickel–phosphine catalyst (equation 38).

$$CH_2{=}CH_2 \xrightarrow{\text{Ni cat.}} CH_2CH(CH_2)_nMe \quad (38)$$

$$n = 1 -> 17$$

The α-olefins are separated into three ranges (C_4–C_8, C_{10}–C_{18}, and $> C_{19}$) by distillation and then isomerized to a mixture of internal olefins over a heterogeneous catalyst (equations 39 and 40). The lighter and heavier fractions of the internal olefins are combined over a heterogeneous metathesis catalyst to give linear C_{10}–C_{18} internal olefins (equation 41). These are simultaneously isomerized to terminal olefins and hydroformylated by a cobalt catalyst to give C_{11}–C_{19} primary alcohols, which are used as components of plasticisers and in the detergent industry.

$$CH_2{=}CHR^1 \rightleftharpoons R^2CH{=}CHR^3 \quad (39)$$

$$(R^1 = R^2 + R^3 = C_2\text{–}C_8)$$

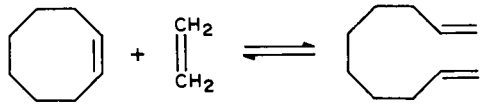
$$CH_2{=}CHR^4 \rightleftharpoons R^5CH{=}CHR^6 \quad (40)$$

$$(R^4 = R^5 + R^6 = C_{10}\text{–}C_{18})$$

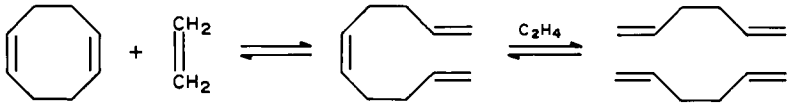
$$\begin{array}{ccccc} R^2CH{=}CHR^3 & & CHR^2 & & CHR^3 \\ + & \rightleftharpoons & \| & + & \| \\ R^5CH{=}CHR^6 & & CHR^5 & & CHR^6 \end{array} \quad (41)$$

In 1986, Shell introduced a second process utilizing metathesis technology. The FEAST process uses excess ethylene to convert cyclooctene and cyclooctadiene to a range of α,ω-dienes (equations 42 and 43) for use in speciality product markets. Several variants of this basic process gives access to a wide variety of di- and polyenes.

Cross-metathesis reactions have been used to prepare olefins which are difficult to synthesize by other methods. For example, the sex pheromone of the common housefly, *cis*-tricos-9-ene (**38**), has been obtained in 95% purity from the co-metathesis of the readily



(42)



(43)

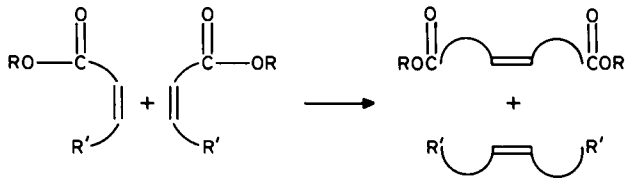
available olefins dec-1-ene and tetradec-1-ene[97] (equation 44).

$$\begin{matrix} Me(CH_2)_7CH{=}CH_2 \\ + \\ Me(CH_2)_{12}CH{=}CH_2 \end{matrix} \longrightarrow \underset{(38)}{\begin{matrix} Me(CH_2)_7CH & Me(CH_2)_{12}CH & Me(CH_2)_7\ CH \\ \| & \| & \| \\ Me(CH_2)_7CH & Me(CH_2)_{12}CH & Me(CH_2)_{12}CH \end{matrix}} \quad (44)$$

B. Functional Olefins

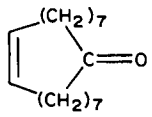
In recent years, much effort has gone into developing catalysts capable of metathesizing functionalized olefins. Olefins possessing a variety of pendant functionalities have been successfully metathesized but catalyst activities are generally lower than for the metathesis of ordinary olefins[89,90].

1. Esters



(45)

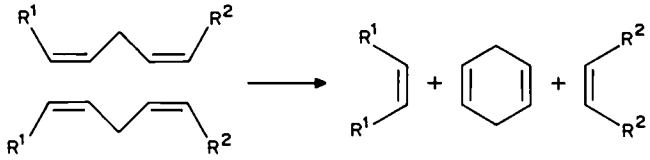
Unsaturated esters of the general type shown on the left-hand side of equation 45 are readily available from natural sources such as olive oil, linseed oil, soya bean oil, and sunflower seed oil, and metathesis has provided a convenient method for converting them to useful precursors for the perfume and polymer industries. An example is the synthesis of civetone (**39**), which is an important constituent of many perfumes[97,98]. The first step involves the metathesis of methyl octadec-9-enoate (**40**) to a mixture of octadec-9-ene (**41**) and dimethyl octadec-9-enedioate (**42**) using WCl_6–Me_4Sn[99,100] (equation 46).



(**39**)

$$\underset{(40)}{2Me(CH_2)_7CH{=}CH(CH_2)_7CO_2Me} \rightleftharpoons \underset{(41)}{Me(CH_2)_7CH{=}CH(CH_2)_7Me} + \underset{(42)}{MeO_2C(CH_2)_7CH{=}CH(CH_2)_7CO_2Me} \quad (46)$$

For polyunsaturated fatty acid esters such as methyl linoleate (**43**), a mixture of products is obtained owing to statistical scrambling of the alkylidene units[101–103]. In addition, intermolecular elimination of cyclohexa-1,4-diene is also observed, which may arise according to equation 47.

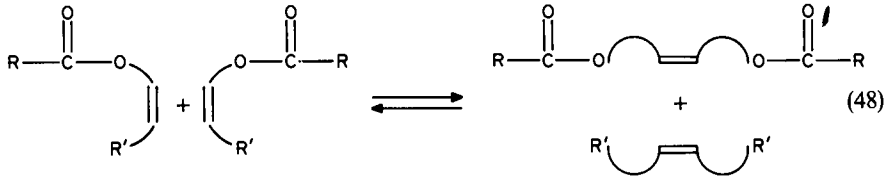


(47)

(**43**)

Similar elimination of cyclohexa-1,4-diene is also found for methyl linolenate and a substantial proportion of higher cyclic olefins. In practice, using tungsten catalysts, it is found that the olefinic bond must be at least one methylene unit removed from the ester functionality in order for metathesis to occur[104].

2. Alkenyl esters



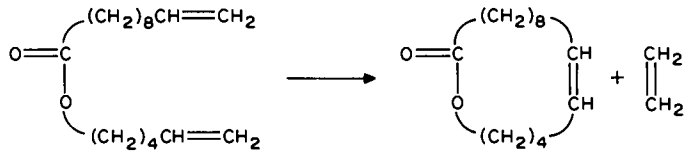
(48)

Alkenyl esters, in which the unsaturated linkage lies in the hydrocarbon chain attached to the oxygen of the ester functionality (equation 48), can be metathesized in modest yield using tungsten-based catalysts[105], but again the catalyst appears to be deactivated if only one methylene group separates the olefin from the functional group. However, this drawback may be overcome by using the heterogeneous rhenium formulation Re_2O_7–Al_2O_3–Me_4Sn[106].

In the metathesis of dec-9-enyl acetate with but-1-ene, removal of ethylene allows the synthesis of dodec-9-enyl acetate (**44**) (equation 49), the sex pheromone of the western pine-shoot borer (*Eucosma sonomana*)[107]. A considerable range of insect pheromones have been prepared by similar techniques and successfully exploited as pest control agents.[107]

$$CH_2{=}CH(CH_2)_8OAc + CH_2{=}CHEt \rightarrow \underset{(\mathbf{44})}{EtCH{=}CH(CH_2)_8OAc} + CH_2{=}CH_2 \quad (49)$$

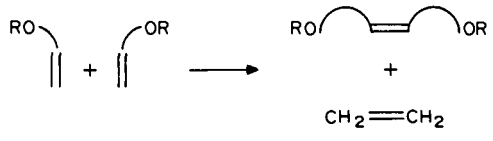
Co-metathesis of unsaturated esters and alkenyl esters has facilitated the synthesis of macrocyclic lactones or macrolides[108]. A more direct approach involves macrocyclic ring closure of an ester unsaturated in both hydrocarbon chains (equation 50)[109].



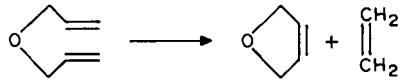
(50)

3. Ethers

Unsaturated ethers are also metathesized by tungsten catalysts[27] with elimination of ethylene (equation 51), although the heterogeneous rhenium formulation is again necessary for allyl ethers[107]. It has also been shown that diallyl ethers may be converted to unsaturated cyclic ethers with 100% selectivity (equation 52)[110].



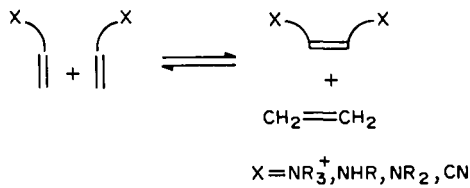
(51)



(52)

To date, acyclic substrates possessing hydroxy functionalities all appear to deactivate the catalyst. However, olefins possessing trimethylsiloxy[111] and OTs[88] functionalities can be metathesized and offer convenient methods of protecting the OH group.

4. Nitrogen-containing olefins



(53)

A number of unsaturated ammonium[112], amine[113,114], and nitrile[111,115] substrates have been metathesized according to the general equation 53. However, for allyl cyanide, isomerization to crotonitrile appears to be favoured over self-metathesis, although in metathesis experiments with symmetrical olefins up to 25% of co-metathesis products can be obtained.

5. Halogen-containing olefins

The Re_2O_7–Al_2O_3–Me_4Sn catalyst system has been used to metathesize a number of halogen-containing olefins. Allyl bromide undergoes 50% conversion to dibromobut-2-ene with 95% selectivity[106] (equation 54).

$$2CH_2{=}CHCH_2Br \rightleftharpoons BrCH_2CH{=}CHCH_2Br + CH_2{=}CH_2 \qquad (54)$$

Olefins in which the halide is attached to the double bond give very slow rates of metathesis[116], although co-metathesis with ordinary olefins proceeds rapidly[117]. These observations are attributed to the unfavourable formation of a 1,2-dihalide-substituted metallacyclobutane[116].

C. Polymerization

The olefin metathesis reaction can be used in two different ways for polymer synthesis.

(i) Chain-growth polymerization

When mono- or poly-cyclic alkenes are used as monomers the polymer is formed by a chain-growth process in which the chain-carrying species alternates between a metallacarbene and metallacyclobutane and the microstructure of the polymer backbone provides a detailed record of the propagation steps in the reaction which produced it, provided, of course, that the record can be read.

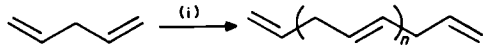
(ii) Step-growth polymerization

Step-growth polymerization processes are also possible. A divinyl monomer, for example, may undergo polymerization via the stepwise elimination of ethylene initiated by a metathesis catalyst. In this kind of process the metathesis steps have the characteristics of a chain reaction but the growth of the polymer backbone occurs in a stepwise fashion. So far this step-growth approach to polymer synthesis via olefin metathesis chemistry has not attracted as much attention as chain-growth ring-opening polymerization. It has been shown that, with some catalysts and under appropriate reaction conditions penta-1,4-diene is converted in 70% yield to octa-1,4,7-triene[118], or alternatively to the distribution of telomers shown in Table 1[119]. There have been very few reports of attempts to apply this reaction to polymer synthesis, although at the time of writing the concept is receiving some attention[120]. It seems likely that careful regulation of this type of reaction will eventually yield genuine high polymers.

Applications of olefin metathesis in polymer science are not restricted to polymer synthesis. Earlier in this chapter we described several useful monomer syntheses, and the degradation of unsaturated polymers via cross-metathesis with acyclic alkenes is also potentially useful in academic investigations of unsaturated networks and as a potential method for recycling scrap elastomers[121]. The idea is illustrated in Scheme 2. Separation and identification of the fragments provides information about the structure of the original network. With simple elastomers degradation may yield significant amounts of useful monomers for recycling.

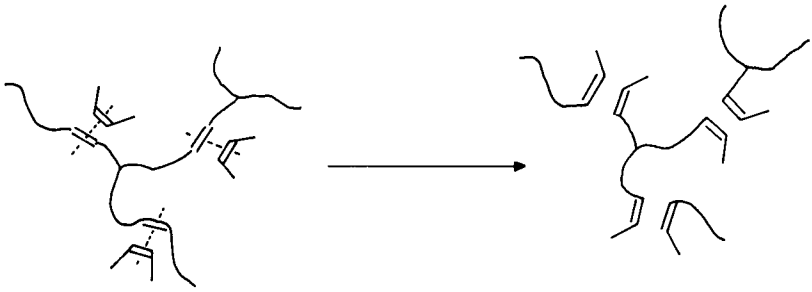
Simple ring-opening polymerization of cycloalkenes has led to the most activity as far as applications of metathesis in polymer science are concerned. A wide range of possible monomers have been investigated and several interesting materials have been prepared. At the time of writing three ring-opening metathesis polymerizations are being commercially exploited. The features of this kind of polymerization which make it interesting and potentially useful are as follows: the olefinic unsaturation of the monomer is retained in the polymer, the kinds of isomeric incorporation of monomer residues which are possible are

TABLE 1. Telomer distribution in penta-1,4-diene metathesis



(i) WCl_6–$Et_3Al_2Cl_3$–$MeCCl(OH)CH_2Cl$–PPh_3 (1:2:1:1) at 0 °C for 6 h

n	wt-%	*n*	wt-%
1	15.7	4	1.8
2	7.9	5	1.6
3	4.1	6	0.6



SCHEME 2. Schematic representation of metathesis degradation of unsaturated networks.

many and hence novel stereoregularities are available; a variety of substituent groups can be tolerated (and the range of groups is constantly expanding), copolymerization is possible; and the recent demonstration of living metathesis allows good control of molecular architecture.

The synthesis of polymers with olefinic unsaturation along the backbone initially focused attention on the possibility of making elastomers; indeed, speciality elastomers are the major commercial success of metathesis polymerization so far established[122].

1. Polymers from monocyclic unsaturated hydrocarbons

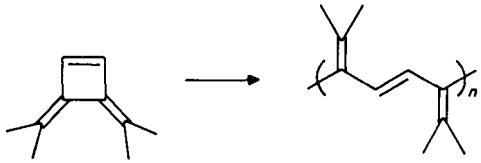
Consideration of thermodynamic factors leads to the prediction that three-, four-, and eight- or larger membered rings will undergo ring-opening polymerization with a large negative free energy change and will therefore be favoured, provided a mechanism is available. In contrast, the ring-opening polymerizations of five- and seven membered rings are predicted to be associated with significantly smaller negative free energies and consequently small changes in structure or reaction conditions may completely inhibit polymerization. Six-membered rings are expected to be unpolymerizable by ring opening[123]. This analysis has been justified by the experimental evidence available to date.

Cyclobutene, cyclooctene, and larger cycloalkenes are polymerized to high polymers by a range of conventional metathesis catalysts. The polymers from cyclobutene and 1-methylcyclobutene are polybuta-1,4-diene and polyisoprene, respectively, and the polymerization of 1-methylcycloocta-1,5-diene gives an alternating copolymer of buta-1,4-diene and isoprene units. All these reactions have been established and thoroughly investigated but none of them is operated commercially since equivalent products may be obtained more cheaply by previously established technologies.

Metathesis polymerizations were investigated initially at a time when the nature of the initiator for most commonly used catalyst formulations was essentially unknown. Many of these catalyst systems have been found to be sensitive to a wide range of common organic structural units which appear to act as inhibitors or poisons for these conventional catalysts. Consequently, a folklore about polymerizable monomers in metathesis developed and; for example, it was widely held that groups containing heteroatoms and conjugated dienes were polymerization inhibitors. A reapparaisal of these views is made necessary by the results of recent work, particularly from the research groups of Osborn, Grubbs and Schrock, on structurally well defined catalysts of the kind discussed earlier in this chapter.

It is clear that, if the appropriate initiator is used, the variety of polymerizable monomers is limited only by the imagination of the synthetic chemist. Thus, for example,

Swager and Grubbs[124] recently reported that 3,4-diisopropylidenecyclobutene may be polymerized using a bis(cyclopentadienyl)titanacyclobutane derivative as initiator (Scheme 3).



SCHEME 3

The cross-conjugated polymer product of this reaction is colourless, soluble and susceptible to oxidative degradation, all of which are to be expected. Solution-cast films of this polymer are insulators in their pristine state but display electrical conductivity of up to $200\,\Omega^{-1}\,cm^{-1}$ after exposure to iodine. When this result was published it was well known that polymers containing long sequences of conjugated double bonds could be reduced or oxidized and converted from insulators to conductors, but this observation that a cross-conjugated system behaved in a similar fashion was a surprise.

More recently Grubbs' group reported that the tungsten–carbene complex discovered by Schrock polymerizes cyclooctatetraene to polyacetylene.[125]

Cyclobutene-derived polymers have been investigated but have not yet merited commercial development. On the other hand, for several years cyclopentene appeared to be an attractive possibility for a successful route to a synthetic elastomer via metathesis. Cyclopentene is readily available via hydrogenation of cyclopentadiene, and its ring-opening polymerization has been investigated in detail. The product, a polypentenamer, is a good general-purpose rubber which can be vulcanized to give products comparable to those obtained from polyisoprene and polybutadiene. The physical properties of the raw gum depend on the frequency and distribution of *cis* and *trans* double bonds: the high-*trans*, natural rubber, and high-*cis* materials have glass transition temperatures of −90, −70, and −14 °C, respectively, and melting points of 20, 30 and −41 °C, respectively. The *cis*-polypentenamer has the lowest glass transition temperature known for any hydrocarbon polymer.

Several companies have developed polypentenamer synthesis to the pilot-plant manufacture, tyre fabrication, and testing stages; however, the materials produced have not yet been commercially exploited because of prevailing market conditions since their development[126].

Methyl substitution at the vinylic and allylic positions in cyclobutene does not inhibit polymerization, but cyclopentene is more sensitive to substituent effects. Thus, 1-methylcyclopentene has not been polymerized whereas, at the 3-position, a methyl substituent can be tolerated but an isopropyl group cannot. Polymerization of cyclopentene is reversible and the reaction constitutes a good example of equilibrium polymerization. This has been the subject of detailed discussion[3], and Schrock[127] recently reported that polymerization of this monomer under living conditions can be regulated to allow the production of narrow molecular weight distribution polypentenamer at −60 °C which can be completely reversed to give a mixture of initiator and monomer at +60 °C.

Cyclohexene is not polymerized by metathesis catalysts to any significant degree. Cycloheptene has not been studied in any detail; its polymer seems unlikely to have sufficiently interesting properties to justify its cost, even in speciality markets.

In contrast, cyclooctene is readily available and easily polymerized. Since 1980 the product of its polymerization has been commercially exploited by Chemische Werke Hüls as a speciality elastomer under the name Vestenamer[126]. It has a low molecular weight (ca

60 000) for an elastomer, it shows a glass transition temperature of −65 °C, it is fairly hard at room temperature owing to its crystallinity (ca 33%), and it melts at 55 °C to a low-viscosity fluid, which aids in its processing into blends. The major outlet for Vestenamer is reported to be in blends with more common elastomers, and these products find specialist applications[128]. At the time of writing Vestenamer is probably the most successful methathesis polymer in terms of production tonnage with Hüls operating a plant with a capacity of 12 000 tonnes per annum[126].

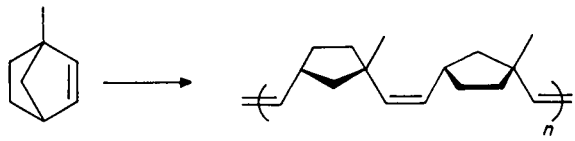
2. *Polymerization of polycyclic alkenes and polyenes*

Polycyclic monomers are more easily polymerized than monocyclic alkenes. This is usually attributed to increased ring strain[3], although this rationalization has been challenged[129]. Generally, all metathesis catalysts will effect the polymerization of bicyclo[2.2.1]heptene (indeed, many research groups use polymerization of this monomer as a check for the presence of active metathesis catalysts), whereas cyclopentene is significantly less reactive. It is not surprising that bicyclo[2.2.1]heptene was the first monomer shown to undergo metathesis ring-opening polymerization[1]. This monomer is also cheap but the polymer was not commercialized until 1976, ca 20 years after its discovery. A polymer having ca 90% *trans* double bonds is sold by CdF Chimie under the name Norsorex. This material has a molecular weight above 10^6, a glass transition temperature of 35 °C, a melting point in excess of 170 °C, and a capacity to absorb large volumes of oil and plasticizers. It is very compatible with fillers and, not surprisingly in view of the two tertiary allylic C—H bonds per repeat unit, it is susceptible to oxidative degradation and requires protection by antioxidants. The highly extended and vulcanized compounds obtained from Norsorex show good tear strength and a high dynamic damping, which makes them useful in noise and vibration applications.

Many bicyclo[2.2.1]heptenes have been polymerized by methathesis catalysts and many patents have been issued[126]. This activity is a consequence of the relatively low cost and ease of synthesis of such monomers and the ease of their polymerization. Streck[126] has recently reported that in a 5-year period two Japanese companies took out 127 patents in this field. Poly(5-cyanonorbornene) seems to have been the most energetically pursued product of this activity (Showa Denko) and was reported to show promise as a thermoplastic[130]. Silyl and tributylstannyl substituents have been reported to impart improved adhesive bonding and biocidal activity, respectively, and such materials have been claimed to be potentially useful speciality polymers[131].

Ring-opening polymerization of bicyclo[2.2.1]heptene, a symmetrical monomer, leads to a polymer with two chiral centres per repeat unit. If the centres on each side of the double bond have the same chirality, a racemic dyad is generated, and centres with opposite chirality give a *meso* dyad. When the monomer is unsymmetrically substituted, head–head (HH), tail–tail (TT), and head–tail (HT) incorporation of repeat units is possible. As a consequence, ring opening of simple substituted norbornenes can give rise, in principle at least, to a very wide range of microstructures defined by the frequency and distribution of the *cis*- and *trans*-vinylenes, the *meso* and racemic dyads, and HH, TT, or HT placements. The outcome of a specific polymerization depends on the interplay of many factors, including the structure of the monomer, the nature of the catalyst, and the reaction conditions (solvent, temperature, and concentrations). Establishing the structures of the polymers depends almost completely on the analysis of high-resolution ^{13}C n.m.r. spectra and Ivin has been the major contributor to this field[3]. In many cases a total specification of the microstructure has been demonstrated and several totally stereoregular polymers have been characterized[3,132]. An excellent example of this area of synthesis is provided in the polymerization of racemic 1-methylnorbornene, initiated by rhenium pentachloride, which gives a polymer with an all head–tail-*cis*-syndiotactic micro-

structure; this result can only be achieved if the enantiomers of the racemic monomer are incorporated into the polymer in a strictly alternating sequence, (Scheme 4).

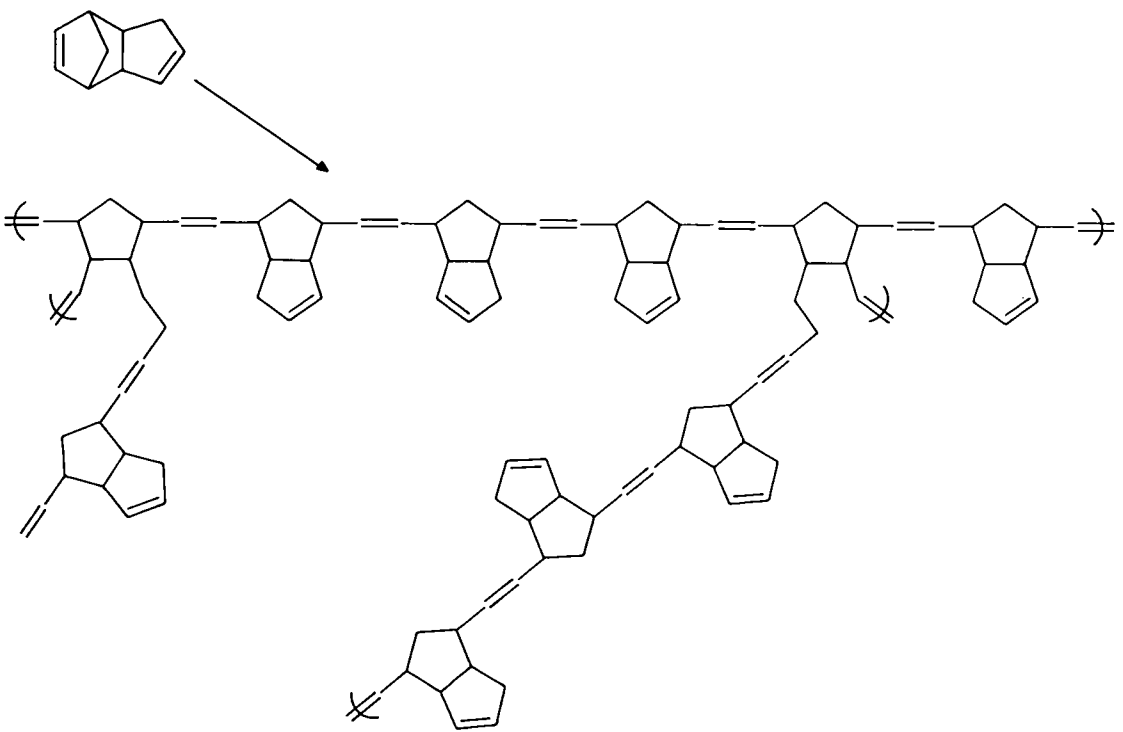


SCHEME 4

The nature and location of substituents on the norbornene skeleton have consequences for the polymerizability of the monomer. Catalyst approach to monomer is believed to occur from the *exo* face, and so it is not surprising that substituents at $C_{(7)}$ which are *syn* to the double bond prevent polymerization, whereas *anti*-$C_{(7)}$ substituents are tolerated. More surprising is the observation that *endo* substituents at $C_{(5)}$ and $C_{(6)}$ often inhibit polymerization whereas *exo* substituents do not, this has been reported for both anhydride and chlorine[133,134]. It is necessary to treat dogmatic classifications of polymerizable and non-polymerizable monomers with some scepticism since the continuing development of new initiator systems seems likely to invalidate them. Substituents which are not inhibitors of the easily prepared conventional metathesis catalysts include fluorine, giving rise to the possibility of making stereoregular fluoropolymers and aryl, ester (including carbonate), and fulvene derivatives[135–138].

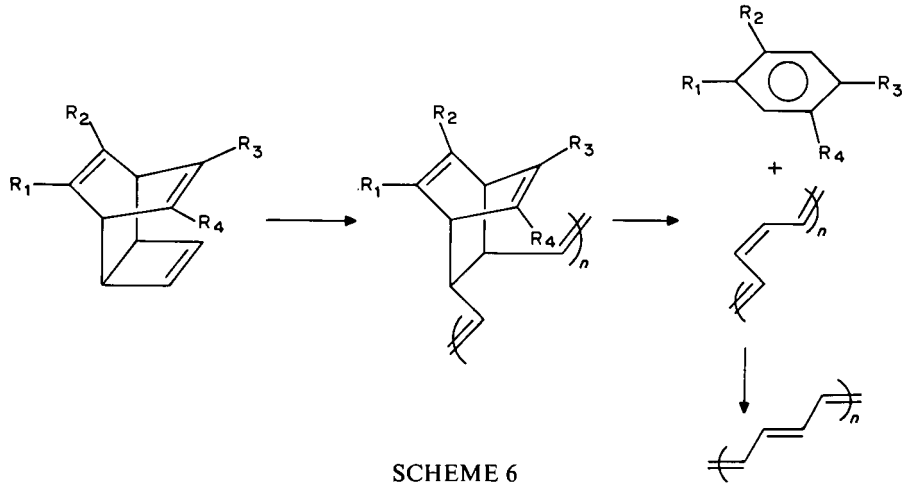
Cyclopentadiene dimer (dcp) {tricyclo[5.2.1.0(2, 6)]deca-3, 8-diene} is a cheap monomer which has been thoroughly studied. The linear polymer obtained by ring opening exclusively at the vinylene in the bicyclo unit was reported to be about to be launched as a thermoplastic by Goodrich under the name Telene in 1982[139], but this does not seem to have happened. In 1985, Hercules established a production unit using dcp in a metathesis reaction injection moulding (RIM) process (Scheme 5). The catalyst which presumably initiates the ring-opening of both the vinylenes of the bicyclo[2.2.1]- and the 3,4-disubstituted cyclopentene units of dcp is generated when a transition metal compound and an activator are combined in the two monomer streams which are mixed prior to injection into the mould. The solutions of the individual catalyst components in the monomer are stable, and the delay between mixing and initiation of network formation can be controlled allowing the kinetics of the process to be regulated to fit the requirements of the object being made. The cycle times for making large items by this technique can be low, and the polydicyclopentadiene product, which is sold under the trade-name Metton, has an unusual and advantageous balance of mechanical properties[140]. The structure shown in Scheme 5 has a high concentration of tertiary allylic C—H bonds and consequently the mouldings develop an oxidatively cross-linked surface fairly quickly after their formation. This oxidation layer serves two useful purposes, first as a barrier to the ingress of further oxygen into the bulk of the polymer and second as a surface suitable for painting directly.

Earlier in this section we emphasized that the retention of monomer unsaturation was one of the useful features of metathesis polymerization. Conjugated polymers have been a major target in polymer synthesis since the first theoretical predictions concerning their electrical properties were published about 50 years ago. The physics of conjugated polymers such as polyacetylene has proved difficult to study in a satisfactory way because the materials are air sensitive, insoluble, and infusible, and consequently not easily purified or processed. A common solution to the problem of making intractable but desirable polymers involves the synthesis and subsequent conversion of a processable precursor. With polyacetylene an unsaturated precursor provides a start on the path to the required



SCHEME 5

material and hence a metathesis polymerization is an obviously attractive option. A successful solution to the polyacetylene synthesis problem is outlined in Scheme 6. The monomer, a tricyclic triene, undergoes ring opening exclusively at the cyclobutene double bond to give the soluble precursor polymer, whhich can be purified and characterized (by gel permeation chromatography, spectroscopy, etc.) prior to its conversion, via a symmetry-allowed elimination, to polyacetylene. The process has been the subject of detailed study and provides access to materials of high purity and in a variety of morphologies[141].



SCHEME 6

Some very exciting developments have occurred in this field recently. These results follow advances made in solving the problem of defining the structure and mechanism of action of metathesis catalysts, and are particularly dependent on the introduction of the well defined initiators which were described earlier in this chapter. The papers by Grubbs, Schrock, and coworkers demonstrate that true living polymerization is possible, providing access to narrow molecular weight distributions and block copolymers[142–144]. Grubbs has also demonstrated the possibility of switching from metathesis to other propagation mechanisms[125], and it is clear that a much wider range of monomers are polymerizable than was previously thought to be the case.

Until very recently there has been an 'entry fee' to be paid for the intending participant in this exciting area of activity, in that the synthesis and use of these newer catalysts places experimental skill at a premium, requiring a high level of competence in glove-box and vacuum-line techniques. Perhaps the most significant recent advance is the demonstration that some ruthenium initiators work very efficiently with heteroatom-containing monomers such as derivatives of 7-oxanorbornene, and that these metathesis reactions can be conducted in aqueous solution and without the need to exclude oxygen[145]. The future for this subject looks very rosy.

V. REFERENCES

1. A. W. Anderson and N. G. Merckling, *US Pat.*, 2721 189 (1955); *Chem. Abstr.*, **50**, 3008 (1955).
2. *Chem. Eng. News*, **45**, 51 (1967).
3. K. J. Ivin, *Olefin Metathesis*, Academic Press, New York, 1983.
4. V. C. Gibson, *Acetylene Metathesis*, to be published.

5. J. L. Herisson and Y. Chauvin, *Makromol. Chem.*, **141**, 161 (1970).
6. R. R. Schrock, S. Routledge, J. H. Wengrovius, G. Rupprecht and J. Fellman, *J. Mol. Catal.*, **8**, 73 (1980).
7. J. H. Wengrovius, R. R. Schrock, M. R. Churchill, J. R. Missert, and W. J. Youngs, *J. Am. Chem. Soc.*, **102**, 4515 (1980).
8. C. P. Casey and H. E. Tuinstra, *J. Am. Chem. Soc.*, **100**, 2270 (1978).
9. H. S. Eluterio, *Ger. Pat.*, 1072811 (1960).
10. W. L. Truett, *J. Am. Chem. Soc.*, **82**, 2337 (1960).
11. G. Natta, G. Dal'Asta, and G. Mazzanti, *Angew. Chem., Int. Ed. Engl.*, **3**, 723 (1964).
12. S. von Warwel, *Erdol-Erdgas-Kohle*, **103**, 238 (1987).
13. R. L. Banks, *ChemTech*, **494** (1979).
14. R. H. Grubbs, *Prog. Inorg. Chem.*, **24**, 1 (1978).
15. J. C. Mol and J. A. Moulijn, *Adv. Catal.*, **24**, 131 (1975).
16. N. Calderon, J. P. Lawrence, and E. A. Ofstead, *Adv. Organomet. Chem.*, **17**, 449 (1979).
17. N. Calderon, E. A. Ofstead, and W. A. Judy, *Angew. Chem., Int. Ed. Engl.*, **15**, 401 (1976).
18. J. J. Rooney and A. Stewart, in *Catalysis*, Vol. 1, Chemical Society SPR, Snr Reporter C. Kemball, London, 1977, p. 277.
19. R. R. Schrock, R. T. DePue, J. Feldman, C. J. Schaverien, J. C. Dewan, and A. H. Liu, *J. Am. Chem. Soc.*, **110**, 1423 (1988).
20. A. K. Rappé and W. A. Goddard, III, *J. Am. Chem. Soc.*, **104**, 448 (1982).
21. J. S. Murdzek and R. R. Schrock, *Organometallics*, **6**, 1373 (1987).
22. K. C. Wallace, A. H. Liu, J. C. Dewan, and R. R. Schrock, *J. Am. Chem. Soc.*, **110**, 4964 (1988).
23. J. Kress, J. A. Osborn, R. M. E. Greene, K. S. Ivin, and J. J. Rooney, *J. Am. Chem. Soc.*, **109**, 899 (1987).
24. J. Kress, J. A. Osborn, K. S. Ivin, and J. J. Rooney, *Recent Adv. Mech. Synth. Aspects Polym., NATO ASI, Ser. C*, **215**, 363 1987.
25. J. C. Mol, J. A. Moulijn, and C. Boelhouwer, *J. Chem. Soc., Chem. Commun.*, 663 (1968).
26. J. C. Mol, F. R. Visser, and C. Boelhouwer, *J. Catal.*, **17**, 114 (1970).
27. H. Sato, Y. Tanaka, and T. Taketomi, *Makromol. Chem.*, **178**, 1993 (1977).
28. K. Saito, T. Yamaguchi, and K. Tanabe, *Bull. Chem. Soc. Jpn.*, **52**, 3192 (1979).
29. J. R. Hardee, *Diss. Abstr. Int. B.*, **40**, 1186 (1979).
30. R. H. Grubbs and S. Swetnick, *J. Mol. Catal.*, **8**, 25 (1980).
31. F. P. J. M. Kerhof, R. Thomas, and J. A. Moulijn, *Recl. Trav. Chim. Pays-Bas*, **96**, M121 (1977).
32. A. Andreini and J. C. Mol, *J. Colloid Interface Sci.*, **84**, 57 (1981).
33. F. Pennella, *J. Catal.*, **69**, 206 (1981).
34. Y. I. Yermakov, B. N. Kuznetzov, Y. P. Grabovski, A. N. Startzev, A. M. Lazutkin, V. A. Zakarov, and A. I. Lazutkina, *J. Mol. Catal.*, **1**, 93 (1975).
35. J. P. Candlin and H. Thomas, *Adv. Chem. Ser.*, No. 132, 212 (1974).
36. Y. Iwasawa, S. Ogasawara, and M. Soma, *Chem. Lett.*, 1039 (1978).
37. Y. Iwasawa, H. Kubo, and M. Yamagishi, *Chem. Lett.*, 1165 (1978).
38. Y. Iwasawa, H. Ichinose, and S. Ogasawara, *J. Chem. Soc., Faraday Trans. I*, **29**, 313 (1981).
39. A Mortreux, F. Petit, and M. Blanchard, *J. Mol. Catal.*, **8**, 97 (1980).
40. A. N. Startsev, B. N. Kutnetsov, and Y. I. Yermakov, *React. Kinet. Catal. Lett.*, **3**, 321 (1976).
41. A. Brenner, D. A. Hucal, and S. J. Hardwick, *Inorg. Chem.*, **18**, 1478 (1979).
42. A. A. Olsthoorn and J. A. Moulijn, *J. Mol. Catal.*, **8**, 147 (1980).
43. R. L. Burwell and A. Brenner, *J. Mol. Catal.*, **1**, 77 (1975).
44. M. F. Farona and R. L. Tucker, *J. Mol. Catal.*, **8**, 85 (1980).
45. W. B. Hughes, *J. Chem. Soc., Chem. Commun.*, 431 (1968).
46. W. B. Hughes, *J. Am. Chem. Soc.*, **92**, 532 (1970).
47. W. B. Hughes, *Organomet. Chem. Synth.*, **1**, 341 (1972).
48. J. McGinnis, T. J. Katz, and S. Hurwitz, *J. Am. Chem. Soc.*, **98**, 605 (1976).
49. N. Calderon, H. Yu. Chen, and K. W. Scott, *Tetrahedron Lett.*, 3327 (1967).
50. N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and K. W. Scott, *J. Am. Chem. Soc.*, **90**, 4133 (1968).
51. J. L. Herisson, Y. Chauvin, N. H. Phung and G. Lefebvre, *C.R. Acad. Sci., Ser. C*, **269**, 661 (1969).
52. W. A. Herrmann, J. G. Kuchler, J. K. Felixberger, E. Herdtweck, and W. Wagner, *Angew. Chem., Int. Ed. Engl.*, **27**, 394 (1988).

53. M. F. Farona and W. S. Greenlee, *J. Chem. Soc., Chem. Commun.*, 759 (1975).
54. S. Warwel and P. Buschmeyer, *Angew. Chem., Int. Ed. Engl.*, **90**, 131 (1978).
55. R. H. Grubbs, S. Swetnick, and S. C. H. Su, *J. Mol. Catal.*, **3**, 11 (1977).
56. S. Tamagaki, R. J. Card, and D. C. Neckers, *J. Am. Chem. Soc.*, **100**, 6635 (1978).
57. A. J. van Roosmalen, K. Polder, and J. C. Mol, *J. Mol. Catal.*, **8**, 185 (1980).
58. E. O. Fischer, *Adv. Organomet. Chem.*, **14**, 1 (1976).
59. T. J. Katz and N. Acton, *Tetrahedron Lett.*, 4251 (1976).
60. C. P. Casey and T. S. Burkhardt, *J. Am. Chem. Soc.*, **95**, 5833 (1973).
61. C. P. Casey and T. S. Burkhardt, *J. Am. Chem. Soc.*, **96**, 7808 (1974).
62. R. R. Schrock, *J. Am. Chem. Soc.*, **96**, 6796 (1974).
63. R. R. Schrock, in *Reactions of Co-ordinated Ligands* (Ed. P. S. Braterman), Plenum Press, New York, 1986, Ch. 3, p. 221–283.
64. S. J. McLain, C. D. Wood, and R. R. Schrock, *J. Am. Chem. Soc.*, **99**, 3519 (1977).
65. S. M. Rocklage, J. D. Fellmann, G. A. Rupprecht, L. W. Messerle, and R. R. Schrock, *J. Am. Chem. Soc.*, **103**, 1440 (1981).
66. F. N. Tebbe, G. W. Parshall, and D. W. Orenall, *J. Am. Chem. Soc.*, **101**, 5074 (1979).
67. P. R. Sharp, D. Astruc, and R. R. Schrock, *J. Organomet. Chem.*, **182**, 477 (1979).
68. J. Kress, M. Wesolek, J. A. Osborn, *J. Chem. Soc., Chem. Commun.*, 514 (1982).
69. J. Kress and J. A. Osborn, *J. Am. Chem. Soc.*, **105**, 6346 (1983).
70. J. Kress, A. Aguero, and J. A. Osborn, *J. Mol. Catal.*, **36**, 1 (1986).
71. M. T. Youinou, J. Kress, J. Fischer, A. Aguero, and J. A. Osborn, *J. Am. Chem. Soc.*, **110**, 1488 (1988).
72. F. Quignard, M. Leconte, and J. M. Basset, *J. Chem. Soc., Chem. Commun.*, 1816 (1985).
73. F. Quignard, M. Leconte, and J. M. Basset, *J. Mol. Catal.*, **36**, 1 (1986).
74. C. J. Schaverien, J. C. Dewan, and R. R. Schrock, *J. Am. Chem. Soc.*, **108**, 2771 (1986).
75. D. S. Edwards, L. V. Biondi, J. W. Ziller, M. R. Churchill, and R. R. Schrock, *Organometallics*, **2**, 1505 (1983).
76. A. D. Horton, R. R. Schrock, and J. H. Freudenberger, *Organometallics*, **6**, 893 (1987).
77. T. R. Howard, J. B. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.*, **102**, 6876 (1980).
78. D. A. Straus and R. H. Grubbs, *J. Mol. Catal.*, **28**, 9 (1985).
79. D. A. Straus and R. H. Grubbs, *Organometallics*, **1**, 1658 (1982).
80. T. H. Upton and A. K. Rappé, *J. Am. Chem. Soc.*, **107**, 1206 (1985).
81. E. V. Anslyn and R. H. Grubbs, *J. Am. Chem. Soc.*, **109**, 4880 (1987).
82. W. C. Finch, E. V. Anslyn, and R. H. Grubbs, *J. Am. Chem. Soc.*, **110**, 2406 (1988).
83. J. B. Lee, G. J. Gajda, W. P. Schaefer, T. R. Howard, T. Ikariya, D. A. Straus, and R. H. Grubbs, *J. Am. Chem. Soc.*, **103**, 7358 (1981).
84. R. R. Schrock, *J. Organomet. Chem.*, **300**, 249 (1986).
85. K. Tanaka, K.-I. Tanaka, H. Takeo, and C. Matsumura, *J. Am. Chem. Soc.*, **109**, 2422 (1987).
86. V. Dragutan, A. T. Balaban, and M. Dimonie, *Olefin Metathesis and Ring Opening Polymerization of Cycloolefins*, Wiley, New York, 1986.
87. R. H. Grubbs, *Prog. Inorg. Chem.*, **24**, 1 (1978); in *Comprehensive Organometallic Chemistry* (Ed. G. Wilkinson), Vol. 8, Pergamon Press,, New York, 1982, pp. 499–551.
88. R. Streck, *Chem. Ztg.*, **99**, 397 (1975).
89. J. C. Mol, *J. Mol. Catal.*, **15**, 35 (1982).
90. J. C. Mol, *ChemTech*, 250 (1983).
91. *Hydrocarbon Process.*, **46**, 232 (1976).
92. *Chem. Week*, **44**, 30 (1976).
93. R. L. Banks, D. S. Banasiak, P. S. Hudson, and J. R. Norell, *J. Mol. Catal.*, **15**, 21 (1982).
94. W. R. Knox and R. N. Moore, *US Pat.*, 3965206.
95. C. Masters, *Homogeneous Transition-Metal Catalysis—a Gentle Art*, Chapman and Hall, New York, 1981.
96. E. R. Freitas and C. R. Gum, *Chem. Eng. Prog.*, **75**, 73 (1979).
97. R. Rossi, *Chim. Ind. (Milan)*, **57**, 242 (1975).
98. J. Tsuji and S. Hasiguchi, *Tetrahedron Lett.*, **21**, 2955 (1980).
99. P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *J. Chem. Soc., Chem. Commun.*, 1221 (1972).
100. P. B. van Dam, M. C. Mittelmeijer, and C. Boelhouwer, *J. Am. Oil. Chem. Soc.*, **51**, 389 (1974).

101. E. Verkuijlen and C. Boelhouwer, *J. Chem. Soc., Chem. Commun.*, 793 (1974).
102. E. Verkuijlen and C. Boelhouwer, *Fette Seifen Anstrichm.*, **78**, 444 (1976).
103. W. Ast, G. Rheinwald, and R. Kerber, *Makromol. Chem.*, **177**, 39 (1976).
104. E. Verkuijlen, R. J. Dirks, and C. Boelhouwer, *Recl. Trav. Chim. Pays-Bas*, **96**, M86 (1977).
105. J. Levisalles and D. Villemin, *Tetrahedron*, **36**, 3181 (1980).
106. J. C. Mol and E. F. G. Woerlee, *J. Chem. Soc., Chem. Commun.*, 330 (1979).
107. D. S. Banasiak, *J. Mol. Catal.*, **28**, 107 (1985).
108. W. Ast, G. Rheinwald, and R. Kerber, *Recl. Trav. Chim. Pays-Bas*, **96**, M127 (1977).
109. D. Villemin, *Tetrahedron Lett.*, **21**, 1715 (1980).
110. E. I. Bogolepova, R. A. Fridman, and A. N. Bashkirov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **27**, 2429 (1978).
111. R. Nakamura, S. Matsumto, and E. Echigoya, *Chem. Lett.*, 1019 (1976).
112. J. P. Lavel, A. Lattes, R. Mutin, and J. M. Basset, *J. Chem. Soc., Chem. Commun.*, 502 (1977).
113. R. Nouguier, R. Mutin, J. P. Laval, G. Chapalet, J. M. Basset, and A. Lattes, *Recl. Trav. Chim. Pays-Bas*, **96**, M91 (1977).
114. C. Edwige, A. Lattes, J. P. Laval, R. Mutin, J. M. Basset, and R. Nouguier, *J. Mol. Catal.*, **8**, 297 (1980).
115. G. C. N. van den Aardweg, R. H. Bosma, and J. C. Mol, *J. Chem. Soc., Chem. Commun.*, 262 (1983).
116. R. A. Fridman, A. N. Bashkirov, L. G. Liberov, S. M. Nosakova, R. M. Smirnova, and S. B. Verbovetskaya, *Dokl. Akad. Nauk SSSR*, **234**, 1354 (1977).
117. R. A. Fridman, L. G. Liberov, S. M. Nosakova, R. M. Smirnova, and A. N. Bashkirov, *Izv. Akad. Nauk SSSR. Khim.*, **28**, 2816 (1979).
118. G. Doyle, *J. Catal.*, **30**, 118 (1973).
119. G. Dall'Asta, *Pure Appl. Chem.*, **1**, 133 (1973–74).
120. K. Wagner, *Sci. Eng.*, **58**, 101 (1988).
121. K. Hummel, *Pure Appl. Chem.*, **54**, 351 (1982).
122. G. Dall'Asta, *Rubber Chem. Technol.*, **47**, 511 (1974).
123. K. J. Ivin, in *Reactivity, Mechanism and Structure in Polymer Chemistry* (Eds A. D. Jenkins and A. Ledwith), Wiley, London, 1974, Ch. 16.
124. T. M. Swager and R. H. Grubbs, *J. Am. Chem. Soc.*, **108**, 2771 (1986).
125. R. H. Grubbs, paper presented at the 7th International Symposium on Olefin Metathesis, Hull, August 1987.
126. R. Streck, paper, presented at the 7th International Symposium on Olefin Metathesis, Hull, August 1987; *J. Mol. Catal.*, **46**, 305 (1988).
127. R. R. Schrock, paper presented at the 7th International Symposium on Olefin Metathesis, Hull, August 1987.
128. A. Draxler, *Kautsch. Gummi*, **12**, 1037 (1983).
129. P. A. Patton and T. J. McCarthy, *Macromolecules*, **20**, 778 (1987).
130. T. Ueshima and S. Kobayashi, *Jpn. Plast. (Engl.)*, **8**, 11 (1974).
131. R. Streck, *J. Mol. Catal.*, **15**, 3 (1982).
132. J. G. Hamilton, K. J. Ivin, J. J. Rooney, and L. C. Waring, *J. Chem. Soc., Chem. Commun.*, 159 (1983); J. G. Hamilton, K. J. Ivin, and J. J. Rooney, *Br. Polym. J.*, **16**, 21 (1984).
133. K. F. Castner and N. Calderon, *J. Mol. Catal.*, **15**, 47 (1982).
134. A. B. Alimuniar, J. H. Edwards and W. J. Feast, *J. Mol. Catal.*, **28**, 313 (1985).
135. P. M. Blackmore and W. J. Feast, *Polymer*, **27**, 1296 (1986); *J. Mol. Catal.*, **36**, 145 (1986); P. M. Blackmore, W. J. Feast, and P. C. Taylor, *Br. Polym. J.*, **19**, 205 (1987).
136. I. F A. F. El-Saafin and W. J. Feast, *J. Mol. Catal.*, **15**, 61 (1982).
137. W. J. Feast and K. Harper, *J. Mol. Catal.*, **28**, 293 (1985).
138. W. J. Feast and I. S. Millichamp, *J. Mol. Catal.*, **28**, 331 (1985).
139. *Plast. Focus*, **14**, No. 22, 3 (July 1982).
140. R. P. Geer and R. D. Stoutland, in *Plastics 85. Proceedings of the SPE 43rd Annual Technical Conference, ANTEC '85*, 1985, p. 1232.
141. J. H. Edwards, W. J. Feast, and D. C. Bott, *Polymer*, **25**, 359 (1984); D. C. Bott, C. S. Brown, C. K. Chai, N. S. Walker, W. J. Feast, P. J. S. Foot, P. D. Calvert, N. C. Billingham, and R. H. Friend, *Synth. Met.*, **14**, 245 (1986); P. D. Townsend, D. D. C. Bradley, M. E. Horton, C. M. Pereira, R. H. Friend, N. C. Billingham, P. D. Calvert, P. J. S. Foot, D. C. Bott, C. K. Chai, N. S. Walker, and K. P. J. Williams, in *Springer Series in Solid State Sciences*, Vol. 63, Electronic

Properties of Polymers and Related compounds, Eds. H. Kuzmany, M. Mehring, and S. Roth, Springer, Berlin 1985, p. 50, and references cited therein.
142. L. R. Gilliom and R. H. Grubbs, *J. Am. Chem. Soc.*, **108**, 733 (1986).
143. R. R. Schrock, J. Feldman, R. H. Grubbs, and L. Cannizzo, *Macromolecules*, **20**, 1169 (1987).
144. J. S. Murdzek and R. R. Schrock, *Macromolecules*, **20**, 2640 (1987).
145. B. M. Novak and R. H. Grubbs, *J. Am. Chem. Soc.*,, **110**, 960 (1988), and papers in press.

Part 3
Synthetic Reagents

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 7

The use of transition metal clusters in organic synthesis

G. SÜSS-FINK[a] and F. NEUMANN

Aachen University of Technology, Institute of Inorganic Chemistry, Templergraben 55, D-5100 Aachen, FRG

[a]Author to whom correspondence should be addressed. Present address: Institut de Chemie, Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland.

I. INTRODUCTION

The past two decades have seen a rapidly growing chemistry of transition metal complexes containing more than one metal atom. Such complexes are generally referred to as 'transition metal clusters', and several definitions have been proposed for the term 'cluster'. The most generally accepted one is that given by Cotton[1], according to which a metal cluster consists of a finite group or skeleton of metal atoms held together completely, mainly, or at least to a considerable extent by bonding directly between those atoms, even though some other atoms may be associated intimately with the cluster. More restrictive definitions such as that offered by Johnson[2], in which a cluster compound is regarded as a discrete unit containing at least three metal atoms with metal–metal bonding being present, are questionable, because they exclude important classes of compounds: dinuclear

transition metal complexes can exhibit chemical and spectroscopic properties similar to those of tri- and tetra-nuclear systems, and heteronuclear systems containing a central M_4X_4 cube in which there may be strong, weak, or no metal–metal bond interactions should not be divided into cluster-type and non-cluster-type species. Hence, metal–metal bond interactions and nuclearities of at least three are doubtful criteria for the cluster terminology. In order to avoid delimitation problems, such definitions should not be used in a strict sense of the term.

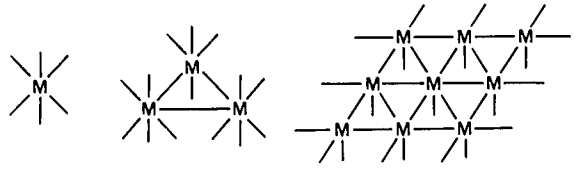
Representatives of metal cluster compounds have been known for a long time: the first transition metal cluster reported in the literature is probably $[Fe_3(CO)_{12}]$, compositionally described as 'iron tetracarbonyl' in 1905[3]. The structure of this compound, however, remained controversial until the resolution of the X-ray crystal data by Wei and Dahl[4]. With the progress in X-ray crystallography and neutron diffraction methods, structural information of more and more complicated cluster compounds became available. Although a general theory accounting for all the structural features of metal clusters is still lacking, the topologies of metal cluster compounds have been rationalized on the basis of different electronic and geometric approaches; particularly noteworthy are the skeleton electron pair theory[5–8], graph theory[9,10], perturbed spherical shell theory[11], isolobal concept[12,13], extended Hückel molecular orbital calculations[14–16], Fenske–Hall approximation, Hartree–Fock calculations[17,18], SCG-Xα-SW calculations[19,20], ligand packing theory[21] and the topological electron counting theory[22].

A. The Challenge of Clusters in Catalysis

The rapid development of transition metal cluster chemistry was stimulated by the prospects of catalytic applications. Although these optimistic expectations have been met only in part, the possible catalytic potential has remained a major impetus in this chemistry.

1. The cluster–surface analogy

As oligonuclear species, metal clusters occupy the no-man's-land between mononuclear clusters on the one hand and polynuclear metal surfaces on the other. Most metal clusters are soluble molecular compounds which react in homogeneous phases with substrates, and which can be isolated and characterized like mononuclear metal complexes. On the other hand, metal clusters show typical phenomena known for polynuclear metal surfaces such as polycentric ligand–metal bonds and delocalized metal–metal bonds. Chini[23] was the first to realise the common features of metal cluster ligand shells and molecules chemisorbed on metal surfaces, and to suggest metal clusters as models for catalytic reactions on metal surfaces. In 1975 Lewis and Johnson[24], Ugo[25], and Muetterties[26] pointed out with many examples the striking analogy between metal clusters and metal surfaces. Muetterties[27] formulated what is known as the 'cluster–surface analogy' by regarding metal clusters as small pieces of metal with chemisorbed species on the periphery. Consequently, one of the main interests in cluster chemistry arises from



studying fundamental transformations of ligands on a cluster skeleton as models for steps discussed in heterogeneous catalysis.

2. *Clusters—a new generations of catalysts?*

As mentioned above, oligonuclear metal clusters can be placed between mononuclear metal complexes and polynuclear metal surfaces. Because of this intermediate position between typical homogeneous and typical heterogeneous catalysts, transition metal clusters may not only be discussed as models for heterogeneous catalysts, but they may equally serve as homogeneous catalysts themselves. The potential of transition metal clusters as homogeneous catalysts was pointed out by Johnson and Lewis[28]. Muetterties and Krause[29] were the first to claim unique catalytic properties for transition metal clusters, raising expectations that transition metal clusters might provide a new generation of soluble catalysts.

B. Reactivity of Coordinated Substrates on Clusters

There are numerous examples of transformations of organic substrates on transition metal clusters. These reactions have been reviewed from many facets[30–38]; two recent reviews concentrated on organometallic cluster chemistry relevant to catalytic pathways[39,40]. In this section only a few topical examples will be selected.

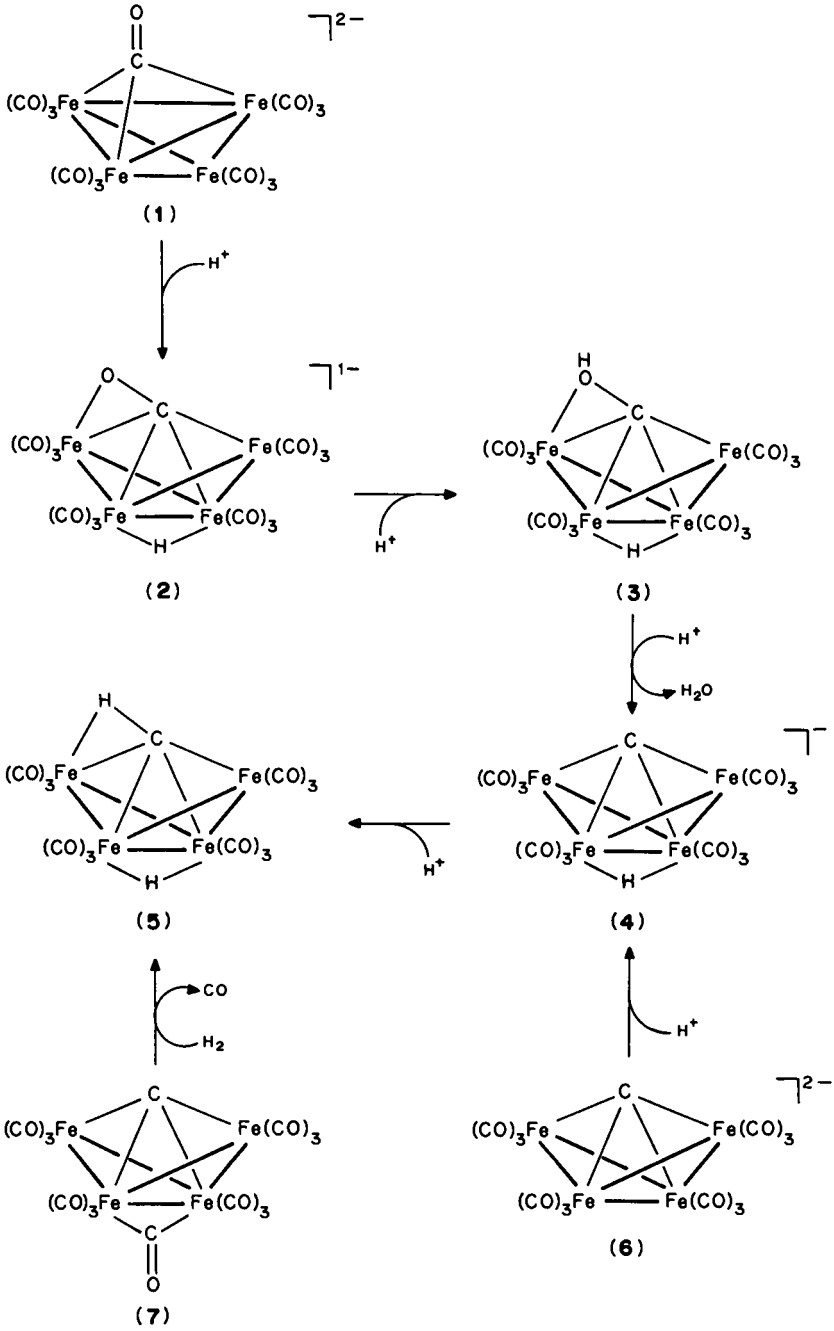
1. *Transformation of carbonyl ligands into carbide and hydrocarbon fragments*

One of the most fascinating developments in organometallic cluster chemistry was launched by recent studies on tetranuclear iron carbide clusters, pioneered by Muetterties, Shriver and Bradley. Unlike metal clusters with interstitial carbide atoms, in these systems the carbide ligand, originating from a carbonyl group, is structurally exposed towards the cluster surface and therefore accessible to various reactions (Scheme 1). The tetranuclear dianion $[Fe_4(CO)_{13}]^{2-}$(**1**), possessing a triple-bridging carbonyl ligand on a slightly distorted tetrahedral metal skeleton, can be protonated at the iron framework to give the anion $[HFe_4(CO)_{13}]^-$ (**2**)[41,42]. In this reaction the iron tetrahedron is opening up to an iron butterfly arrangement held together by an η^2-CO ligand. A second protonation step takes place at the oxygen atom of the carbonyl bridge resulting in the formation of the neutral cluster **3**[42]. Further protonation leads to the elimination of H_2O, generating the anionic carbide cluster $[HFe_4(CO)_{12}C]^-$ (**4**)[43–45], also accessible by protonation of the dianion $[Fe_4(CO)_{12}C]^{2-}$ (**6**)[43–45]. The carbide cluster **4** further protonates to the methylidine cluster **5**[43–45], which alternatively can be synthesized by hydrogenation of $[Fe_4(CO)_{13}C]$ (**7**)[46]. This reaction sequence mimics fundamental reduction steps assumed in heterogeneous Fischer–Tropsch chemistry[47].

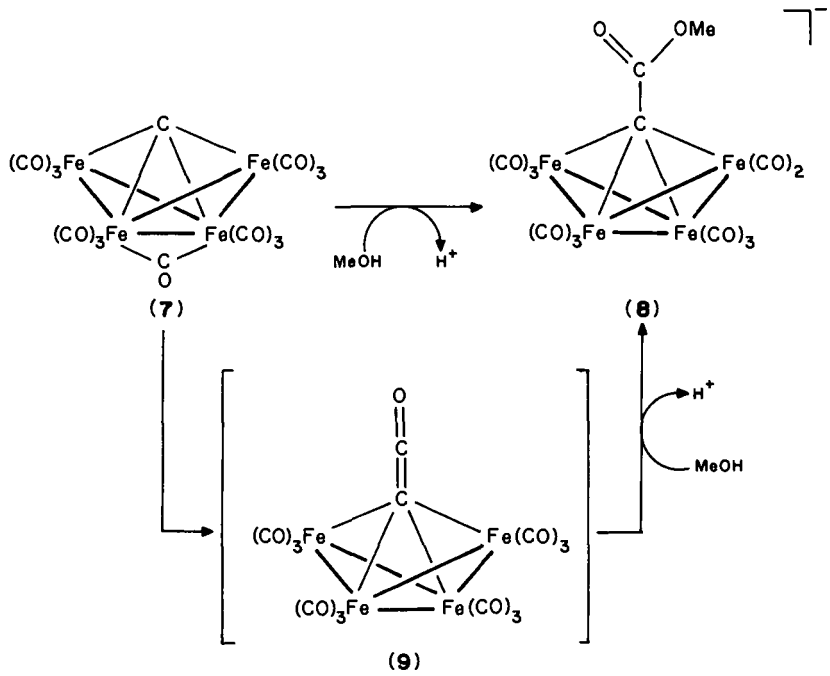
The carbido ligand in $[Fe_4(CO)_{13}C]$ (**7**) is attacked by methanol to give a CCOOMe ligand in the anionic cluster **8** (Scheme 2)[45], also accessible by oxidation of the hexanuclear cluster anion $[Fe_6(CO)_{16}C]^{2-}$ containing an encapsulated carbide ligand[47,48]. The reaction presumably proceeds through the intermediacy of the ketenylidene intermediate. This transformation clearly demonstrates the reactivity of a carbide enveloped by a metal skeleton provided that it is structurally exposed.

2. *Coordination and reduction of π-systems*

A reaction sequence particularly related to catalysis was studied by Andrews and Kaesz[49]. By a complete series of isolated and structurally characterized intermediates, the stepwise reduction of acetonitrile on the face of a triangular iron cluster was demonstrated.



SCHEME 1



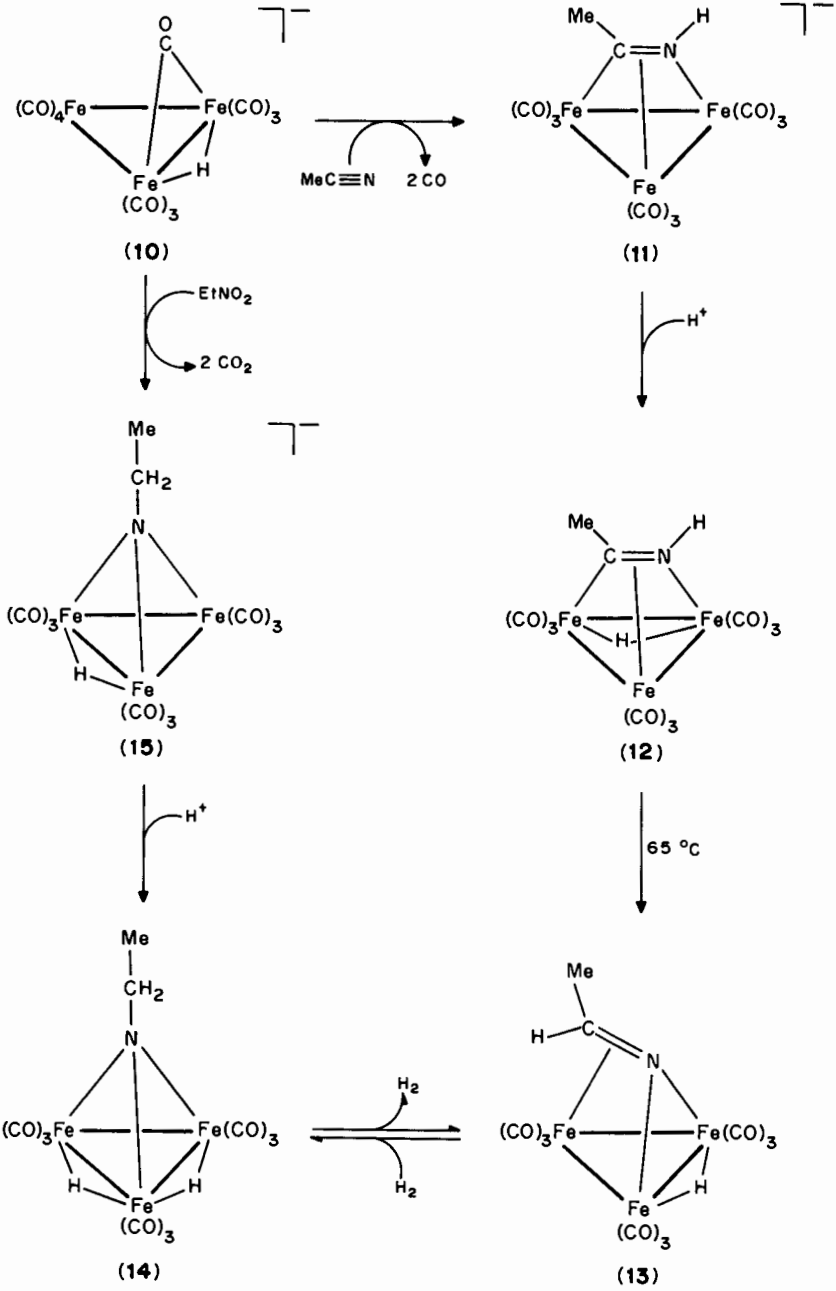
SCHEME 2

Acetonitrile reacts with the cluster anion $[HFe_3(CO)_{11}]^-$ (**10**) with replacement of two carbonyl groups (Scheme 3); the hydride is transferred from the metal framework to the incoming acetonitrile to give a MeC=NH ligand coordinated in a μ_3–η^2 fashion to the metal triangle[49,50]. The resulting cluster anion **11** may be protonated at the metal skeleton to give the neutral acetimidoyl cluster **12**, which is isomerized irreversibly at 65 °C to give the ethylidenimido cluster **13**[49–51]. Under a pressure of hydrogen **13** is reversibly converted into the ethylnitreno cluster **14**[50,52,53], also accessible from **10** with nitroethane followed by protonation of the intermediate anion **15**[49]. Although all efforts to make this reaction sequence catalytic failed[54], the stepwise conversion of MeCN and H_2 into the coordinated $MeCH_2N$ and H fragments of ethylamine on a triangular cluster face is an expressive example of the substrate conversion capability of transition metal clusters.

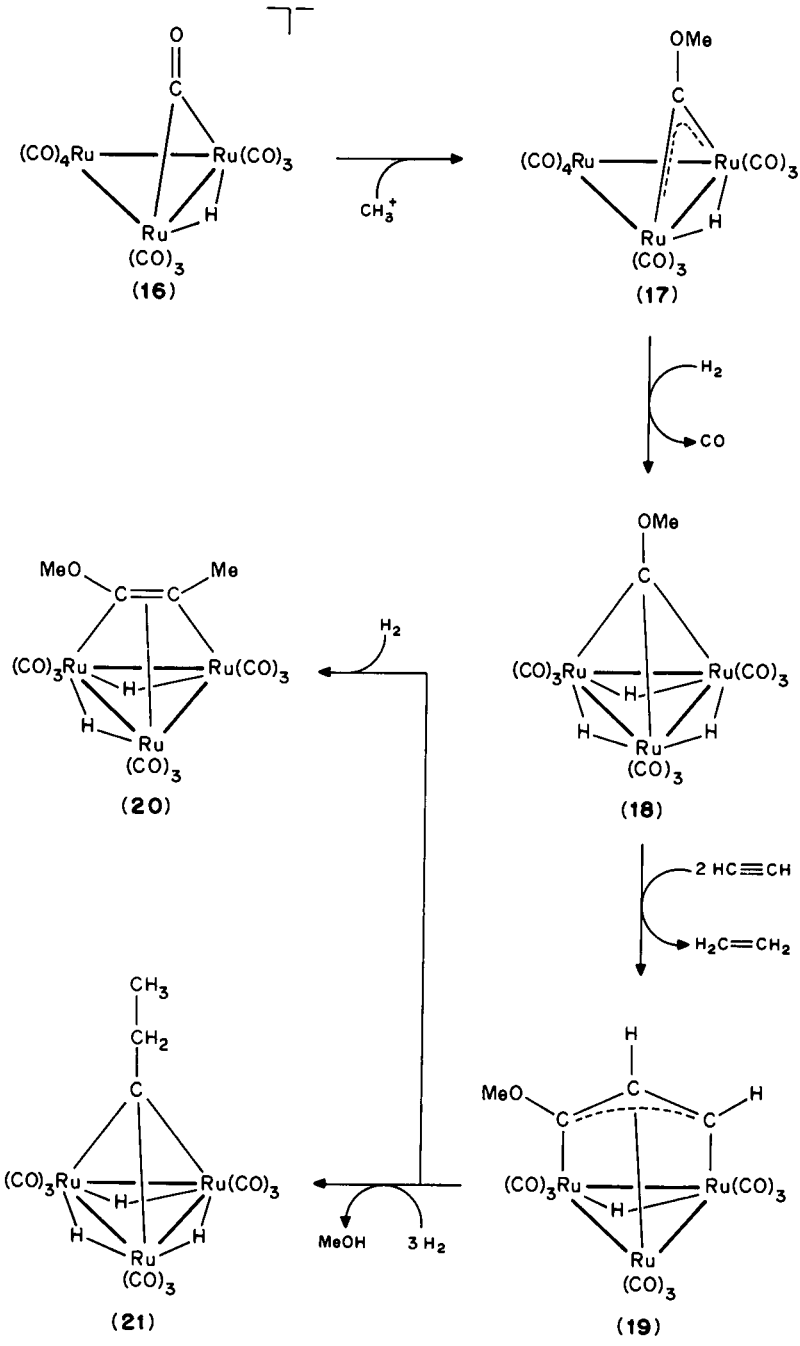
3. Coupling of π-systems with polyhapto ligands

Many reactions are known in which two organic systems are coupled together on coordination to a transition metal cluster. A remarkable example was worked out recently by Keister and coworkers.

The μ_2-methoxycarbyne cluster **17**, obtained from the methylation of the cluster anion $[HRu_3(CO)_{11}]^-$ (**16**) with either $MeSO_3F$[53] or $[Me_3O][BF_4]$[55], reacts with hydrogen to give the μ_3-methoxycarbene cluster **18** (Scheme 4)[53,56]. In this cluster the μ_3-COMe ligand can be coupled with an alkyne to give a MeOCCHCH ligand; a second alkyne molecule is required to remove two hydride ligands, producing the corresponding olefin[57,58]. The resulting cluster **19** undergoes hydrogenation to give the μ_3,η^2-MeOC=


(CO)4Fe
Fe(CO)3
Fe(CO)3
MeC≡N
2 CO
(10)
(11)
EtNO2
2 CO2
H+
Me
CH2
N
(15)
(12)
H+
65 °C
H2
H2
(14)
(13)

SCHEME 3


O
C
(CO)4Ru
Ru(CO)3
H
Ru
(CO)3
(16)
CH3+
OMe
C
(CO)4Ru
Ru(CO)3
H
Ru
(CO)3
(17)
H2
CO
OMe
C
(CO)3Ru
Ru(CO)3
H
H
H
Ru
(CO)3
(18)
2 HC≡CH
H2C=CH2
MeO
Me
C
C
(CO)3Ru
Ru(CO)3
H
H
Ru
(CO)3
(20)
H2
CH3
CH2
C
(CO)3Ru
Ru(CO)3
H
H
H
Ru
(CO)3
(21)
MeOH
3 H2
H
MeO
C
C
C
H
(CO)3Ru
Ru(CO)3
H
Ru
(CO)3
(19)

SCHEME 4

CMe cluster **20**[59]; the main product, however, is the μ_3-ethylcarbyne cluster **21**[57,58]. The conversion of the alkylidene cluster **18** into the alkylidyne cluster **21** with a longer carbon chain has been suggested as a model for Fischer–Tropsch carbon chain growth[57].

II. STOICHIOMETRIC REACTIONS

A. General Considerations

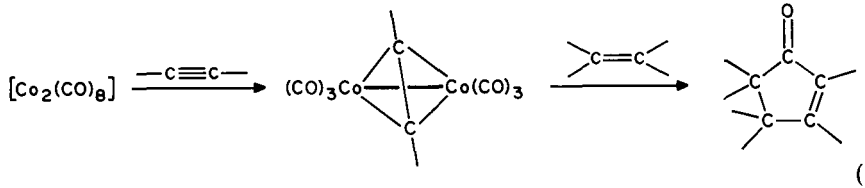
The number of organic syntheses involving stoichiometric amounts of transition metal clusters is limited. Useful synthetic reactions that have been reported employ almost exclusively inexpensive iron and cobalt clusters. Two of the drawbacks in stoichiometric applications are the high cost and the inefficient preparation of precious metal clusters[60]. Many reactions of transition metal clusters leading to organic compounds are known, but they are of no synthetic value since the organic compounds in question are more easily accessible by conventional methods. This problem is exemplified by the formation of amides, imidates and carbamates from the trinuclear iron nitrene clusters **22**–**25** reported by Geoffroy *et al.*[61] (Scheme 5). Of more synthetic interest are stoichiometric reactions of transition metal clusters leading to more sophisticated organic systems such as heterocycles. In this fashion the nitrene cluster $[Ru_3(CO)_{10}(NPh)]$ (**29**) can be used via **30** as a precursor to pentaphenylpyridone and 1,3,4-triphenylmaleimide[62,63] (Scheme 6). However, these compounds are also accessible in a more efficient way via mononuclear nickel complexes[64]. In general, stoichiometric reactions of transition metal clusters to give organic products can only compete with other synthetic routes if these clusters are inexpensive and easily accessible, or if the organic products formed are difficult to make by alternative methods.

B. Reactions Involving Co_2C_2 Clusters

The most useful stoichiometric cluster reactions for organic synthesis involve pseudo-tetrahedral Co_2C_2 clusters of the type $[Co_2(CO)_6(R^1C_2R^2)]$, which can be prepared from $[Co_2(CO)_8]$ and alkynes.

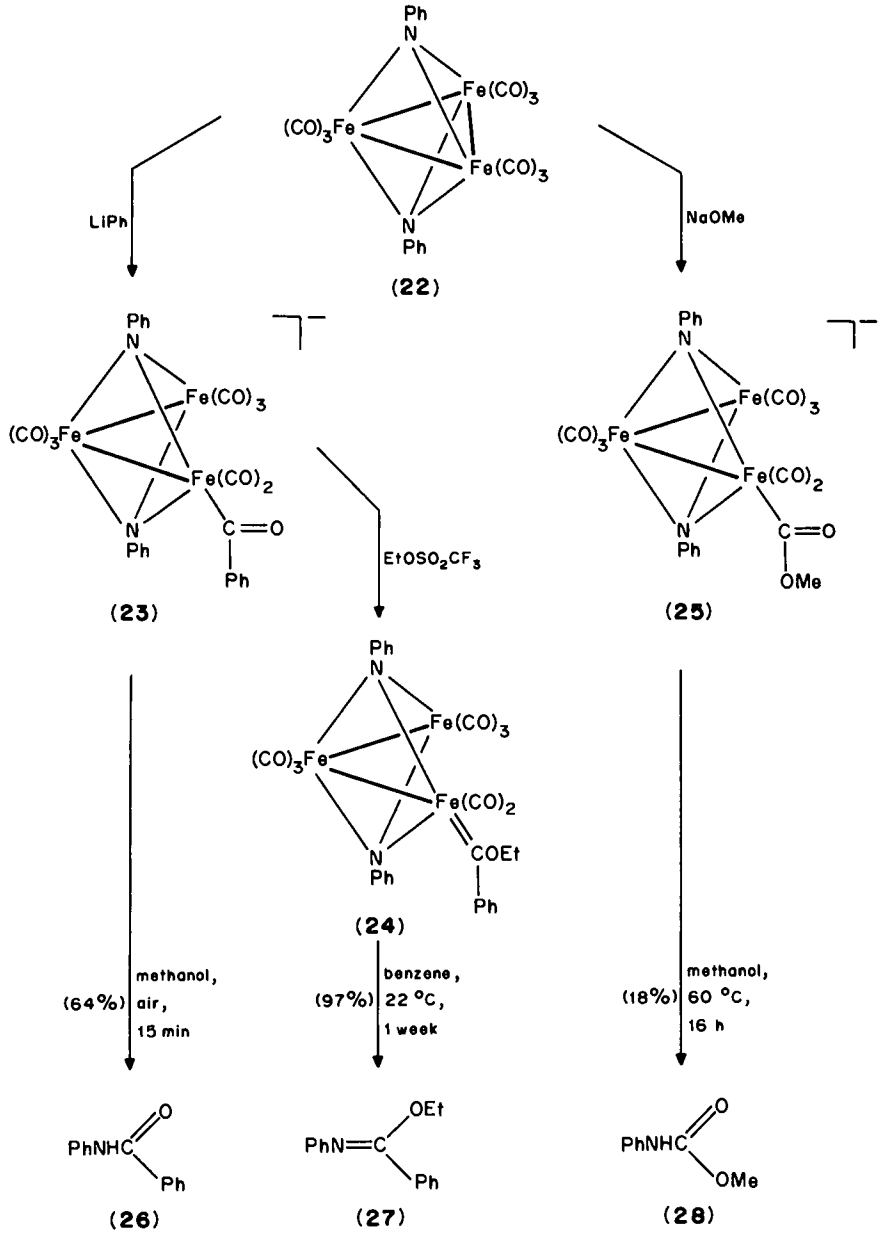
1. The Khand–Pauson reaction

The Khand–Pauson reaction is the formation of cyclopentenones in a single step from the clusters $[Co_2(CO)_6(R^1C_2R^2)]$ and alkenes. The utility of this reaction[65,66] is due to the facile formation of the clusters $[Co_2(CO)_6(R^1C_2R^2)]$ from dicobaltoctacarbonyl and the alkyne. Although in most synthetic applications these clusters have been isolated, it has been established that this is not essential[67]. In many cases the cyclopentenones can be built up in a one-pot preparation from the alkyne, the alkene and carbon monoxide with $[Co_2(CO)_8]$ being present in an equimolar ratio (equation 1).

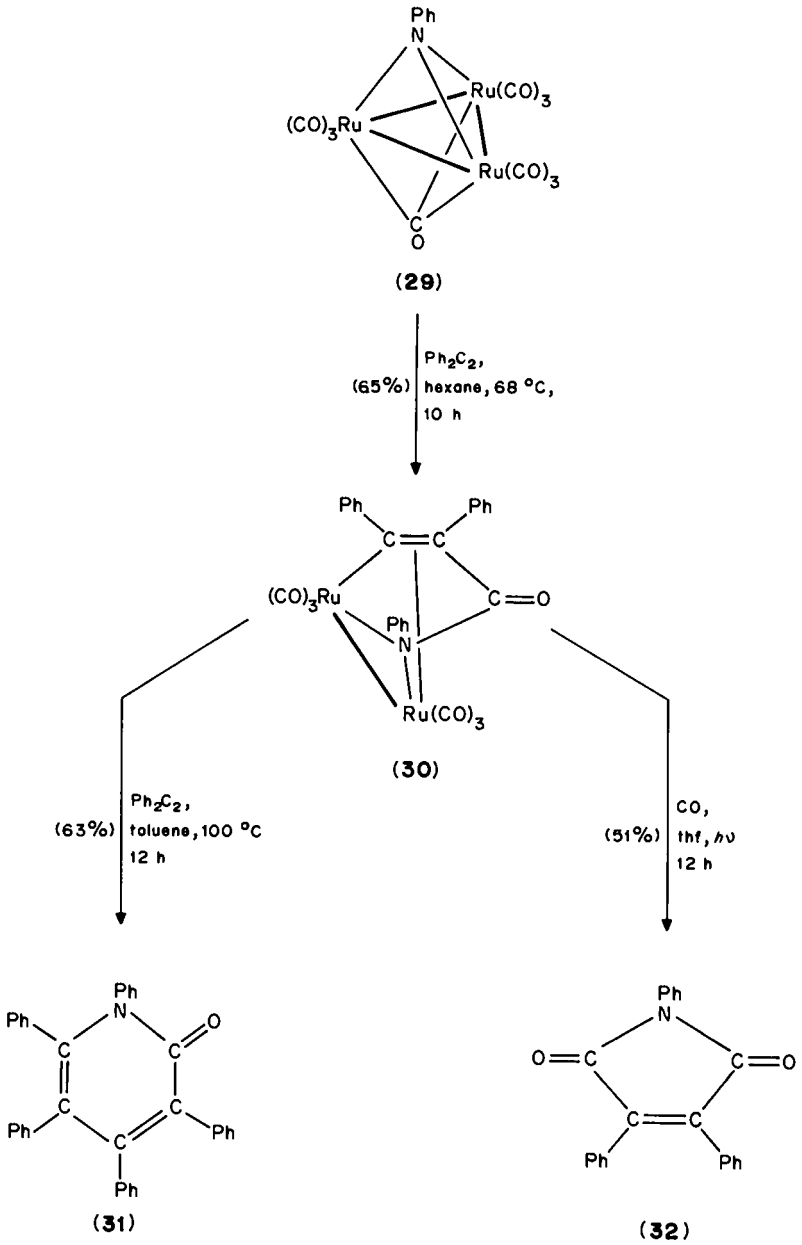


(1)

This reaction sequence occurs with a high degree of both regio- and stereo-selectivity: The carbonyl group inserts mostly in vicinity to the larger substituent of the alkyne, and by

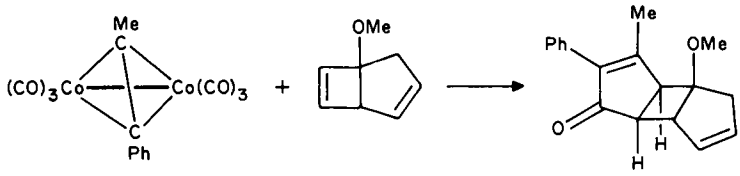

Ph
N
Fe(CO)3
(CO)3Fe
Fe(CO)3
N
Ph
(22)
LiPh
NaOMe
Fe(CO)2
C=O
Ph
(23)
EtOSO2CF3
OMe
(25)
COEt
(24)
methanol,
(64%) air,
15 min
benzene,
(97%) 22 °C,
1 week
methanol,
(18%) 60 °C,
16 h
PhNHC
O
OEt
PhN=C
OMe
(26)
(27)
(28)

SCHEME 5


Ph
N
Ru(CO)3
(CO)3Ru
Ru(CO)3
C
O
(29)
(65%)
Ph2C2,
hexane, 68 °C,
10 h
Ph
C=C
Ph
(CO)3Ru
C=O
Ph
N
Ru(CO)3
(30)
(63%)
Ph2C2,
toluene, 100 °C
12 h
(51%)
CO,
thf, hν
12 h
Ph
N
O
Ph
C
C
O
C
C
Ph
C
Ph
Ph
(31)
Ph
N
O=C
C=O
C=C
Ph
Ph
(32)

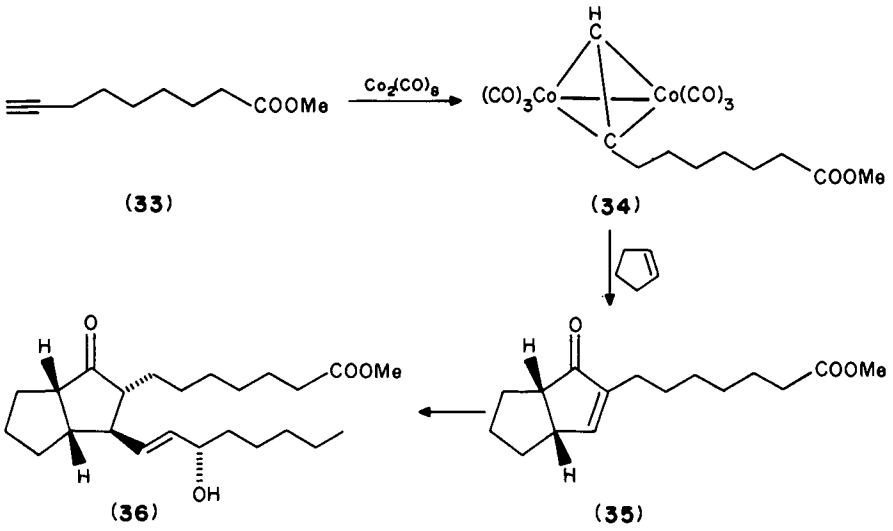
SCHEME 6

the addition of cyclic olefins the *exo* product is formed. The remarkable stereoselectivity is demonstrated by the annelation to cyclobutenes using acetylenehexacarbonyldicobalt clusters (equation 2)[68].



(2)

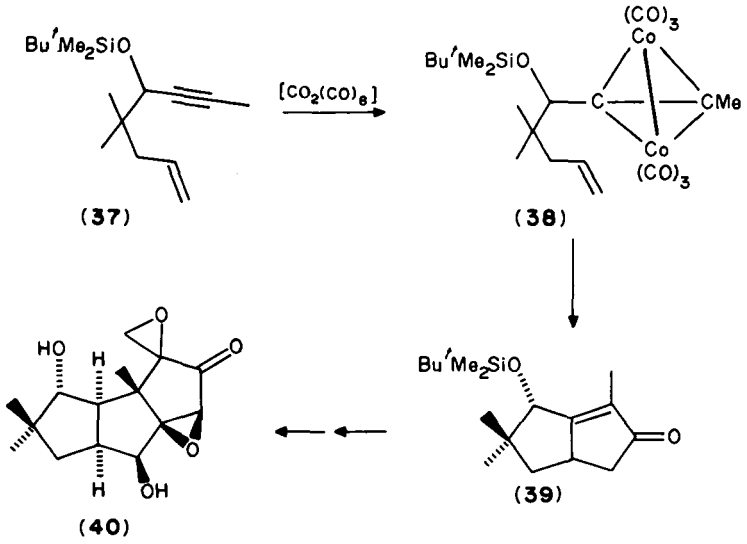
The scope of the Khand–Pauson reaction is remarkable; it has been widely used in the synthesis of natural products and its synthetic applications have been reviewed several times[69,70], two recent reviews[71,72] covering the literature up to 1986. Therefore, only a few topics will be selected here as examples. Specially designed Co_2C_2 clusters have been used as prostaglandin synthons: Pauson *et al.*[73] developed a synthesis of (±)-11-desoxy-10α, 11α-trimethyleneprostaglandine E_1 (**36**), starting from the alkyne **33** (Scheme 7). The key step is the annelation of cyclopentene to the cluster **34**.



SCHEME 7

The total synthesis of the antitumour sesquiterpene *d,l*-coriolin (**40**) is based on a stereoselective intramolecular cyclization involving the appropriate Co_2C_2 cluster **38**[74,75] (Scheme 8). This step yields 15% of the desired stereoisomer of the bicyclic system **39**, which can be converted in a series of consecutive steps into **40**.

The fate of the metal carbonyl moiety in the Khand–Pauson reactions remains unclear; since $[Co_2(CO)_8]$ can be easily recovered from almost every cobalt residue under CO pressure, there is no recycling problem for the metal carbonyl.

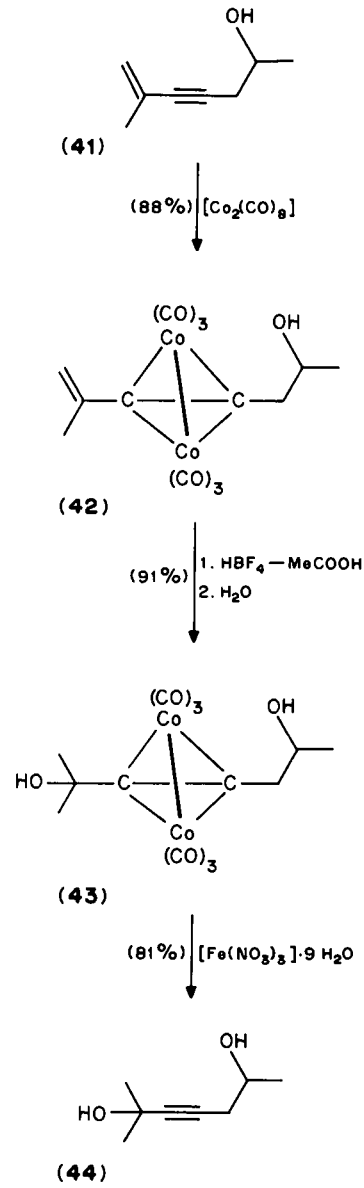


SCHEME 8

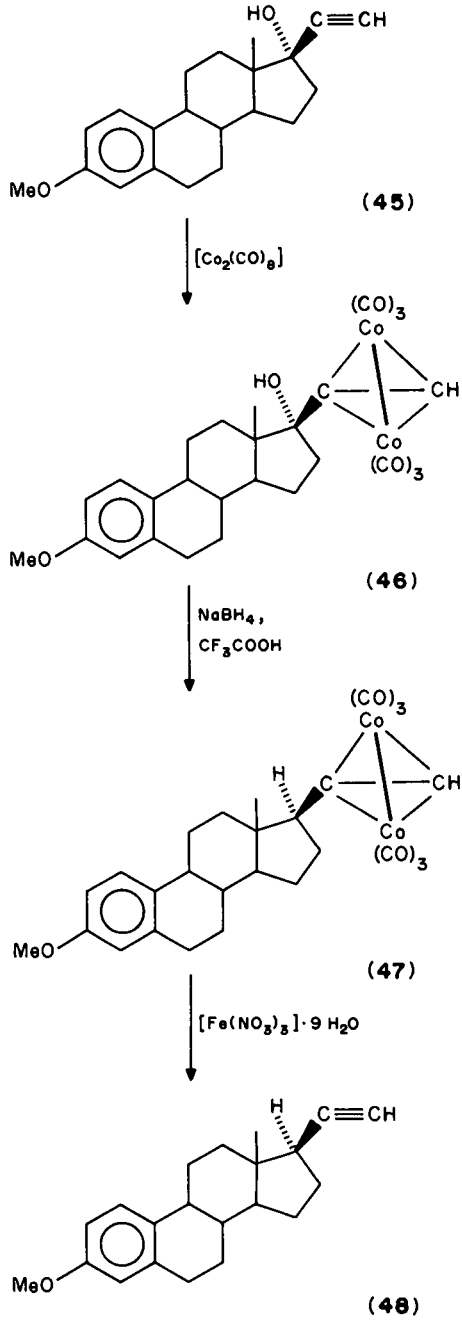
2. *Miscellaneous*

A number of synthetic applications of Co_2C_2 clusters use the dicobalt hexacarbonyl unit as an alkyne-protecting group. The principle of this strategy is based on the facile coordination of the carbon—carbon triple bond to the dicobalt unit and the possibility of removing the metal fragment with oxidizing agents such as $[Fe(NO_3)_3]\cdot 9H_2O$. An efficient functionalization of olefinic bonds without affecting the reactive C≡C bonds present in the same molecule was achieved with this method[76] (Scheme 9). In the complex **42** and **43** the alkyne moiety is protected while the olefinic bond is hydrolysed. A similar reaction sequence resulting in both the hydrolysis and the methanolysis of the olefin moiety of enynes has been reported[77]. The strategy can be extended to other transformations of functionalized alkynes; e.g. alcoholic groups can be removed by reduction with sodium borohydride without reducing the C≡C triple bond in the presence of the $Co_2(CO)_6$ protecting group (Scheme 10)[78]. The steroid **48** can be obtained from **45** in an overall yield of 85% with a stereoselectivity greater than 90%.

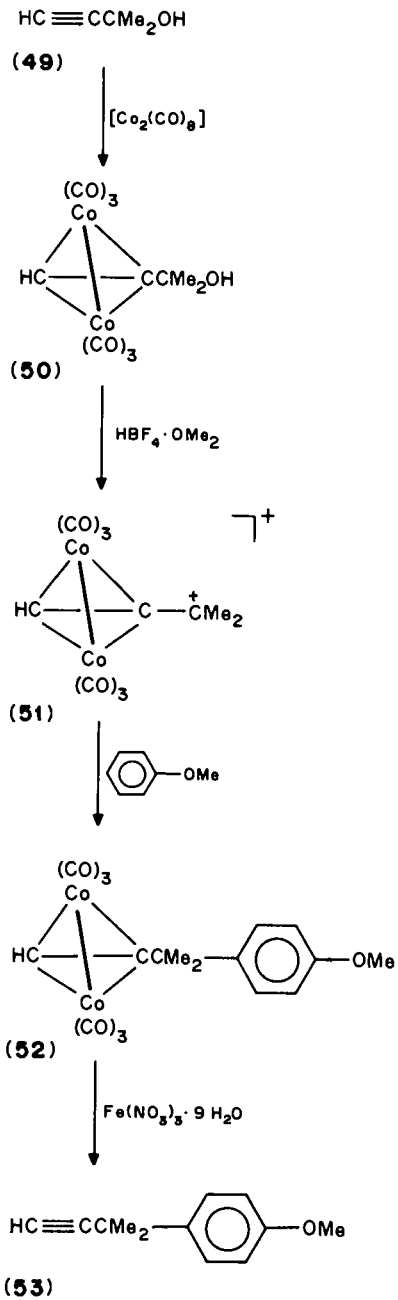
Protonation of Co_2C_2 clusters containing an alcohol function in the α-position of the side-chain with HBF_4 or $HSbF_6$ leads to carbonium cations of the type $[Co_2(CO)_6(R^1C{\equiv}CCR^2R^3]^+$, which can be isolated as stable salts[79]. These cationic clusters have been used for electrophilic substitution reactions with aromatics[80] or ketone derivatives[81] (Schemes 11 and 12). In this way aromatic compounds with alkyl substituents containing a C≡C triple bond in the β-position can be prepared; thus **53** is accessible from the acetylene **49** in an overall yield of 43% via the carbonium ion **51**[79]. In this example only the *para*- derivative **53** was obtained. With less bulky substituents in the α-position of the acetylene there is a considerable amount of the *meta* product in addition to the *para*-product[80]. Alternatively, **51** can be transformed with the *O*-trimethylsilylated cyclohexanone into the alkyne **55** in an overall yield of 57%[81]. The opening of the cyclopropene ring containing a 2-yn-1-ol substituent with $HBr–ZnBr_2$ to give the corresponding *E* and *Z* olefins can be controlled to give almost exclusively the *E* isomer by going through the intermediacy of the Co_2C_2 clusters (Scheme 13)[82]. The cyclopropane **56**, which on


OH
(41)
(88%) [Co2(CO)8]
(CO)3
Co
OH
C
C
Co
(CO)3
(42)
(91%) 1. HBF4 — MeCOOH
2. H2O
(CO)3
Co
OH
HO
C
C
Co
(CO)3
(43)
(81%) [Fe(NO3)3]·9 H2O
OH
HO
(44)

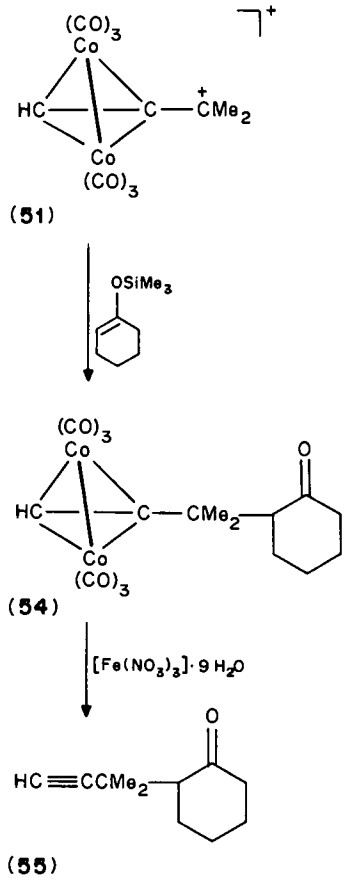
SCHEME 9


HO
C≡CH
MeO
(45)
[Co2(CO)8]
(CO)3
Co
HO
C
CH
Co
(CO)3
MeO
(46)
NaBH4,
CF3COOH
(CO)3
Co
H
C
CH
Co
(CO)3
MeO
(47)
[Fe(NO3)3]·9 H2O
H
C≡CH
MeO
(48)

SCHEME 10


HC≡CCMe2OH
(49)
[Co2(CO)8]
(CO)3
Co
HC
CCMe2OH
Co
(CO)3
(50)
HBF4·OMe2
(CO)3
Co
HC
C
+
CMe2
Co
(CO)3
(51)
OMe
(CO)3
Co
HC
CCMe2
OMe
Co
(CO)3
(52)
Fe(NO3)3·9 H2O
HC≡CCMe2
OMe
(53)

SCHEME 11



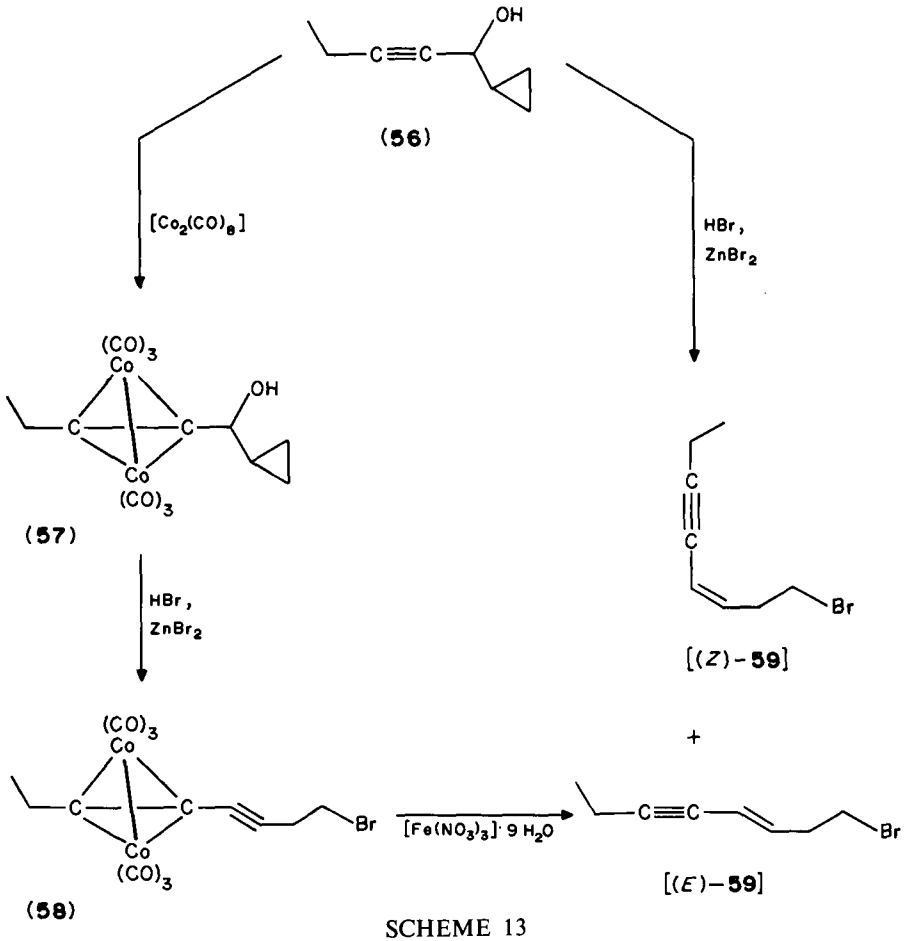
SCHEME 12

reaction with HBr–$ZnBr_2$ yields 1-bromoct-3-en-5-yne (**59**) with an *E*/*Z* ratio of 33:67, can be converted into cluster **57**. After treatment with HBr–$ZnBr_2$, resulting in the formation of **58**, the compound can be demetallated with $[Fe(NO_3)_3]\cdot 9H_2O$; in this case the *E*/*Z* ratio of the product **59** is 99:1[82].

Another synthetic use of Co_2C_2 clusters was reported by Seyferth and Wehman[98]: whereas diphenylacetylene is not accessible to Friedel–Crafts reactions, the cluster $[Co_2(CO)_6(C_2Ph_2)]$ undergoes facile acylation with MeCOCl–$AlCl_3$ in the *para* position of one (51%) or both phenyl substituents (36%). Oxidative work-up with ammonium cerium(IV) nitrate gives phenyl(*p*-acetylphenyl)acetylene (75%) and bis(*p*-acetylphenyl)-acetylene (72%), respectively.

C. Reactions Involving Other Cobalt Clusters

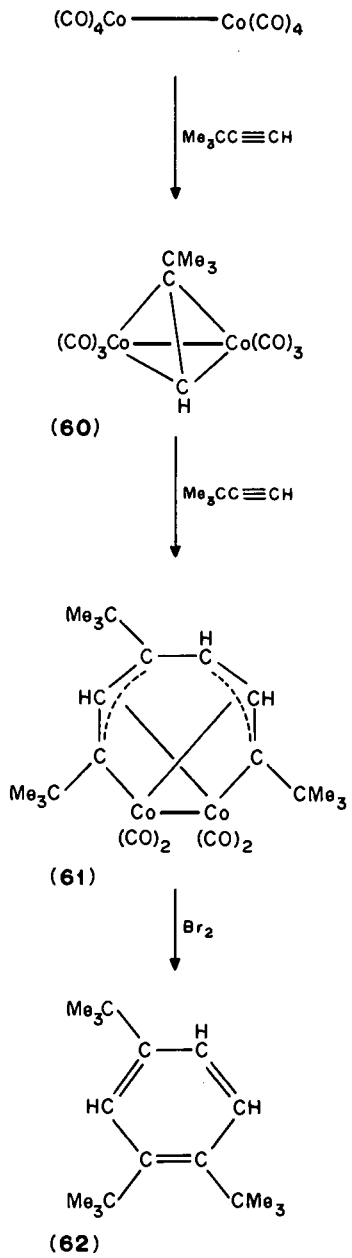
The pseudotetrahedral clusters $[Co_2(CO)_6(R^1C_2R^2)]$ (**60**) can take up acetylenes to give complexes of the general formula $[Co_2(CO)_4(R^1C_2R^2)_3]$[83,84]. These compounds contain a six-carbon atom flyover bridge formed by the head-to-tail–head-to-head trimerization



SCHEME 13

of three alkyne molecules[85]. The thermal or chemical decomposition of these compounds gives substituted benzenes; sterically strained 1,2,4-tri-*tert*.-butylbenzene (**62**) has been synthesised for the first time by this method (Scheme 14)[86].

A major class of cluster compounds with considerable interest for organic synthesis are the alkylidyne tricobalt nonacarbonyl complexes of the general type $[Co_3(CO)_9(CR)]$. The first representative, $[Co_3(CO)_9(CCH_3)]$[87], was prepared by acidification of $[Co_2(CO)_6(C_2H_2)]$; X-ray crystal structure analysis established the pseudo-tetrahedral Co_3C cluster[88]. A more general preparative route to such clusters is the reaction of $[Co_2(CO)_8]$ with the trihalides RCX_3[89–91]. The chemistry of these compounds has been reviewed several times[92–96]. By decomposition of the Co_3C clusters the alkylidyne unit is released from the metal framework and can be used for synthetic applications. Decomposition of $[Co_3(CO)_9(CR)]$ with ammonium cerium(IV) nitrate mainly yields the acetylene $RC{\equiv}CR$[97]; with an excess of the oxidizing agent the carboxylic acid RCOOH is formed cleanly[98,99]. The ethylidyne cluster $[Co_3(CO)_9(CMe)]$ has been reported to give the ester $MeCH(COOMe)_2$ on reaction with sodium methanolate in methanol in 50%


(CO)4Co
Co(CO)4
Me3CC≡CH
CMe3
C
(CO)3Co
Co(CO)3
C
H
(60)
Me3CC≡CH
Me3C
H
C
C
HC
CH
C
C
Me3C
CMe3
Co
Co
(CO)2
(CO)2
(61)
Br2
Me3C
H
C
C
HC
CH
C
C
Me3C
CMe3
(62)

SCHEME 14

yield[100], or to give propionaldehyde under hydroformylation conditions[100]. The benzylmethylidyne unit in $[Co_3(CO)_9(CCH_2Ph)]$ can be removed as PhEt with sodium borohydride[97], or as $PhCH_2CBr_3$ with bromine[101]. The benzylidyne cluster $[Co_3(CO)_9(CPh)]$ (**63**) has been used for the preparation of *para*-acylated benzoic acids; the phenyl substituent in this cluster readily undergoes Friedel–Craft-acylation with acetyl chloride or benzoyl chloride and the organic unit modified in this way can be released by oxidation with ammonium cerium(IV) nitrate in acetone to give **65** or **67**, respectively[98] (Scheme 15).

D. Reactions Involving Iron Clusters

Dodecacarbonyltriiron can be used as an effective reducing agent for the conversion of nitroaryls into the corresponding amines (Table 1). The reaction is carried out either in methanol–benzene[103] or under phase-transfer conditions ($PhCH_2NEt_3Cl$ in aqueous sodium hydroxide)[104,105]. The source of hydrogen is methanol or water, respectively, and the active species formed in both cases seems to be the cluster anion $[HFe_3(CO)_{11}]^-$ [103–105].

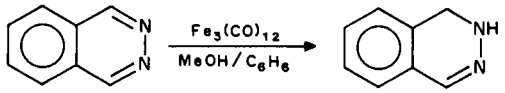
TABLE 1. Reduction of nitroaryls to anilines by $[Fe_3(CO)_{12}]$

$$RC_6H_4NO_2 \longrightarrow RC_6H_4NH_2$$

R	Yield (%)[103] (method a)[a]	Yield (%)[104] (method b)[b]
H	77	
p-Me	73	85
p-OMe	84	92
p-Cl	86	88
p-COMe	91	60[c]
p-NH_2	63	
p-COOEt	83	
p-OH	38	
p-NHCOMe	77	
o-Me	87	
o-Cl	83	
m-NH_2	95	
m-NO_2	77	

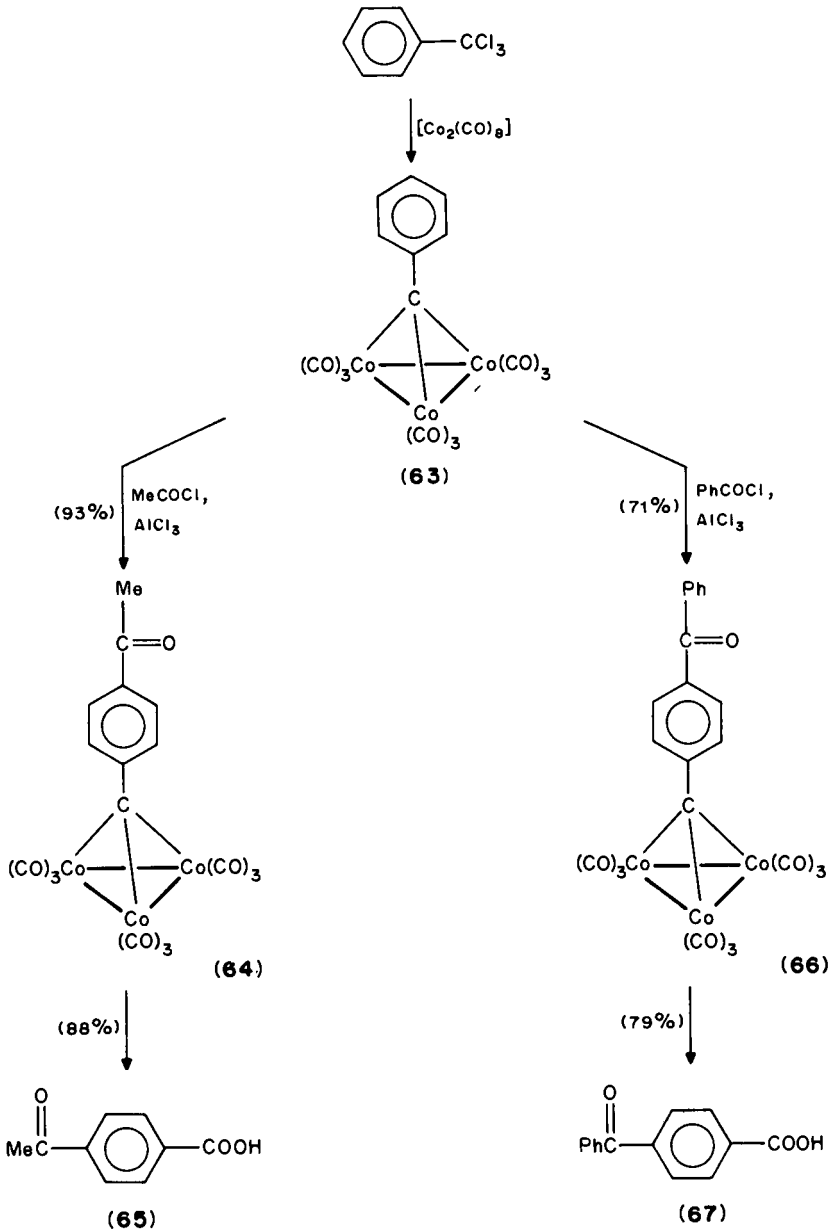
[a] Method a: MeOH, C_6H_6, reflux, 10–17 h[103].
[b] Method b: H_2O, NaOH, C_6H_6, PhMeNEtCl, 20 °C, 2 h[104].
[c] 4,4-Azoxyacetophenone formed as a byproduct (16%).

Methanolic solutions of $[Fe_3(CO)_{12}]$ also reduce carbon—nitrogen double bonds. By this method Schiff bases can be converted into amines with high yields[106]; a special application is reduction of phthalazine to 1,2-dihydrophthalazine (equation 3)[106].



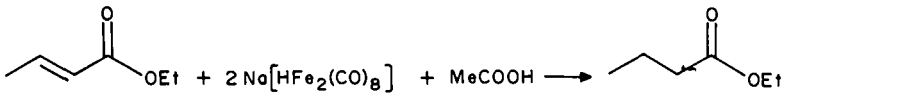
(3)

The anionic diiron cluster $[HFe_2(CO)_8]^-$ has been used for the selective hydrogenation of C=C bonds in conjugation with C=O bonds; e.g. ethyl carbonate with


CCl3
[Co2(CO)8]
(CO)3Co
Co(CO)3
Co
(CO)3
(63)
(93%)
MeCOCl,
AlCl3
(71%)
PhCOCl,
AlCl3
Me
Ph
C=O
(64)
(66)
(88%)
(79%)
MeC
PhC
COOH
(65)
(67)

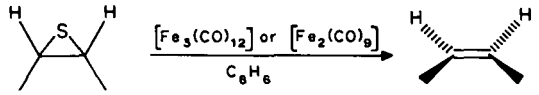
SCHEME 15

$Na[HFe_2(CO)_8]$ and MeCOOH gives selectively ethyl butyrate (92% yield within 3 h) equation 4)[190].



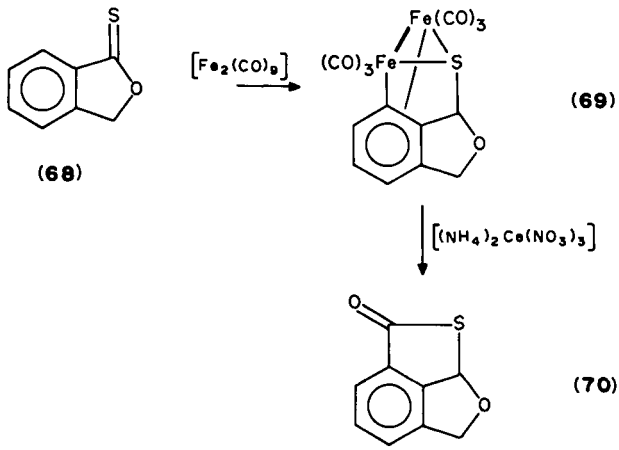
(4)

Episulphides have been reported to undergo a desulphurization reaction to give the corresponding olefins with either $[Fe_3(CO)_{12}]$ or $[Fe_2(CO)_9]$ in refluxing benzene (equation 5)[107].



(5)

Nonacarbonyldiiron has been used in the synthesis of novel heterocycles. The thiolactone **68** reacts with $[Fe_2(CO)_9]$ to give the complex **69** in 39% yield (Scheme 16). Oxidative demetallation with ammonium cerium(IV) nitrate in acetone results in the formation of the tricyclic thiolactone **70**; the yield was not given[107].



SCHEME 16

A number of C–C coupling reactions have been reported with di- and tri-nuclear ironcarbonyls: Benzyl chloride reacts with $[Fe_2(CO)_9]$ at 30 °C to give mainly dibenzylketone (56%); with $[Fe_3(CO)_{12}]$ benzyl chloride reacts with acrylonitrile at 67 °C in thf solution to give mainly 4-phenylbutyronitrile[108].

III. CATALYTIC REACTIONS

The implication of transition metal clusters in catalytic reactions has been addressed in a general context by several workers[102,109–113] and the use of the cluster compounds as homogeneous catalysts has been reviewed[28,29,114–116]. Special aspects of clusters in catalysis can be referred to[117–121]. There are also a considerable number of reviews on supported metal clusters as heterogeneous catalysts[115,122–127]. The most comprehensive recent discussion of homogeneous catalysis by metal clusters is that by Markó and Vizi-Orosz[116].

A. Classical Applications: Conventional Catalytic Reactions Using Transition Metal Clusters as Catalytic Precursors

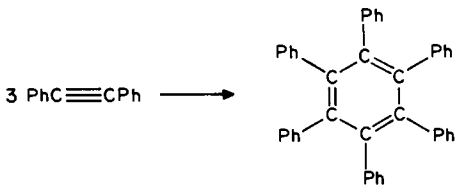
There are a large number of catalytic reactions such as hydrogenations or hydroformylations which are catalysed by many different catalysts, partly homogeneous and partly heterogeneous. Some of these processes play a major role in industrial chemistry. It is not surprising that many of these reactions are also catalysed by transition metal clusters. Although transition metal clusters have not succeeded in replacing traditional homogeneous or heterogeneous catalysts in technical processes, they may have advantages over other catalysts in the small-scale synthesis of special compounds or fine chemicals.

The catalytic applications cited in this section are regarded as cluster-based reactions in as far as these reactions are catalysed on addition of a transition metal cluster; whether or not the cluster is a catalyst precursor or a catalytically active species will not be discussed here. The question of cluster disintegration throughout the reaction remains a debatable point, since in most catalytic reactions the mechanism is not clear; special attention is drawn to this problem in some selected cases Section III.D.

One of the major problems encountered in reviewing catalytic applications of transition metal clusters is the need for comparable data describing the catalytic activity of the clusters employed. There is no consistency in the use of the term 'catalytic turnover'. Very often it means the number of catalytic cycles irrespective of the time, sometimes it is related to the time unit. In general it is calculated on the basis of the product formed, sometimes on the basis of the starting material assumed, not taking into account side products. Several authors only give yields based on the organic starting material; in many cases the necessary data are missing completely. Throughout this text the term 'catalytic turnover' is defined as 'the number of moles of product per mole of catalyst'. For continuous reactions it is more useful to describe the activity by the 'number of moles of product per mole of catalyst formed in unit time; this will be referred to as 'catalytic turnover rate'. Wherever possible all published data have been recalculated to the units moles of product per mole of catalyst ('catalytic turnover'); the reaction time is given as complementary information.

1. One-component reactions

a. Cyclization of acetylenes and olefins. The trimerization of diphenylacetylene to give hexaphenylbenzene (equation 6) is catalysed by a number of metal carbonyl derivatives



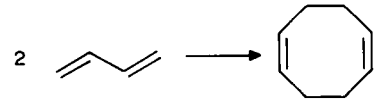
(6)

TABLE 2. Trimerization of diphenylacetylene to give hexaphenylbenzene

Catalyst	Conditions	Time	Yield (%)	Catalytic turnover	Ref.
$[Fe_3(CO)_{12}]$	Neat, 266–280 °C	seconds	75	ca 3–4	128
$[Fe_2(CO)_6(C_2Ph_2)_2]$	Neat, 270 °C	seconds	60	ca 3–4	128
$[Mn_2(CO)_{10}]$	Neat, 270 °C	seconds	55	ca 3–4	128
$[Co_2(CO)_8]$	Neat, 280 °C	seconds	60	ca 3–4	128
$[Co_2(CO)_6(C_2Ph_2)]$	Neat, 150 °C	seconds	70	ca 3–4	128
$[Co_2(CO)_6(C_2Ph_2)]$	Dioxane, 100 °C	1 h	95	31	128
$[Co_4(CO)_{10}(C_2Ph_2)]$	Dioxane, 100 °C	1 h	80	26	128
$[Co_2(CO)_6(HC_2CH_2N_3P_3Cl_4)]$	Octane, 150 °C	24 h	20	14	129

(Table 2). In general, the yields were higher with cluster compounds than with mononuclear metal carbonyls: $[Fe_3(CO)_{12}]$ gave 75%, whereas with $[Fe_2(CO)_9]$ and with $[Fe(CO)_5]$ only 25% and 20% were obtained, respectively[128].

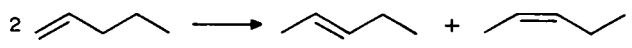
The tetranuclear nickel cluster $[Ni_4(CNBu^t)_7]$ has also been reported to catalyse the trimerization of acetylene to give benzene[130]; it also catalyses the synthesis of cycloocta-1,5-diene from buta-1,3-diene (equation 7)[130,131]. The dimerization takes place at 20 °C;



(7)

after 27 h the solution contains 76% of the 1,5-isomer and 4% of the 1,3-isomer, corresponding to a catalytic turnover of 33.

b. Isomerization of olefins. The isomerization of terminal olefins to a mixture of internal olefins (equation 8) has been studied mainly with ruthenium and osmium clusters.

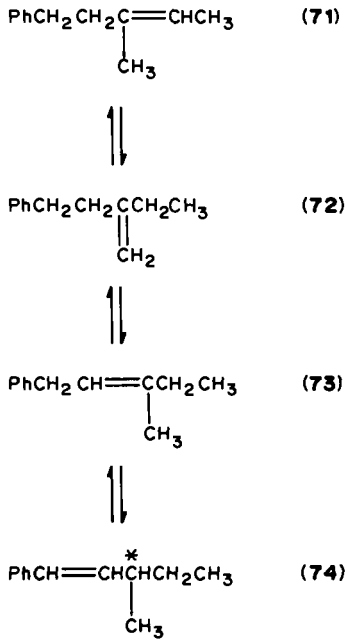


(8)

Pent-1-ene is converted to (*E*)-pent-2-ene and (*Z*)-pent-2-ene when refluxed in hexane with $[Ru_3(CO)_{12}]$; the equilibrium 3% pent-1-ene–74% (*E*)-pent-2-ene–23% (*Z*)-pent-2-ene is reached within a few hours[135]. Similar results were obtained with $[H_4Ru_4(CO)_{12}]$[136] and the phosphorus derivatives $[H_4Ru_4(CO)_{11}L]$; the isomerization rate decreases in the sequence $L = P(OEt)_3 > P(OPh)_3 > PPh_3 > CO$[137]. The influence of the solvent on the isomerization rate decreases in the order chlorobenzene > benzene > toluene > cyclohexene > mesitylene[138]. The catalytic turnovers were not given. The same isomerization was also studied with $[H_2Ru_4(CO)_{13}]$ and $[HRu_3(CO)_9C_6H_9]$[139] and with $[Os_3(CO)_{12}]$[140]; by comparing several metals the *Z*/*E* ratio was found to vary from 0.4–0.5 for $[Os_3(CO)_{12}]$[140], 0.3–0.4 for $[Ru_3(CO)_{12}]$[135], 0.35 for $[Fe_3(CO)_{12}]$[141] to 0.26 with $[Co_3(CO)_6(PBu_3)_3]$[142]. By analogy with pent-1-ene, other terminal olefins can be converted into the corresponding isomers: hex-1-ene yields (*Z*)- and (*E*)-hex-2-ene by reaction with $[Ru_3(CO)_{12}]$ at 70 °C[167] and with $[H_2Os_3(CO)_{10}]$ at 32.5 °C[143]; the *Z*/*E* ratio was not given. Hept-1-ene is converted at 90 °C in dioxane solution by $[NEt_4][HRu_3(CO)_{11}]$ into the expected mixture of heptene isomers-(*E*)-2-, 40.5%; (*Z*)-2, 13.9%; (*E*)-3-, 34.8%; (*Z*)-3-, 8.6%); after 15 h the convertion is 98%, corresponding to a catalytic turnover of 104[144]. The isomerization of pent-1-ene using $[Fe_3(CO)_{12}]$, $[Ru_3(CO)_{12}]$,

$[Ru_3(CO)_9(PPh_3)]_3$[145], or $[H_4Ru_4(CO)_{12}]$[146] has also been studied under photolytic conditions. By comparison with the mononuclear catalysts $[Fe(CO)_5]$ and $[Ru(CO)_4PPh_3]$ under photocatalytic conditions, the *Z*/*E* ratio of the pent-2-enes formed was shown to be substantially different, suggesting different active species[145].

There are only a few reports on synthetic applications of the double-bond isomerization reaction. Methyl linoleate (*Z*,*Z* isomer) has been isomerized to a mixture of the *Z*,*E* and *E*,*E* isomers with a number of ruthenium, iron, osmium and cobalt clusters[147,148]. The highest conversion was observed with $[H_4Ru_4(CO)_{12}]$, but there was a substantial amount of the hydrogenation product, methyl oleate. An *enantio*-face discriminating isomerization process has been reported with the chiral cluster $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ (Scheme 17)[149]. The prochiral substrate **71** was heated with $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ at 80 °C under 130 bar of hydrogen. After 23 h the reaction mixture contained 12.5% of the *E* isomer of the chiral olefin **74**; its optical purity was 0.5%[149].



SCHEME 17

c. Refunctionalizations. The isomerization of olefinic bonds can lead to a refunctionalization of the molecule if it contains the appropriate substituents. In this fashion allyl alcohol is not isomerized to methylvinyl alcohol but to propionaldehyde (equation 9); the reaction can be catalysed (32.5 °C) by the osmium cluster $[H_2Os_3(CO)_{10}]$[143]. The effect of substituents on the isomerization has also be studied: but-2-en-1-ol and but-3-en-2-ol react similary to give butan-1-al and butan-2-one, respectively (equation 10), but 2-methylprop-2-en-1-ol does not react; substituents at $C_{(2)}$ lead to a complete suppression of the isomerization. The isomerization of monodeuterated allyl alcohol, $CH_2{=}CHCH_2OD$, leads to $CH_3CHDCHO$, thus demonstrating the shift of the

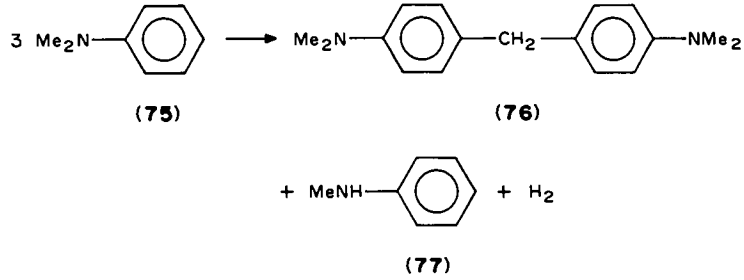
$$CH_2{=}CHCH_2OH \xrightarrow{[H_2Os_3(CO)_{10}]} CH_3CH_2CHO \tag{9}$$

$$CH_2{=}\underset{\underset{OH}{|}}{CHCH_3} \xrightarrow{[H_2Os_3(CO)_{10}]} CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3 \tag{10}$$

$$CH_2{=}\underset{\underset{OH}{|}}{CHCH_3} \xrightarrow{[Rh_6(CO)_{16}]} CH_3CH_2CH_2OCH_3 \tag{11}$$

alcoholic hydrogen[143]. By using $[Rh_6(CO)_{16}]$ as the catalyst but-3-en-2-ol is isomerized to give not butan-2-one but methyl propyl ether (equation 11)[150].

d. Miscellaneous. A carbon–carbon coupling of aromatic amines has been reported to occur in the presence of $[Os_3(CO)_{12}]$ or $[H_4Os_4(CO)_{12}]$. *N,N*-Dimethylaniline (**75**) converted into bis(*p*-*N,N*-dimethylaminophenyl)methane (**76**) and *N*-methylaniline (**77**) (equation 12). The fate of the hydrogen eliminated in this reaction is not clear, the

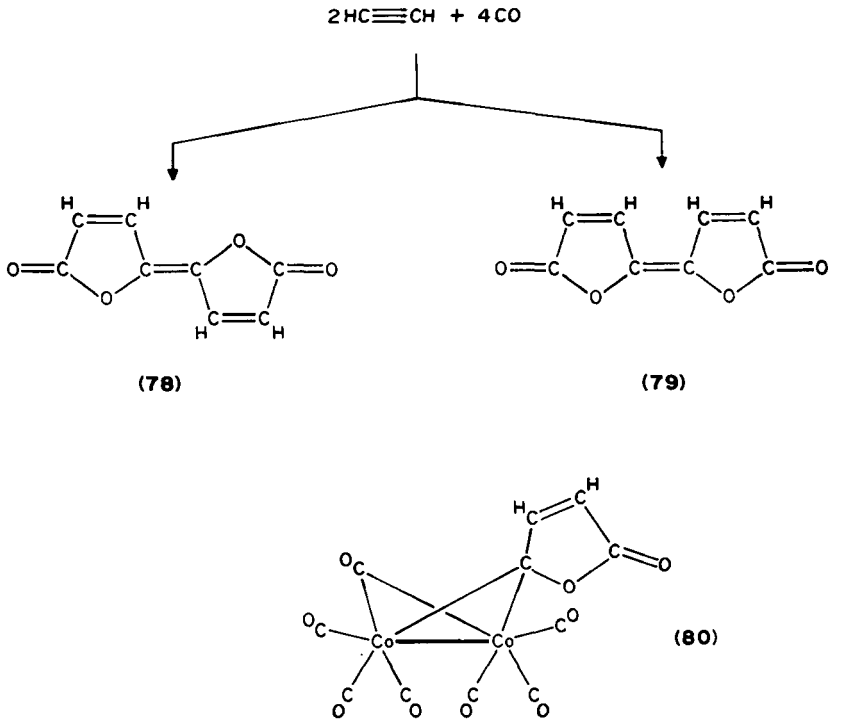


(12)

stoichiometry of the reaction not being precisely established[130]. The catalytic reaction proceeds in refluxing *N,N*-dimethylaniline solution (140 °C); after 36 h the catalytic turnover is 742 mol of **76** per mole of $[Os_3(CO)_{12}]$. The reaction is inhibited by CO pressure[130].

2. *Two-component reactions*

a. Cyclocarbonylation reactions. Acetylene reacts with carbon monoxide in the presence of $[Co_2(CO)_8]$ with cyclization to give bifurandiones. The C—C coupling occurs with either a *cis* or *trans* configuration; both isomers **78** and **79** have been isolated and separated by fractional crystallisation[151] (Scheme 18). The synthesis can be controlled in its stereochemistry; with acetonitrile–methanol as solvent and a pressure of 600 bar (90 °C, 17 h) the reaction yields the *E* isomer (**78**) with 59% conversion (catalytic turnover 45). The *Z* isomer (**79**) is obtained by using tetramethylurea as solvent and a pressure of 275–315 bar at 90 °C; the convertion after 15.8 h is 30% (catalytic turnover 20)[152]. Interestingly, Mills and Robinson[153] isolated a cobalt complex (**80**) from the reaction of carbon monoxide with $[Co_2(CO)_6(HC_2H)]$ accessible from $[Co_2(CO)_8]$ and acetylene. Complex **80** contains a μ_2-C-coordinated lactone ring formed from acetylene and two CO units; the intermediacy of such complexes in the bifurandione synthesis has been demonstrated by

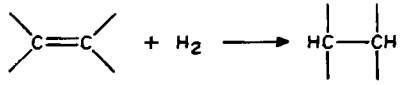


SCHEME 18

Pauson *et al.*[154]. The cyclocarbonylation reaction can be extended also to mono- and disubstituted acetylenes; however, complex isomeric mixtures are formed[152].

b. Hydrogenation reactions.

(*i*) Hydrogenation of C=C double bonds. Numerous clusters have been reported to catalyse the hydrogenation of olefins to alkanes (equation 13). Catalytic turnover and practicability vary a great deal; the details are presented in Table 3.


(13)

Photocatalytic hydrogenation of olefinic carbon—carbon double bonds has also been studied with several transition metal clusters. $[H_4Ru_4(CO)_{12}]$ catalyses the hydrogenation of ethylene to ethane in heptane at 35 °C, the ethylene and hydrogen partial pressure being 0.13 bar; the catalytic turnover in these experiments was less than 1[168]. Kinetic studies indicate that photodissociation of CO from $[H_4Ru_4(CO)_{12}]$ is the first step of the catalytic cycle[169]. The iron cluster $[Fe_3(CO)_{10}(NSiMe_3)]$ has been used for the photocatalytic hydrogenation of several olefins; the resulting cluster $[H_2Fe_3(CO)_9(NSiMe_3)]$ is assumed to act as the catalyst[170]. In this fashion methyl acrylate can be converted into

TABLE 3. Hydrogenation of alkenes to alkanes by various transition metal clusters

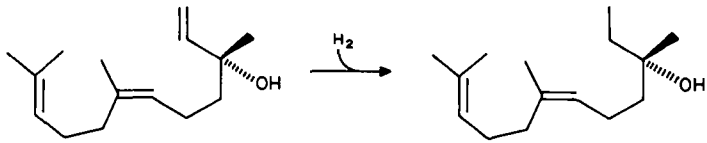
Substrate	Product	Catalyst	Conditions	Time	Catalytic turnover	Remarks	Ref.
Cyclohexene	Cyclohexane	$[Os_3(CO)_{12}]$	Toluene, 150 °C, 30 bar	10 h	400	$[H_4Os_4(CO)_{12}]$ formed	155
Cyclohexene	Cyclohexane	$[N(PPh_3)_2][HOs_3(CO)_{11}]$	Toluene, 150 °C, 30 bar	10 h	30	Cluster unchanged	155
Cyclohexene	Cyclohexane	$[H_4Os_4(CO)_{12}]$	Toluene, 150 °C, 30 bar	10 h	610	Cluster unchanged	155
Cyclohexene	Cyclohexane	$[N(PPh_3)_2][H_3Os_4(CO)_{12}]$	Toluene, 150 °C, 30 bar	10 h	80	Cluster unchanged	155
Cyclohexene	Cyclohexane	$[H_3Os_4(CO)_{12}I]$	Toluene, 150 °C, 30 bar	10 h	880	Cluster unchanged	155
Cyclohexene	Cyclohexane	$[H_3Os_4(CO)_{12}(NO)]$	Toluene, 150 °C, 30 bar	10 h	480	$[H_4Os_4(CO)_{12}]$ formed	155
Cyclohexene	Cyclohexane	$[H_3Os_4(CO)_{12}(MeCN)_2][BF_4]$	Toluene, 150 °C, 30 bar	10 h	630	$[H_4Os_4(CO)_{12}]$ formed	155
Cyclohexene	Cyclohexane	$[Ru_3(CO)_9(PPh_3)_3]$	Cyclohexane, 70 °C, 1.7 bar	5 h	17.5	$[H_4Ru_4(CO)_{12-x}(PPh_3)_x]$ formed	156
Cyclohexene	Cyclohexane	$[Ru_3(CO)_7(PPh_2)_2(C_6H_4)]$	No solvent, 70 °C, 1.7 bar	5 h	19	Cluster unchanged	156
Cyclohexene	Cyclohexane	$[H_4Ru_4(CO)_{12}]$	thf, 80 °C, 40 bar	n.g.[a]	n.g.	Cluster unchanged, catalytic turnover rate $0.567\,s^{-1}$	157
Cyclohexene	Cyclohexane	$[H_3Ru_4(CO)_{10}(PhPCH_2PPh_2)]$	thf, 80 °C, 40 bar	n.g.	n.g.	Cluster unchanged, catalytic turnover rate $0.211\,s^{-1}$	157
Cyclohexene	Cyclohexane	$[H_4Ru_4(CO)_{10}(Ph_2PCH_2PPh_2)]$	thf, 80 °C, 40 bar	n.g.	n.g.	$[H_3Ru_4(CO)_{10}(PhPCH_2PPh_2)]$ formed, catalytic turnover rate $0.194\,s^{-1}$	157
Cyclohexene	Cyclohexane	$[Ru_2(CO)_4(Ph_4C_4CO)_2]$	No solvent, 100 °C, 34.5 bar	15 min	1976	Quantitative	158
Cyclohexene	Cyclohexane	$[Rh_6(CO)_{12}\{P(OPh)_3\}_4]$	60 °C	n.g.	n.g.	No details	159
Cyclohexene	Cyclohexane	$[Rh_6(CO)_{10}(PPh_3)_6]$	Benzene, 25 °C, 2 bar	1 h	190	Cluster unchanged	171
Styrene	Ethylbenzene	$[H_3Os_4(CO)_{12}I]$	Decalin, 100 °C, 1.05 bar	2 h	1166	Fragmentation probable	160
Styrene	Ethylbenzene	$[H_4Os_4(CO)_{12}]$	Decalin, 100 °C, 1.05 bar	2 h	174	Fragmentation probable	160
Styrene	Ethylbenzene	$[N(PPh_3)_2][H_2Os_4(CO)_{12}I]$	Decalin, 100 °C, 1.05 bar	2 h	126	Fragmentation probable	160
Styrene	Ethylbenzene	$[N(PPh_3)_2][H_3Os_4(CO)_{12}]$	Decalin, 100 °C, 1.05 bar	2 h	104	Fragmentation probable	160
Styrene	Ethylbenzene	$[Rh_2(OOCMe)_4]$	dmf, 30 °C, 1 bar	n.g.	n.g.		161

Hex-1-ene	Hexane	$[Rh_2(OOCMe)_4]$	dmf, 30 °C, 1 bar	n.g.	n.g.		161
Hex-1-ene	Hexane	$[H_3Ni_4(C_5H_5)_4]$	No solvent, 40 °C, 1 bar	40 h	~300	Quantitative	162
Hex-2-ene	Hexane	$[H_3Ni_4(C_5H_5)_4]$	No solvent, 40 °C, 1 bar	40 h	~150	60% conversion, *Z* isomer reacts faster	162
3,3-Dimethyl-butene	3,3-Dimethyl-butane	$[N(PPh_3)_2][Ru_3(CO)_{10}(NCO)]$	thf, 25 °C, 0.75 bar	0.3 h	104		163
Pent-1-ene	Pentane	$[H_3Ni_4(C_5H_5)_4]$	No solvent, 40 °C, 1 bar	15 h	~300	Quantitative	162
Pent-2-ene	Pentane	$[Ru_2(CO)_4(Ph_4C_4CO)_2]$	No solvent, 145 °C, 34.5 bar	0.4 h	1860	Quantitative	158
Oct-1-ene	Octane	$[Ru_2(CO)_4(Ph_4C_4CO)_2]$	No solvent, 145 °C, 34.5 bar	0.6 h	1720	Quantitative	158
Oct-1-ene	Octane	$[NBu_4][Fe_4S_4Cl_4]$	Diethyl ether, LiPh, 20 °C, < 1 bar	20 h	46	Conversion 92%	166
Oct-1-ene	Octane	$[Ru_3O(OOCMe)_6(H_2O)_3][OOCMe]$	dmf, 80 °C, < 1 bar	n.g.	n.g.	substrate/cluster ratio 13	164
Oct-2-ene	Octane	$[Ru_3O(COOMe)_6(H_2O)_3][OOCMe]$	dmf, 80 °C, < 1 bar	n.g.	n.g.	Substrate/cluster ratio 13	164
Cyclohex-1-en-2-one	Cyclohexanone Cyclohexanol (1.45:1)	$[Ru_3(CO)_9(PPh_3)_3]$	Cyclohexane, 70 °C, 1.7 bar	5 h	16.5	$[Ru_3(CO)_7(PPh_2)_2(C_6H_4)]$ formed	156
Cyclohex-1--1-en-2-one	Cyclohexanone cyclohexanol (13:1)	$[Ru_3(CO)_7(PPh_2)_2(C_6H_5)]$	Cyclohexane, 70 °C 1.7 bar	5 h	70	Cluster unchanged	156
Propene	Propane	$[Co_3(CO)_6(PBu_3)_3]$	Heptane, 65 °C, 15 bar	n.g.	n.g.	Substrate/cluster ratio 50	165

[a] n.g. = not given in the reference cited (all tables).

methyl propionate in toluene solution; the catalytic turnover is 100 after 106 h, whereas without irradiation it is only 0.37 after 72 h.

Examples in which clusters have been used as selective catalysts in the hydrogenation of complicated structures are rare. The anionic ruthenic cluster $[HRu_3(CO)_{11}]^-$ catalyses specifically the terminal C=C double bond of *cis*-nerolidol (**81**); under mild conditions (dmf, 20 °C, 40 bar) exclusively **82** is obtained with 51% conversion (equation 14)[172].



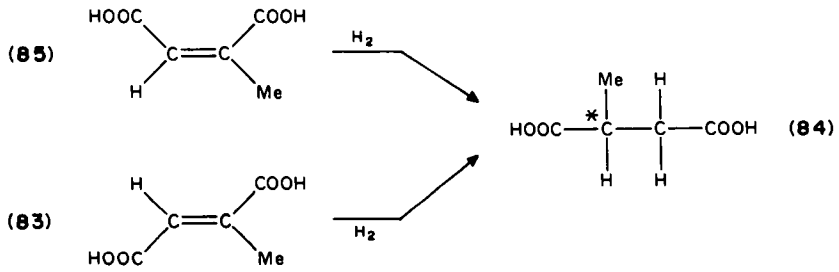
(**81**) (**82**) (14)

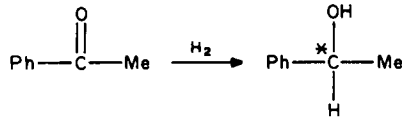
The tetranuclear cluster $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$, in which the metal framework is modified by two chiral diphosphine ligands, is the main cluster candidate for asymmetric hydrogenation reactions (Scheme 19). This cluster catalyses the enantioselective hydrogenation of mesaconic acid (**83**) to methylsuccinic acid (**84**); the reaction proceeds in toluene–diethyl ether (2:1) at 20 °C and a hydrogen pressure of 130 bar giving 88.7% of **84** with an enantiomeric excess (ee) of 8.1% for the *S*-enantiomer, the catalytic turnover being 200. The hydrogenation of citraconic acid (**85**), the *E*-isomer of **83**, under the same conditions gives 83.3% of **84** with an optical purity of only 1.1%[173,174]. Saturated and unsaturated lactones were observed with small yields as side-products in this reaction. This example shows that the different steric arrangement of the carbonyl groups around the double bond in **83** and **85** plays a fundamental role in determining the extent of asymmetric reduction.

Using the same catalyst prochiral ketones and ketimines have been hydrogenated: acetophenone (**86**) gives the corresponding alcohol **87** with an ee of 8.1% for the *S*-enantiomer. The best reaction conditions are toluene solution, 130 °C, 100 bar and 5 h. The conversion is 40%, corresponding to a catalytic turnover of 280; it is essential that the chiral ligand *R,R*-diop is present in excess[175].

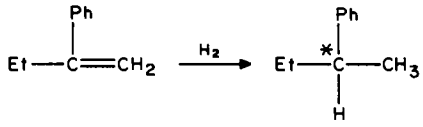
For the hydrogenation of 2-phenylbut-1-ene (**88**) to 2-phenylbutane (**89**) $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ was used at 80 °C and 100 bar to give **89** with 74% yield (catalytic turnover 203) and an optical purity of 4.5% (*S*-enantiomer)[176]. α-Methylcinnamic acid (**90**) was hydrogenated in toluene–ethanol (1:1) at 100 °C and 130 bar to give preferentially the *S*-enantiomer of **91**; with $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ as the catalyst the ee is 58.0%; with a cluster formulated as $[Ru_6(CO)_{18}(R,R\text{-diop})_3]$ the ee is 45.3% or 61.4% with trimethylamine present[177]. The hydrogenation of tiglic acid (**92**) was used to study the enantiomeric discrimination by a whole series of dinuclear and tetranuclear carboxylato complexes: $[Ru_4(CO)_8(OOCCH_2COO)_2(R,R\text{-diop})_2]$ in toluene–ethanol (1:1) at 80 °C and 130 bar gives (*S*)-2-methylbutanoic acid (**93**) with a conversion of 99% after 65 h and an optical purity of 41% (catalytic turnover 248). $[Ru_2(CO)_4[S\text{-}OOCH(CH_3C_2H_5]_2(R,R\text{-diop})_2]$ under similar conditions gives 95% of **93** after 4 h with an optical purity of 37.3% (catalytic turnover 622)[178]. There is also a report that $[Ru_3(CO)_{12}]$ has been used as an enantioselective hydrogenation catalyst precursor in the presence of chiral diphosphinites without isolating or characterizing the modified clusters; with glucophenite **90** can be converted to **91** in 85% yield and ee 38% (thf, 120 °C, 40 bar, 100 h, catalytic turnover 62); for the conversion of **92** to **93** the yield is 74% with an optical purity of 11% (catalytic turnover 34)[179].

Rhodium clusters modified with chiral diphosphines have been reported to catalyse the

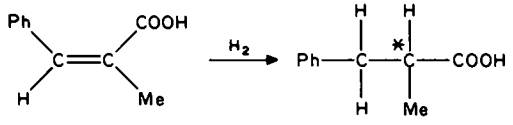




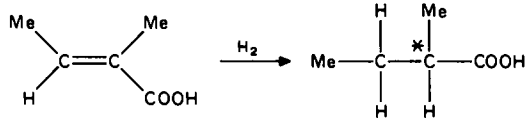
(86) (87)



(88) (89)



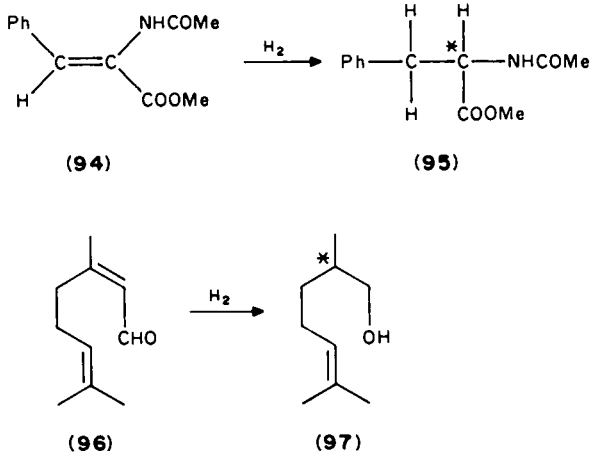
(90) (91)



(92) (93)

SCHEME 19

enantioselective hydrogenation of prochiral dehydroamino acids (Scheme 20). In ethanol as the solvent **94** is hydrogenated by $[Rh_6(CO)_{10}(R,R\text{-diop})_3]$ (80 °C, 1 bar, 24 h) giving the *R*-enantiomer of **95** with ee 47% (100% conversion; catalytic turnover 100)[180]. With $[Rh_4(CO)_{10}(R,R\text{-diop})]$ (70 °C, 1 bar, 3 h) (*R*)-**95** is formed in an optical purity of 65% (100% conversion, catalytic turnover 220)[180]. Similar results were obtained by using a



SCHEME 20

mixture of $[Rh_6(CO)_{16}]$ and *R,R*-diop[181]. A catalytic system derived from $[Rh_6(CO)_{16}]$ or $[Rh_4(CO)_{12}]$ and (*E*)-1,2-bis(methylenephosphino)cyclobutane can be used for the enantioselective hydrogenation of neral (**96**) to citronellal (**97**) in toluene at ambient temperature and normal pressure. The conversion is quantitative with a catalytic turnover of ca 120. For the hexanuclear cluster the enantiomeric excess was determined to be 59% and for the tetranuclear cluster 66%; use of the (−)-enantiomeric ligand leads to (*S*)-**97**, whereas the (+)-enantiomer produces predominantly (*R*)-**97**[182]. In all the cases where rhodium clusters have been used with chiral ligands the asymmetric hydrogenation could also be performed using the mononuclear complex $[HRh(CO)(PPh_3)_3]$ and the same ligand with even better results, suggesting that the tetra- or hexa-nuclear cluster is only a precursor for the formation of a mononuclear catalytic species[180–182].

(*ii*) Hydrogenation of C≡C triple bonds. Most of the catalytic systems derived from transition metal clusters catalyse the hydrogenation of acetylenes to give predominantly olefins (equation 15), the corresponding alkane being only a side product (Table 4).

$$RC{\equiv}CH \xrightarrow{H_2} RCH{=}CH_2 \qquad (15)$$

Since most of the clusters used for hydrogenation also catalyse the double bond shift (cf. Section III.A.1.a), the situation is complicated by isomerization: for acetylenes with an internal C≡C unit also an *E/Z* problem arises. The examples reported demonstrate that carbon—carbon triple bonds are more readily reduced than carbon—carbon double bonds. However, in most cases further hydrogenation and isomerization lead to complex product mixtures.

(*iii*) Hydrogenation of C≡O bonds. Several rhodium and ruthenium clusters are reported to catalyse the reduction of carbonyl compounds (Table 5). The hydrogenation of aldehydes and ketones yields the corresponding primary and secondary alcohols (equation 16); in the case of carbonic acids the reduction to the alcohol is often followed by the esterification of the alcohol with unreacted acid (equation 17).

A special case is lactone formation after the partial reduction of a dicarbonic acid (equation 18). Esters of dicarbonic acids are partially reduced with the elimination of

TABLE 4. Hydrogenation of alkynes catalysed by various transition metal clusters

Substrate	Products (%)	Catalyst	Conditions	Time	Catalytic turnover	Remarks	Ref.
Pent-1-yne	Pent-1-ene (84.0), Pent-2-ene (10.1), pentane (3.0)	$[Cp_4Fe_4(CO)_4]$	Benzene, 120 °C, 7.2 bar	88 h	340	[a]	183
Pent-1-yne	Pent-1-ene (6), (*E*)-pent-2-ene (2), (*Z*)-pent-2-ene (2)	$[H_4Ru_4(CO)_{11}][P(OEt)_3]$	Toluene, 80 °C, 1 bar	5.5 h	14	[b]	184
Pent-1-yne	Pent-1-ene (19), (*E*)-pent-2-ene (4), (*Z*)-Pent-2-ene (4)	$[H_4Ru_4(CO)_9][P(OEt)_3]_3$	Toluene, 80 °C, 1 bar	5.5 h	42	[c]	184
Pent-2-yne	(*E*)-Pent-2-ene (69), (*Z*)-pent-2-ene (25), pent-1-ene (3), pentane (2)	$[H_4Ru_4(CO)_{12}]$	Toluene, 80 °C, 1 bar	15 h	10		185
Pent-2-yne	(*Z*)-Pent-2-ene (10), (*E*)-pent-2-ene (4.5), pent-1-ene (3.5)	$[H_4Ru_4(CO)_9][P(OEt)_3]_3$	Toluene, 80 °C, 1 bar	5.5 h			184
Pent-2-yne	(*Z*)-Pent-2-ene (64),(*E*) (*E*)-pent-2-ene (17), pent-1-ene (2), pentane (12)	$[Rh_4(CO)_{12}]$	Toluene, 80 °C, 1 bar	3 h	n.g.	[d]	186
But-2-yne	(*Z*)-But-2-ene (presumably 2–5%)	$[Ni_4(NCBu^t)_7]$	Benzene, 20 °C, 3 bar	72 h	n.g.	[e]	187,188
Hex-3-yne	(*Z*)-hex-3-ene, (*E*)-hex-3-ene, hexane (3–5%, rel. ratio 128:1:3)	$[Ni_4(NCBu)_7]$	Benzene, 3 bar	1–6 d	33–50	[e]	187, 188
Hex-3-yne	(*Z*)-Hex-3-ene (4)	$[Cp_4Fe_4(CO)_4]$	Benzene, 100 °C, 6.9 bar	11 h	16	[f,g]	183
Phenylacetylene	Styrene (3), ethylbenzene (53), oligomers (44)	$[Pt_5(CO)_6(PPh_3)_4]$	Toluene, 50 °C, 50 bar	20 h	61	[h]	363

(*continued*)

TABLE 4. (*continued*)

Substrate	Products (%)	Catalyst	Conditions	Time	Catalytic turnover	Remarks	Ref.
Diphenylacetylene	(*E*)-Stilbene (2.5), (*Z*)-stilbene (50), 1,2-diphenylethane (2.5)	$[Pt_5(CO)_5(PPh_3)_4]$	Toluene, 50 °C, 50 bar	20 h	63		363
Diphenylacetylene	(*E*)-Stilbene, (*Z*)-stilbene, 1,2-diphenylethane (10.5; rel. ratio 100:6:3805)	$[Ru_4(CO)_{12}(C_2Ph_2)]$	Heptane, 120 °C, 0.9 bar	24 h	n.g.		189
Diphenylacetylene	(*E*)-Stilbene, (*Z*)-stilbene, 1,2-diphenylethane (15%, rel. ratio 100:18.6:3540.7)	$[Fe_3(CO)_9(C_2Ph_2)]$	Heptane, 120 °C, 0.9 bar	18 h	n.g.		189
Diphenylacetylene	(*E*)-Stilbene	$Na[HRu_3(CO)_{11}]$	dmf, 100 °C, 50 bar	15 h	38	*f,i*	172

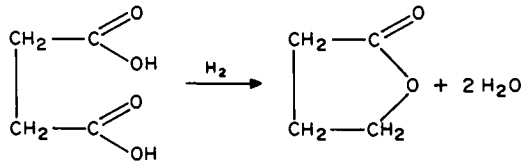
[a] Cluster unchanged.
[b] No effect of CO.
[c] Suppression by CO.
[d] Supporting on Al_2O_3 increases pentane formation.
[e] Report imprecise.
[f] Selectivity 100%.
[g] Conversion 4%.
[h] Related to the total of hydrogenation products.
[i] Conversion 96%.

TABLE 5. Hydrogenation of carbonyl compounds by various transition metal clusters

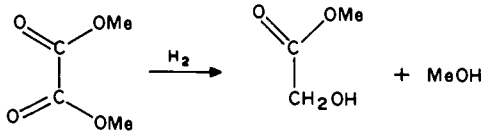
Substrate	Product (%)	Catalyst	Conditions	Time	Catalytic turnover	Remarks	Ref.
Benzaldehyde	Benzyl alcohol	$[Rh_6(CO)_{16}]$	Methanol, 110 °C, 14 bar H_2, 55 bar CO, $NaHCO_3$	1 h	110	$NaHCO_3$ and CO required	191
Butan-1-al	Butan-1-ol	$[Rh_4(CO)_{12}]$	Hexane, 160 °C, 115 bar H_2, 55 bar CO	3.6 h	701	Formation of $[HRh(CO)_3]$ as active species	192
Pentan-1-al	Pentan-1-ol (40), *n*-pentyl pentan-1-oate (60)	$[Ru_2(CO)_4(Ph_4C_4CO)_2]$	Toluene, 145 °C, 34.5 bar H_2	1 h	200	100% conversion	158
2-Ethylhexan-2-al	2-Ethylhexanal (58), 2-ethylhexanol (16)	$[Co_3(CO)_6(PBu_3)_3]$	Heptane, 80 °C, 150 bar H_2	12 h	8	Reduction unselective	165
Cyclohexanone	Cyclohexanol	$[Ru_2(CO)_4(Ph_4C_4CO)_2]$	Neat, 100 °C, 34.5 bar H_2	5 h	1960	98% conversion	158
Cyclohexanone	Cyclohexanol	$[H_4Ru_4(CO)_{12}]$	thf, 100 °C, 100 bar H_2	6 h	880	59.6% conversion	193
Cyclohexanone	Cyclohexanol	$[H_4Ru_4(CO)_{10}(PPh_3)_2]$	thf, 100 °C, 100 bar H_2	6 h	125	8.6% conversion	193
Cyclohexanone	Cyclohexanol	$[H_4Ru_4(CO)_9(PPh_3)_3]$	thf, 100 °C, 100 bar H_2	6 h	200	13.5% conversion	193
Cyclohexanone	Cyclohexanol	$[H_4Ru_4(CO)_8(PPh_3)_4]$	thf, 100 °C, 100 bar H_2	6 h	800	54.3% conversion	193
Dimethyl oxalate	Methyl glycolate	$[Ru_2(CO)_4(OOCCH_3)_2(PBu_3)_2]$	Benzene, 180 °C, 130 bar H_2	144 h	240	79.2% conversion, 100% selectivity	194, 195
Dimethyl oxalate	Methyl glycolate	$[H_4Ru_4(CO)_8(PBu_3)_4]$	Benzene, 20 °C, 130 bar H_2	39 h	156	100% conversion	196
Dimethyl succinate	γ-Butyrolactone	$[H_4Ru_4(CO)_8(PBu_3)_4]$	Benzene, 180 °C, 130 bar H_2	144 h	160	7% conversion, 100% selectivity	196
Succinic acid	γ-Butyrolactone	$[H_4Ru_4(CO)_8(PBu_3)_4]$	Dioxane, 180 °C, 130 bar H_2	22 h	263	83% conversion	197
Acetic acid	Ethyl acetate	$[H_4Ru_4(CO)_8(PBu_3)_4]$	Dioxane, 180 °C, 130 bar H_2	48 h	2285	No ethanol obtained	198
Propionic acid	Propyl acetate (97.4), Propanol (2.6)	$[H_4Ru_4(CO)_8(PBu_3)_4]$	Dioxane, 180 °C, 130 bar H_2	48 h	1625		198

$$RCHO \xrightarrow{H_2} RCH_2OH \quad (16)$$

$$2\ RCOOH \xrightarrow{H_2} RCOOCH_2R \quad (17)$$



(18)

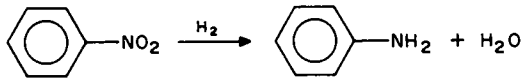


(19)

alcohol; in this fashion methyl glycolate is obtained from dimethyl oxalate (equation 19). The fact that carbon monoxide is required for the hydrogenation of aldehydes catalysed by Rh_6 and Rh_4 clusters[191,192] has been interpreted in terms of a cluster breakdown to give the mononuclear complex $[HRh(CO)_3]$, which is the active catalyst. This is supported by kinetic studies[192].

(*iv*) Hydrogenation of N=O, C≡N, and C=N bonds. Whereas trinuclear iron clusters have been used in the stoichiometric reduction of aromatic nitro compounds (cf. Section II.D), the tetranuclear iron cluster $[Cp_4Fe_4(CO)_4]$ can be used for the catalytic hydrogenation of nitrobenzene to aniline (equation 20; Table 6).

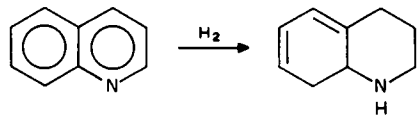
The hydrogenation of nitriles and isonitriles (equations 21 and 22) has been achieved with a tetranuclear nickel cluster, but the reduction is not very efficient (Table 6). Quinoline (**98**) was formed to give tetrahydroquinoline (**99**) on pressurising with hydrogen in the presence of trinuclear osmium clusters (equation 23)[201,202]. The two clusters isolated from this reaction, $[HOs_3(CO)_{10}(NC_9H_8)]$ and $[HOs_3(CO)_{10}(NC_9H_6)]$ are regarded as intermediates[203].



(20)

$$RC{\equiv}N \xrightarrow{H_2} RCH_2NH_2 \quad (21)$$

$$R\overset{+}{N}{\equiv}\overset{-}{C} \xrightarrow{H_2} RNHCH_3 \quad (22)$$



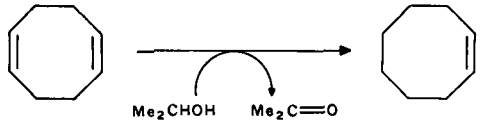
(23)

(98) **(99)**

TABLE 6. Hydrogenation of nitroaryls, nitriles, isonitriles and related substrates

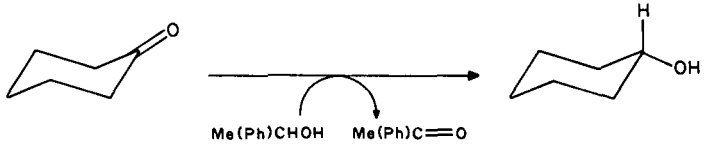
Substrate	Product	Catalyst	Conditions	Time	Catalytic turnover	Remarks	Ref.
Nitrobenzene	Aniline	$[Cp_4Fe_4(CO)_4]$	Benzene, 130 °C, 21 bar	24 h	126	31% conversion	183
Isopropylnitrile	2-Methylpropylamine	$[H_2Rh_2(N)_2\{P(C_6H_{11})_3\}_4]$	thf, 20 °C, 1 bar	20 h	156	78% conversion	199
Benzylnitrile	2-Phenylethylamine	$[H_2Rh_2(N)_2\{P(C_6H_{11})_3\}_4]$	thf, 20 °C, 1 bar	20 h	138	69% conversion	199
Acetonitrile	Ethylamine	$[Ni_4(CNBu^t)_7]$	Neat, 90 °C, 1 bar	n.g.	n.g.	Report imprecise	187, 200
tert-Butylisonitrile	*tert*-Butylmethylamine	$[Ni_4(CNBu^t)_7]$	Toluene, 90–120 °C, 1–3 bar	n.g.	n.g.	Report imprecise	187
Quinoline	Tetrahydroquinoline	$[Os_3(CO)_{12}]$	Heptane, 145 °C, 41 bar	24 h	1200	Intermediates isolated	201, 202
Quinoline	Tetrahydroquinoline	$[H_2Os_3(CO)_{10}]$	Methanol, 145 °C, 41 bar	24 h	2088	Intermediates isolated	201, 202

(*v*) Hydrogen transfer reactions. Catalytic hydrogen transfer from a hydrogen donor molecule to an unsaturated substrate sometimes presents advantages over hydrogenation by molecular hydrogen. This type of reaction can be catalysed by a number of ruthenium or rhodium catalysts. Cycloocta-1,5-diene and hexa-1,5-diene can be selectively reduced to cyclooctene and a mixture of hexenes, respectively, by $[Rh_6(CO)_{16}]$ via hydrogen transfer from iso-propanol. The reaction proceeds at 145 °C and a CO pressure of 45 bar. For cycloocta-1,5-diene (equation 24) the conversion is 99% after 23 h (catalytic turnover 150) and for hexa-1,5-diene and hexa-1,5-diene the conversion is 97% after 55 h (catalytic turnover 162)[204].



(24)

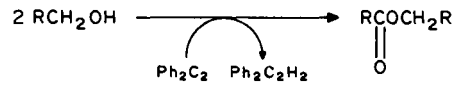
Cyclohexanone can be reduced to cyclohexanol by using 1-phenylethanol as hydrogen donor in the presence of $[Fe_3(CO)_{12}]$ or $[Fe_2(CO)_9]$ (equation 25). The reaction proceeds under phase-transfer conditions (benzyltriethylammonium chloride and 18-crown-6) at



(25)

28 °C. After 2.5 h cyclohexanol is formed with 78% conversion by $[Fe_3(CO)_{12}]$ and 64% by $[Fe_2(CO)_9]$ (catalytic turnover 20 and 16, respectively)[205]. With $[Ru_3(CO)_{12}]$ methanol can be used as the hydrogen source for the cyclohexanone reduction; a large excess of triphenylphosphine increases the conversion considerably. After 18 h at 150 °C 44% of cyclohexanol was formed, corresponding to a catalytic turnover of 44[206].

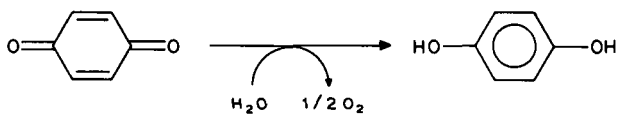
Ruthenium carbonyl catalyses the oxidative coupling of alcohols to esters via hydrogen transfer to diphenylacetylene, chalcone or maleic anhydride (equation 26). For instance,



(26)

propanol is converted into propyl propionate (93% conversion, 98% selectivity) in acetone at 145 °C with $[Ru_3(CO)_{12}]$ and diphenylacetylene, the catalytic turnover being 140[207,208]. This reaction can be extended to other alcohols with exellent yields and selectivity[208]. The intermediacy of the unsaturated mononuclear complex $[Ru(CO)_2(C_4Ph_4CO)]$ seems to be the key step in this catalysis[209]; 1,4- and 1,5-diols give rise to lactones; 1,6- and 1,10-diols are polymerized in this reaction[210].

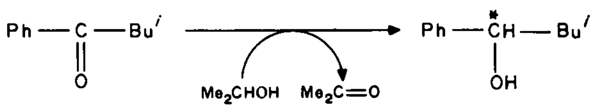
Water can be used as the hydrogen source in reduction of *p*-benzoquinone to *p*-dihydroxybenzene in the presence of the anionic platinum cluster $[Pt_{12}(CO)_{24}]^{2-}$ (equation 27). The reaction proceeds in acetonitrile at 30 °C; after 5 h ca 50% of the quinone is converted, corresponding to a catalytic turnover of 25. The interesting point is



(27)

that molecular oxygen is developed from water in this reaction[211,212]. Spectroscopic data suggest the involvement of $[Pt_9(CO)_{18}]^{2-}$ and $[Pt_{12}(CO)_{24}]^{2-}$ as active intermediates in the catalytic process[212].

Hydrogen transfer reactions have also been carried out in an asymmetric variant using the chiral cluster $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ as the catalyst. A racemic mixture of 1-phenylethanol can be used as hydrogen donor for the reduction of isobutyl phenyl ketone to give 1-phenyl-3-methylbutan-1-ol with the *S* configuration in an optical purity of 6.8%. The reaction takes place at 120 °C with 18.3% conversion after 112 h (catalytic turnover 244)[213]. With isopropanol as hydrogen donor isobutyl phenyl ketone gives under the same conditions 1-phenyl-3-methylbutan-1-ol (equation 28) with an enantiomeric excess of



(28)

9.8% (*S* enantiomer), the yield being 37.1% after 86 h (the catalytic turnover was not given)[214].

For the asymmetric reduction of tiglic acid (**92**) to 2-methylbutanoic acid (**93**) isopropanol can also be used as the hydrogen source. In the presence of $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$ at 120 °C 42.4% of **92** was converted after 227 h, giving (*R*)-**93** (catalytic turnover 210) with 5.4% optical purity (cf. Scheme 19)[215]. Similar results for this reaction with optical yields up to 26.4% have been obtained with the dinuclear ruthenium complex $[Ru_2Cl_4(R,R\text{-diop})_3]$[216–218].

If the Cannizzaro reaction of racemic 2-methylbutanal is catalysed by $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$, an enantiomeric selection takes place for 2-methylbutanoic acid (equation 29); the *S* configuration is prefered with an enantiomeric excess of 1.7%. The

$$2\mathrm{Et}\overset{*}{\mathrm{C}}\mathrm{H(Me)CHO} + H_2O \longrightarrow \mathrm{Et}\overset{*}{\mathrm{C}}\mathrm{H(Me)COOH} + \mathrm{Et}\overset{*}{\mathrm{C}}\mathrm{H(Me)CH_2OH} \qquad (29)$$

alcohol formed, however, is found to be racemic. The reaction proceeds in dioxane at 120 °C over 103 h with a conversion of 18.1%, corresponding to a catalytic turnover of 296[219]. The different discriminating ability of the catalyst in the dehydrogenation and hydrogenation steps of the reaction on the same substrate may be explained by assuming that the molecule which is dehydrogenated is the hydrated form of the substrate, which may enter as a bidentate ligand in the intermediate complex, while the hydrogen acceptor acts as a monodentate ligand.

c. Syngas reactions. A series of reactions involving carbon monoxide and hydrogen (synthesis gas) as building blocks for basic organic chemicals are commonly referred to as 'syngas reactions'. These reactions, based on the catalytic hydrogenation of carbon monoxide, involve the formation of oxygenates, mainly methanol, ethanol, ethylene glycol and methyl formate, and hydrocarbons, mainly methane, higher alkanes and olefins (equations 30–37). The catalytic synthesis of hydrocarbons from syngas is also represented by the Fischer–Tropsch synthesis[287] (described in Chapter 9 of volume 2 of this series).

$$CO + 2H_2 \longrightarrow CH_3OH \qquad (30)$$

$$2CO + 4H_2 \longrightarrow CH_3CH_2OH + H_2O \qquad (31)$$

$$2CO + 3H_2 \longrightarrow HOCH_2CH_2OH \qquad (32)$$

TABLE 7. Hydrogenation of carbon monoxide by various transition metal clusters

Catalyst precursor	Products (%)	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Remarks	Ref.
$[Rh(CO)_2acac]$	Ethylene glycol (48.6), methanol (41.5), methyl formate (3.7), glycerol (3.2), ethylene glycol formate (2.1), ethanol (0.9)	Tetraglyme, 220 °C, (800/533), 2-hydroxypyridine	4 h	110[a] 94[b]	Rhodium clusters formed	233
$[Rh(CO)_2acac]$	Ethylene glycol (54.8), methanol (41.3), methyl formate (2.1), glycerol (0.4), ethylene glycol formate (0.7), ethanol (0.8)	Tetraglyme, 220 °C, (272/272), 2-hydroxypyridine, caesium formate	4 h	23[a] 17[b]	Rhodium clusters formed	224
$[Rh(CO)_2acac]$	Ethylene glycol (67.1), methanol (31.2), ethanol (1.7)	*N*-Methylpyrrolidone, 230 °C (430/430), Cs[OOCPh], 2-hydroxypyridine	4 h	135[a] 63[b] 3[c]	Rhodium clusters formed	225
$[Rh(CO)_2acac]$	Ethylene glycol (53), methanol (44), glycerine (3)	thf, 230 °C, (689/689), 2-hydroxypyridine	3 h	100 82[b] 6[d]	Rhodium clusters formed	226
$[Ir(CO)_4]$	Methane	Toluene, 140 °C, 2 bar	3–5 d	3–5	1% conversion	227
$[Ir(CO)_4]$	Methane, ethane, propane, isobutane	NaCl–$AlCl_3$, 180 °C, (1.12/0.37)	12–24 h	n.g.	Report inprecise	228
$[Ir(CO)_4]$	Methanol (45.1), methyl formate (18.4), ethylene glycol (4.9), methyl acetate (2.7), ethanol (2.1)	Toluene, 230 °C, (1000/1000)	2 h	n.g.	2% conversion	229
$[Co_2(CO)_8]$	Methyl acetate (28.9), methanol (14.4), methyl formate (6.4), ethanol (5.9)	*N*-Methylpyrrolidine, 230 °C, (1000/1000)	1 h	n.g.	4% conversion	229
$[Co_2(CO)_6(C_2Ph_2)]$	Methanol (47.8), ethanol (28.5), methyl formate (14.7), ethyl formate (5.7), propanol (3.6)	Dioxane, 173 °C (100/100)	7 d	4[b] 2[c]	$[HCo(CO)_4]$ formation	230
$[Co_3(CO)_9(CMe)]$	Methanol (52), ethanol (25), propanol (15), methyl formate (4), ethyl formate (3)	Dioxane, 200 °C, (100/100)	7 d	6[b] 3[c] 2[e]	$[HCo(CO)_4]$ formation	230
$[Co_4(CO)_{10}(PPh)_2]$	Methanol (42), ethanol (30), propanol (9), methyl formate (14), ethyl formate (5)	Dioxane, 185 °C, (100/100)	7 d	3[b] 2[c]	$[HCo(CO)_4$ formation	230
$[Ru_3(CO)_{12}]$	Methanol (62.3), methyl formate (22.2), ethanol (1.2), ethylene glycol formate (1.2), methyl acetate (0.8)	*N*-Methylpyrrolidone, 230 °C (1000/1000)	2 h	n.g.	25% conversion	231, 229
$[Ru_3(CO)_{12}]$	Methane (81), ethane (3), propane (2), C_4–C_{30} alkanes (13)	Heptane, 300 °C, (100/100)	20 h	109[d]	Probably erroneous[233,234]	232

$[Ru_3(CO)_{12}]$ or $[H_4Ru_4(CO)_{12}]$ or $[Ru(acac)_3]$	Methanol (75), methyl formate (24)	thf, 268 °C, (520/780)	3 h	75[b] 24[f]	$[Ru(CO)_5]$ formation	233, 234
$[Ru_3(CO)_{12}]$	Methanol(45), dimethyl ether (6), dimethyl ketone (4), methyl formate (2)	2-Methoxyethanol, 180 °C (120/60)	48 h	49[b]	60% conversion	235
$[Ru_3(CO)_{12}]$	Methyl acetate (99), ethylene glycol diacetate (1)	Acetic acid, 260 °C, (170/170)	2 h	177[h]		236
$[Ru_3(CO)_{12}]$	Ethylene glycol (52), methanol (44), ethanol (4)	Sulpholane, 180 °C, (425/425), I_2 promoter	2.76 h	~1[a] ~1[b]	$[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$ formed	237, 238
$[Ru_3(CO)_{12}]$	Ethanol (62), methanol (34), ethylene glycol (<4)	230 °C (430/430), Pr_3PO, I_2 promoter	1 h	146[c] 81[b]	$[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$ formed	239
$[Ru_3(CO)_{12}]$	Methanol (74), ethylene glycol (10)	*N*-Methylpyrrolidone, 240 °C, (250/250), benzimidazole promoter	2 h	938[b] 322[a]		240–242
$[Ru_3(CO)_{12}]$	Methanol (90), ethylene glycol (10)	1,3-Dimethyl-imidizolidin-2-one, $[N(PPh_3)_2]$ promoter	1 h	313[b] 34[a]		243
$[Ru_3(CO)_{12}]$	Methanol (50), ethanol (36), ethylene glycol monoesters (9), ethylene glycol (5)	$[PBu_4]$Br melt, 220 °C, (215/215)	6–18 h	188[b] 135[c]		244
$[PBu_4][HRu_3(CO)_{11}]$	Methanol (48), ethanol (37), ethylene glycol (8), ethylene glycol monoesters (8)	$[PBu_4]$Br melt, 220 °C, (215/215)	6–18 h	178[b] 138[c]		244
$[PBu_4][Ru_6(CO)_{18}]$	Methanol (86), ethanol (7), ethylene glycol (5), ethylene glycol monoesters (2)	$[PBu_4]$Br melt, 220 °C, (215/215)	6–18 h	105[b]		244
$[Ru_3(CO)_{12}]$	Acetic acid (57), methane (18), ethyl acetate (17), propyl acetate (3), methyl acetate (2), propionic acid (2)	$[PBu_4]$Br melt, 220 °C, (241/241), CoI_2 co-catalyst	18 h	87[i]	$[Ru(CO)_3I_3]^-$ and $[Ru(CO)_4]^-$ formed	245

[a]related to ethylene glycol.
[b]related to methanol.
[c]related to ethanol.
[d]related to glycerine.
[e]related to propanol.
[f]related to methyl formate.
[g]related to methane.
[h]related to methyl acetate.
[i]related to acetic acid.

$$2CO + 2H_2 \longrightarrow HCOOCH_3 \quad (33)$$

$$nCO + (4n-1)H_2 \longrightarrow C_nH_{2n+1}OH + (n-1)H_2O \quad (34)$$

$$CO + 3H_2 \longrightarrow CH_4 + H_2O \quad (35)$$

$$nCO + 2nH_2 \longrightarrow C_nH_{2n} + nH_2O \quad (36)$$

$$nCO + (2n-1)H_2 \longrightarrow C_nH_{2n+2} + nH_2O \quad (37)$$

With the exception of the methanol synthesis, which is a major industrial process, heterogeneously catalysed syngas reactions are very unselective and yield a variety of products. Much effort has therefore been invested in a homogeneous process to produce mainly ethanol and ethylene glycol with high selectivity. Metal clusters are thought to play a key role in these reactions. Syngas chemistry is of less interest for organic synthesis, but of great commercial potential, particulary since the oil crisis has revealed the need for basic chemical feedstocks independent of primary resources. The generation of ethylene glycol and ethanol from syngas has been reviewed in great detail[220]. The potential of metal carbonyl clusters in the catalytic hydrogenation of carbon monoxide has also been reviewed[117], and the industrial aspects of cluster chemistry with regards to syngas reactions have been summarized[222,226]. Therefore, only a few typical examples have been selected in this section.

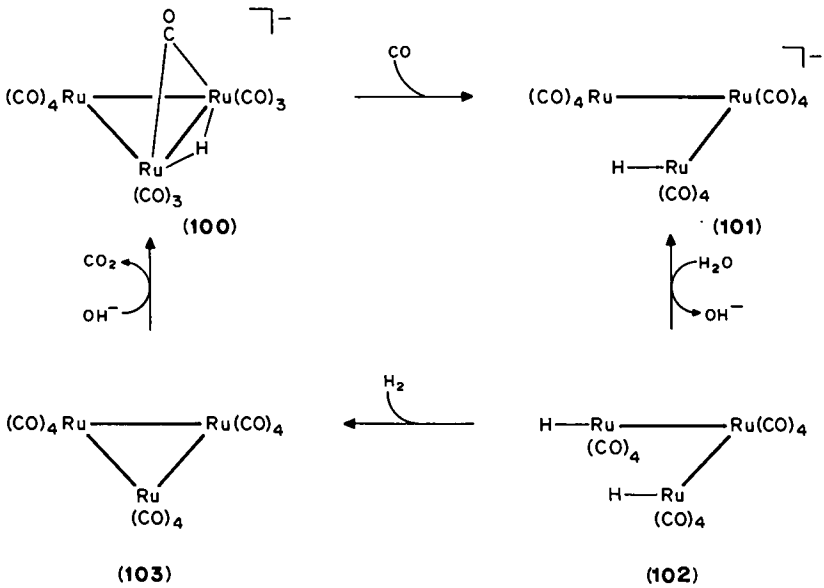
Most of the catalytic systems used for syngas reactions are based on rhodium or ruthenium, but there are also some reports on the use of cobalt and, to a lesser extent, iron complexes (Table 7). Of special interest is the selective synthesis of ethylene glycol, which has attracted intense industrial activity. Several patents were disclosed in the 1970s describing a high-pressure ethylene glycol synthesis using rhodium carbonyl catalysts[223–225,246,254]. A process based on the procedure of Pruett[223] reached the stage of a pilot plant[253]. This process operates with rhodium clusters; the reactor is charged with the mononuclear complex $[Rh(CO)_2(acac)]$, which is converted into various rhodium clusters depending on the reaction conditions. Infrared studies of the catalyst solution under pressures of 550–1030 bar and temperatures up to 200 °C suggested the presence of anionic rhodium clusters. The ν_{CO} i.r. bands were initially assigned to an anionic species described as $[Rh_{12}(CO)_{\sim 34}]^{2-}$[247,248], which is in a CO pressure-dependent equilibrium with the isolated and structurally characterized anion $[Rh_{12}(CO)_{30}]^{2-}$[249]. Later studies by high-pressure i.r. spectroscopy[222,250] and high-pressure ^{13}C n.m.r. spectroscopy[251] showed that the species present under the catalytic conditions is $[Rh_5(CO)_{15}]^-$, which finally could be isolated at low temperatures[252]. However, the presence of other anionic rhodium clusters at conditions generally employed for catalytic experiments cannot be excluded. In particular, $[H_3Rh_{13}(CO)_{24}]^{2-}$, $[H_2Rh_{13}(CO)_{24}]^{3-}$, $[Rh_{14}(CO)_{25}]^{4-}$, and $[Rh_{15}(CO)_{27}]^{3-}$ are under discussion[220]. Up to now the role of these anionic rhodium clusters remains uncertain; because of the labile fragmentation and rearrangement processes, the identity of the active species is not apparent.

A particularly broad potential for application in syngas reactions is shown by ruthenium carbonyl clusters. Iodide promoters seem to favour ethylene glycol[237,238]; the formation of $[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$ was observed under the catalytic conditions. These species possibly have a synergistic effect on the catalytic process. Imidazole promoters have been found to increase the catalytic activity for both methanol and ethylene glycol formation[240–242]. Quaternary phosphonium salt melts have been used as solvents; in these cases the anion $[HRu_3(CO)_{11}]^-$ was detected in the mixture[244]. Cobalt iodide as co-catalyst in molten $[PBu_4]Br$ directs the catalytic synthesis towards acetic acid[245]. With cobalt catalysts the clusters seem to break down to monomolecular species[229,230]. It is believed that in these cases clusters are of no importance[229].

d. Water gas shift reaction. The term 'water gas' shift reaction' denotes the conversion of carbon monoxide and water into carbon dioxide and hydrogen (equation 38). This reaction is of considerable commercial interest because the hydrogen content of synthesis gas can be increased by this equilibrium. Current methods for effecting this reaction involve heterogeneous catalysis at high temperature.

$$CO + H_2O \rightleftharpoons CO_2 + H_2 \tag{38}$$

Several metal clusters are reported to catalyse this conversion in the homogeneous phase. Most of the reports focus on ruthenium clusters. Ford and coworkers[255] used alkaline solutions of $[Ru_3(CO)_{12}]$ in ethoxyethanol and water, stirred at 100 °C under 1 bar of CO. Over a period of 30 days the total hydrogen produced by this system corresponded to a catalytic turnover of 150 mol of H_2 per mole of $[Ru_3(CO)_{12}]$. In later studies it was found that alkaline aqueous ethoxyethanol solutions of $[Ru_3(CO)_{12}]$ contain the two known cluster anions $[HRu_3(CO)_{11}]^-$ and $[H_3Ru_4(CO)_{12}]^-$ as the principle species present under catalytic conditions[256]. These two cluster anions were regarded as the active species for which feasible catalytic cycles have been proposed[256–259]. At first it was speculated that $[HRu_3(CO)_{11}]^-$ can be protonated by water to give $[H_2Ru_3(CO)_{11}]$, which on reaction with CO yields $[Ru_3(CO)_{12}]$ and H_2. $[Ru_3(CO)_{12}]$ is then reconverted into $[HRu_3(CO)_{11}]^-$ by attack of OH^- accompanied by the elimination of CO_2[256]. Because of the instability of $[H_2Ru_3(CO)_{11}]$ in alkaline solutions, this proposal has been dropped in favour of a cycle depicted in Scheme 21. It is assumed that $[HRu_3(CO)_{11}]^-$ (**100**) takes up carbon monoxide to give the open-chain anion $[HRu_3(CO)_{12}]^-$ (**101**), which is protonated by water to give the neutral $[H_2Ru_3(CO)_{12}]$ (**102**). With elimination of H_2, **101** gives ruthenium carbonyl **103**, from which **100** is recycled by OH^- [257,258]. This view is supported by the synthesis of the



SCHEME 21

osmium analogue with an open Os_3 chain, $[H_2Os_3(CO)_{12}]$[260]. A similar cycle has been proposed for the second anionic species detected in the catalytic solution, the tetranuclear $[H_3Ru_4(CO)_{12}]^-$; this anion has been assumed to react with CO with elimination of H_2 to give $[HRu_4(CO)_{13}]^-$, which in turn adds water to give $[H_3Ru_4(CO)_{12}(CO_2)]^-$. This species would decarboxylate to regenerate $[H_3Ru_4(CO)_{12}]^-$[256,257]. Careful studies by Bricker *et al.*[261], however, demonstrated that the tetranuclear cluster anion is formed as a side product of $[HRu_3(CO)_{11}]^-$ and $[Ru_3(CO)_{12}]$ under hydrogen pressure; it does not seem to be a catalytic species in the water gas shift reaction. The equilibrium between tetra- and tri-nuclear species explains that the trinuclear combination **103–100** plays the major role in the catalytic water gas reaction, irrespective of whether the reaction is initiated by tri- or tetra-nuclear ruthenium carbonyl complexes[261]. Solutions of $[Ru_3(CO)_{12}]$ or $[H_4Ru_4(CO)_{12}]$ in thf with aqueous trimethylamine have been reported as water gas shift catalysts; the hydrogen produced was 3300 and 3400 mol, respectively, per mole of catalyst at 150 °C and 24 bar of CO after 10 h[265].

A catalytic system for the water gas shift reaction based on $[Ru_3(CO)_{12}]$ in aqueous acetic acid–diglyme solution has also been described[262]. The reaction proceeds in diglyme with H_2SO_4 and H_2O added at 100 °C and a partial pressure of CO of 0.9 bar. After an induction period of 6–10 h the activity rises to a maximum level and remains constant for about 120 h; the catalytic turnover is ca. 1200 related to hydrogen. After 6–7 days the catalytic activity drops substantially owing to the limited lifetime of the catalyst. In contrast to alkaline media, $[Ru_3(CO)_{12}]$ seems to form dinuclear species in acidic solutions; a mechanism based on cationic Ru_2 clusters has been proposed[262]. An aqueous methanol solution of $[Ru_3(CO)_{12}]$ containing sodium sulphide has been reported as a sulphur-tolerant homogeneous catalyst for the water gas shift reaction[263]. A very active catalytic system was obtained from $[Ru_3(CO)_{12}]$ and 2,2-bipyridine in water; at 150 °C at 0.8 bar CO the catalytic turnover was as high as 4400 after 24 h[264].

There are several reports of rhodium clusters as water gas shift catalysts. A system prepared from $[Rh_2(CO)_4Cl_2]$, glacial acetic acid, concentrate HCl, sodium iodide, and water produces H_2 and CO_2 at 90 °C and a CO pressure of 0.5 bar with a catalytic turnover of 9 per day[266]. $[Rh_6(CO)_{16}]$ is reported to catalyse the water gas shift reaction in aqueous trimethylamine–tetrahydrofuran solutions (125 °C, 24 bar CO, 10 h, catalytic turnover 1700)[265]. With ethylenediamine in 2-ethoxyethanol and water (100 °C, 0.9 bar CO) a catalytic turnover of 98 was observed within 4 h[267].

The water gas shift reaction has been applied to the catalytic exchange of deuterium for hydrogen in trialkylamines[268] and for hydroformylation reactions using carbon monoxide and water in the place of molecular hydrogen[265,269]. This application will be discussed in Section III.A.3.a.

e. Miscellaneous. Trinuclear ruthenium clusters catalyse the carbonylation of nitrobenzene to phenyl isocyanate (equation 39). The reaction proceeds with $[Ru_3(CO)_{12}]$ or $[HRu_3(CO)_{11}]^-$ as the catalyst. In the latter case a conversion of 100% was observed in acetonitrile solution at 140 °C under a CO pressure of 21 bar within 3 h; the selectivity is 95% (with 5% aniline formed), and the catalytic turnover 57. The catalysis seems to involve the imido clusters $[Ru_3(CO)_{11}(NPh)]$ and $[Ru_3(CO)_{10}(NPh)_2]$[270].

$$PhNO_2 + 3CO \longrightarrow PhN{=}C{=}O + 2CO_2 \qquad (39)$$

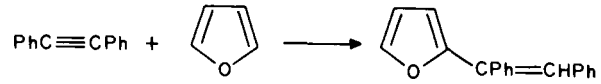
The rhodium clusters $[Rh_4(CO)_{12}]$ and $[Rh_6(CO)_{16}]$ have been found to catalyse the addition of benzene under C—H activation to unsaturated compounds such as ketenes, isocyanates, and acetylenes (equation 40–42)[271]. These reactions are carried out at temperatures between 180 and 220 °C and under a pressure of carbon monoxide (20–30 bar); exact data for calculating the catalytic turnovers were not reported[271].

$$Ph_2C{=}C{=}O + PhH \longrightarrow Ph_2CHCPh \quad (\text{O}) \tag{40}$$

$$PhN{=}C{=}O + PhH \longrightarrow PhNHCPh \quad (\text{O}) \tag{41}$$

$$PhC{\equiv}CPh + PhH \longrightarrow PhCH{=}CPh_2 \tag{42}$$

In a similar reaction, furans have been added to acetylenes to give furylethylenes using $[Rh_4(CO)_{12}]$ as catalyst (equation 43). The reaction requires a pressure of 25 bar in order to supress the trimerization of the acetylene. The products are formed within 7 h at 220 °C, giving yields up to 86% (catalytic turnover up to 1000)[272].



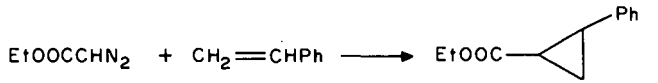
(43)

Several reports concern the hydrosilylation of olefins. Oct-1-ene has been converted into 1-triethoxysilyloctane using $[Rh_2(OOCMe)_4]$ as the catalyst (100 °C, 8 h, 98% conversion, catalytic turnover 627) (equation 44)[273]. Ruthenium carbonyl, $[Ru_3(CO)_{12}]$, catalyses the dehydrogenating hydrosilylation of olefins to give substituted vinylsilanes: styrene reacts with triethylsilane to give (*E*)-2-triethylsilylstyrene in 96% yield (benzene, 80 °C, 5 h, catalytic turnover 186) (equation 45)[274,275]. With trifluoromethylethylene the ratio of hydrosilylation and dehydrogenation hydrosilylation depends on the nature of the silane: $HSiEt_3$ gives specifically (*E*)-1-triethylsilyl-2-trifluoromethylethylene {$[Ru_3(CO)_{12}]$, 70 °C, 6 h, conversion 78%, catalytic turnover 210}, whereas $HSi(OEt)_3$ yields exclusively the saturated product 1-triethoxysilyl-2-trifluoromethylethane {$[Ru_3(CO)_{12}]$, 150 °C, 24 h, conversion 52%, catalytic turnover 140}[276] The cluster anion $[HRu_3(CO)_{10}(SiEt_3)_2]^-$ catalyses the reaction of triethylsilane with ethylene to give both vinyltriethylsilane (52%) and tetraethylsilane (22%); the reaction proceeds in CH_2Cl_2 at 100 °C with an initial ethylene pressure of 5 bar (total catalytic turnover 280)[277].

$$Me(CH_2)_5CH{=}CH_2 + (EtO)_3SiH \longrightarrow Me(CH_2)_5CH_2CH_2Si(OEt)_3 \tag{44}$$

$$PhCH{=}CH_2 + Et_3SiH \longrightarrow PhCH{=}CHSiEt_3 \tag{45}$$

Cyclopropanation and cyclopropenation reactions are catalysed by rhodium clusters. Styrene reacts with ethyl diazoacetate to give the cyclopropane derivative **104**, catalysed by $[Rh_6(CO)_{16}]$ (25 °C, conversion 87%, catalytic turnover 174) (equation 46)[278]. The analogous reaction at 83 °C with cyclohexene produces the corresponding bicycle in 43% yield (*anti/syn* ratio = 3), the catalytic turnover being 430[279]. The cyclopropanation of styrene with ethyl diazoacetate has also been reported with dinuclear rhodium complexes such as $[Rh_2(OOCMe)_4]$ as catalysts; at 22 °C the yield is 92% with an *E*/*Z* ratio of 1:5 (catalytic turnover 184)[280].



(46)

(104)

The same complex also catalyses the reaction of alkynes with ethyl diazoacetate to give cyclopropenes; hex-1-yne yields 84% of **105** at 25 °C (catalytic turnover 67; the reaction time was not given) (equation 47)[281].

TABLE 8. Catalytic alkyl exchange between Et_3N and Pr_3N

Catalyst	Products (%)	Conditions	Time	Catalytic turnover	Ref.
$[Os_3(CO)_{12}]$	Et_2NPr (26.7), $EtNPr_2$ (28.4)	150 °C[a]	3 h	40	282–285
$[Ru_3(CO)_{12}]$	Et_2NPr (22.8), $EtNPr_2$ (25.6)	150 °C[a]	3 h	36	282–285
$[Ir_4(CO)_{12}]$	Et_2NPr (6.2), $EtNPr_2$ (7.1)	150 °C[a]	2 h	10	282
$[Rh_6(CO)_{16}]$	Et_2NPr (5.2), $EtNPr_2$ (4.6), Et_2NBu (0.6), Et_2NH (0.2), Pr_2NH (0.1)	200 °C[a]	20 h	15	283
$[Os_3(CO)_{10}S]$	Et_2NPr (25), $EtPr_2$ (27)	143 °C[b]	16 h	150	286

[a]H_2O added.
[b]methanol added.

$$EtOOCCHN_2 + HC{\equiv}CBu \longrightarrow EtOOC\text{-}(C_3H_2)\text{-}Bu + N_2 \qquad (47)$$

(105)

Catalytic transalkylation reactions of tertiary amines (equation 48) have been described with $[Os_3(CO)_{12}]$[282–284], $[Ru_3(CO)_{12}]$[282–285], $[Ir_4(CO)_{12}]$[282], and $[Os_3(CO)_{10}S]$[286] (Table 8).

$$Et_3N + Pr_3N \rightleftharpoons Et_2NPr + Pr_2NEt \qquad (48)$$

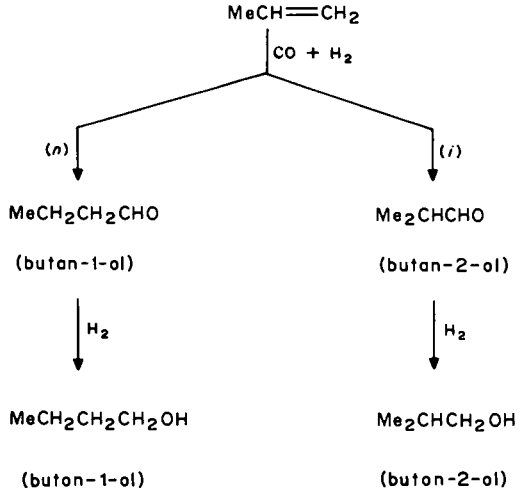
3. *Three-component reactions*

a. *Reactions involving CO–H_2.*

(*i*) Hydroformylation reactions. Hydroformylation refers to the addition of hydrogen and carbon monoxide to unsaturated systems. It has already been considered in Chapter 8 of Volume 3 of this series. The hydroformylation of olefins to give mainly aldehydes is also known as the 'oxo synthesis' or the roelen reaction, in honour of its inventor. It is one of the major industrial processes. The technical plants use cobalt- or rhodium-based catalysts; the active species are supposed to be mononuclear complexes[288]. The most desired oxo product is butan-1-al, generated by the hydroformylation of propylene[289].

The hydroformylation of olefins yields predominantly aldehydes. In the case of terminal olefins there are two selectivity problems which are illustrated for propene in Scheme 22. The carbon–carbon coupling can occur with either $C_{(1)}$ or $C_{(2)}$ of the olefin to give the *n*- or the *iso*-aldehyde; further, many hydroformylation catalysts catalyse also the hydrogenation of the aldehydes formed to give the corresponding alcohols. The ratio of aldehydes to alcohols (al/ol ratio) describes the chemoselectivity of the catalysis; the regioselectivity can be expressed as the ratio of linear to branched products (*n*/*i* ratio). The technical processes based on cobalt catalysts usually yield a mixture of about 80% butanals, 10% butanols and 10% other products; the *n*/*i* ratio is 3:1[289]. With rhodium catalysts in combination with phosphine co-catalysts, the *n*/*i* ratio is adjustable within the range between 8:1 and 16:1[289]. In contrast to the technical catalysts, most of the transition metal clusters reported as hydroformylation catalysts show a very high chemoselectivity for aldehydes,

some of them even being chemospecific (Table 9). The regioselectivity, however, depends markedly on the cluster. A very high *n/i* ratio for the hydroformylation of propene was observed with the cluster anion $[HRu_3(CO)_{11}]^-$; in diglyme at 75 °C under a total pressure of 10 bar, 98.6% of *n*-butanal and only 1.4% of isobutanal are formed[292]. This catalysis is almost specific for the formation of *n*-butanal.



SCHEME 22

With rhodium clusters the nuclearity of the species involved is doubtful. Chini *et al.*[300] showed in a clean stoichiometric reaction that propene is converted into a 1:1 mixture of butan-1- and -2-al by $[Rh_4(CO)_{12}]$ and hydrogen; the hexanuclear cluster $[Rh_6(CO)_{16}]$ is formed quantitatively (equation 49). The reaction is not catalytic, but it becomes catalytic with excess of triphenylphosphine. It appears, however, that in catalytic reactions the unsaturated mononuclear species $[HRh(CO)_3]$ is formed[297,298].

$$3Rh_4(CO)_{12} + 4MeCH{=}CH_2 + 4H_2 \longrightarrow 2Rh_6(CO)_{16} + 2MeCH_2CH_2CHO + 2Me_2CHCHO \qquad (49)$$

Chiral hydroformylation reactions have been studied using the tetranuclear ruthenium cluster $[H_4Ru_4(CO)_8(R,R\text{-diop})_2]$. The hydroformylation of bicyclo[2.2.2]oct-2-ene (toluene, 140 °C, 100 bar, $CO/H_2 = 1$) yields bicyclo[2.2.2]octane-2-carboxaldehyde with 51% conversion in an optical purity of 1.2% for the *R* enantiomer (the catalytic turnover was not given)[301]. The enantioselectivity is inferior to that reported for the same reaction using the mononuclear system $[HRh(CO)(PPh_3)_3]$-*R,R*-diop[302].

There is also a report on the hydroformylation of formaldehyde (employed as paraformaldehyde) to give glycol aldehyde (equation 50). With $[N(PPh_3)_2][Rh_5(CO)_{15}]$ and PPh_3 the reaction proceeds in acetone at 110 °C under a pressure of 95 bar ($H_2(H_2/CO)CO = 1$); after 2 h paraformaldehyde is completely consumed. The yield of glycolaldehyde is

TABLE 9. Hydroformylation of olefins by various metal clusters

Alkene	Products (%)	Catalyst	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Remarks	Ref.
Ethylene	Propanal (74), ethane (traces)	$[NEt_4][HRu_3(CO)_{11}]$	dmf, 100 °C, (13/26), $P_{C_2H_4} = 13$ bar	5 h	355	[a,c]	291
Propene	Butan-1-al (37), butan-2-al (0.5)	$[NEt_4][HRu_3(CO)_{11}]$	Diglyme, 75 °C, (1.7/3.3), $P_{C_3H_6} = 5$ bar	66 h	57	[a,c]	292
Propene	Butan-1-al (27.9), butan-2-al (12.5), propane (19.8)	$[Ru_3(CO)_{12}]$	Toluene, 150 °C, (63/98)	1.5 h	250	[a]	290
But-1-ene	Pentan-1-al (38.2), pentan-2-al (12.3), butane (25.6)	$[Ru_3(CO)_{12}]$	Toluene, 150 °C, (45/29)	2.5 h	155	[a]	290
Pent-1-ene	Hexan-1-al (19.4), hexan-2-al (5.2)	$[Rh_4(CO)_{12}]$–PPh_3 (1:4)	Benzene, 25 °C, (0.5/0.5)	6 h	67	[b]	293
Pent-1-ene	Hexan-1-al (78), hexan-2-al (21)	$[Rh_4(CO)_{12}]$–PPh_3 (1:5)	Benzene, 25 °C, (0.5/0.5)	6 h	237	[b]	293
Pent-1-ene	Hexan-1-al (27), hexan-2-al (1)	$[Rh_4(CO)_{12}]$–$P(OPh)_3$ (1:4)	Benzene, 25 °C, (0.5/0.5)	24 h	74	[b]	293
Pent-1-ene	Hexan-1-al (3.6), hexan-2-al (0.2)	$[AsPh_4][H_3Ru_4 \cdot (CO)_{12}]$	thf, 150 °C, (10.3/62)	0.25 h	19	[b]	269
Pent-1-ene	Hexan-1-al (49), hexan-2-al (23)	$[Co_4(CO)_{10}(PPh)_2]$	Toluene, 140 °C, (110/110)	6 h	20	[b,c](89%)	294

Hex-1-ene	Heptan-1-al (17.8), internal heptanals (5.4)	$[Co_3(CO)_9(CPh)]$	Toluene, 100 °C, (69/69)	22 h	55	[b]	295
Hex-1-ene	Heptan-1-al (20.6), internal heptanals	$[Co_3(CO)_9CC_6H_4—R]$ (R = polymer)	Toluene, 100 °C, (69/69)	23 h	65	[b,d]	295
Hex-1-ene	Heptan-1-al (80), heptan-2-al (20)	$[Rh_2(CO)_2(SBu^t)_2L_2]$ (L = $P(OPh)_3$)	Toluene, 80 °C, (5/5)	1.67 h	440	[b,e]	296
Hept-1-ene	Octan-1-al (presumably octan-2-al)	$[Rh_4(CO)_{12}]$	*n*-Hexane, 75 °C, (44/46)	1 h	962	[a] *n/i* ratio not given, $[HRh(CO)_3]$ formed	297, 298
Cyclohexene	Cyclohexanal (23.4), cyclohexane (5.4)	$[Ru_3(CO)_{12}]$	Toluene, 150 °C, (55/20)	2 h	145	[a]	290
Cyclohexane	Cyclohexanal (97)	$[Rh_6(CO)_{16}]$	Dioxane, 150 °C, (100/150)	3 h	n.g.	[b] contradictory data	299

[a] No alcohols observed.
[b] No comments on alcohol formation.
[c] Catalyst recoverable.
[d] Catalyst not recoverable.
[e] No alkane or alkene formation.

42.7% (catalytic turnover 42.2); side products are methanol (46.8%), ethylene glycol (9.9%), and methyl formate (0.6%)[309]. The proportion of glycol aldehyde can be increased to 87.9% by using a synergistic catalytic system of $[Rh_5(CO)_{15}]^-$, $[Rh(CO)_2Cl_2]^-$, and PPh_3[309].

$$CH_2{=}O + CO + H_2 \longrightarrow O{=}HCCH_2OH \qquad (50)$$

(*ii*) Homologation reactions. There is considerable interest in building up basic organic substrates such as alcohols, carboxylic acids and esters from their lower molecular weight homologues using synthesis gas (equations 51 and 52). The elongation of the carbon chain of these molecules by a CH_2 unit derived from $CO{-}H_2$ is called 'homologation'. Without any doubt the syngas homologation of methanol to ethanol, once achieved on an industrial scale, would have enormous commercial potential, since it represents the key step in a syngas route to ethylene[316].

$$MeOH + CO + 2H_2 \longrightarrow MeCH_2OH + H_2O \qquad (51)$$

$$MeCOOH + CO + 2H_2 \longrightarrow MeCH_2COOH + H_2O \qquad (52)$$

Several transition metal clusters, mainly ruthenium compounds, are known to catalyse homologation reactions (Table 10). One of the intrinsic problems with this type of reaction is the formation of several higher homologues since the homologation product itself is accessible to homologation catalysis. However, it appears that substrates become less active with increasing carbon chain length. A special application is the conversion of acetic acid into ethylene glycol diacetate with syngas[321], but methyl acetate is the dominant reaction product in this case.

(*iii*) Related reactions. Aryl carboxylic acids exhibit a different reaction pattern to aliphatic carboxylic acids in catalytic syngas reactions: instead of homologation to the higher molecular weight homologue, reduction to the corresponding arylalkanes takes place. Diphenylacetic acid is converted into diphenylmethane under a syngas pressure of 435 bar ($CO/H_2 = 2$) using a catalytic system composed of $[Ru_3(CO)_{12}]$ and MeI (220 °C, 16 h) with a 30% yield, corresponding to a catalytic turnover of 7.5[323].

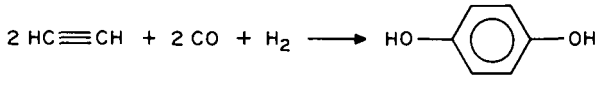
$$NH_3 + CO \longrightarrow H_2NCHO \qquad (53)$$

$$NH_3 + 2CO + 2H_2 \longrightarrow MeNHCHO + H_2O \qquad (54)$$

$$NH_3 + 3CO + 4H_2 \longrightarrow Me_2NCHO + 2H_2O \qquad (55)$$

Formamides can be obtained from ammonia and syngas using ruthenium catalysts (equations 53–55). $[Ru_3(CO)_{12}]$ in molten $[PBu_4]I$ yields predominantly methyl- and dimethyl-formamides[324,325]; with $[Ru_3(CO)_{12}]$ in sulpholane the main product is formamide[326] (Table 11).

Ruthenium carbonyl, $[Ru_3(CO)_{12}]$, has been reported to catalyse the cyclo-hydrocarbonylation of acetylene to give hydroquinone (equation 56). The reaction proceeds in thf at 220 °C ($p_{CO} = 127$ bar, $p_{H_2} = 5$ bar); after 170 min 58.7% of the acetylene is converted into hydroquinone (catalytic turnover 449)[327]. A similar reaction has been described in a patent, giving lower yields in hydroquinone at lower temperature[328].



(56)

TABLE 10. Homologation of alcohols, acids and esters

Substrate	Products (%)	Catalyst	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Ref.
Methanol	Ethanol (26 mmol), methane (26 mmol)	$[Ru_3(CO)_{12}]$–1-methylpiperidine (5:2)	200 °C, (50/150)	3.4 h	3.3	317,318
Methanol	Ethanol, methane	$[Mn_2(CO)_{10}]$–1-methylpiperidine (11:2)	200 °C, 50/150)	6 h	5.4	317,318
Acetic acid	Propionic acid (25%), butyric acids (7.2%)[a], valeric acids (3.2%)	$[Ru_3(CO)_{12}]$–MeI (10:1)	220 °C, (135/135)	18 h	145	319,320
Acetic acid	Propionic acid (34%), butyric acids (5.3%), valeric acids (< 1%)	$[H_4Ru_4(CO)_{12}]$–MeI (10:1)	220 °C, (135/135)	18 h	87	319,320
Acetic acid	Methyl acetate (25 mmol), ethylene glycol acetate (0.7 mmol), ethyl acetate (0.5 mmol)	$[Ru_3(CO)_{12}]$	220 °C, (215/215)	6 h	13	321
Acetic acid	Methyl acetate (18 mmol), ethyl acetate (12 mmol)	$[Ru_3(CO)_{12}]$–PBu_3 (1:6)	220 °C, (215/215)	6 h	15	321
Methyl propionate	Ethyl propionate (127 mmol), *n*-propyl propionate (12 mmol), acetic acid (19 mmol)	$[Ru_3(CO)_{12}]$	200 °C, (138/138)	8 h	207	322

[a] $n/i = 5.1$.

TABLE 11. Reaction of ammonia with carbon monoxide and hydrogen

Catalyst	Products (%)	Conditions (bar H_2/bar CO)	Time	Catalytic turnover[a]	Ref.
$[Ru_3(CO)_{12}]$	Methyl formamide (42.7), dimethylformamide (23.9)	$[PBu_4]I$, 220 °C, (215/215)	4 h	180	324, 325
$[Ru_3(CO)_{12}]$	Formamide (10.9), methylformamide (12.7), dimethylformamide (59.1)	$[PBu_4]I$, 220 °C, (215/215)	18 h	n.g.	324, 325
$[Ru_3(CO)_{12}]$	Formamide (59.6), methylformamide (21.1), dimethylformamide (13.6)	$[PBu_4]I$, 220 °C, (215/215)	4 h	84	324, 325
$[Ru_3(CO)_{12}]$	Formamide (22.8), methylformamide (1.0), dimethylformamide (0.1)	Solvolane, 204 °C, (170/170)	3.5 h	645	326

[a]Total catalytic turnover ($\sum$ formamides).

Nitrobenzene is reduced to aniline by synthesis gas in the presence of $[Ru_3(CO)_{12}]$ (equation 57); the reaction proceeds without solvent at 140 °C under a pressure of 200 bar ($H_2/CO = 1$). After 6 h, 66% of the nitrobenzene is converted to aniline, the catalytic turnover being 800[334].

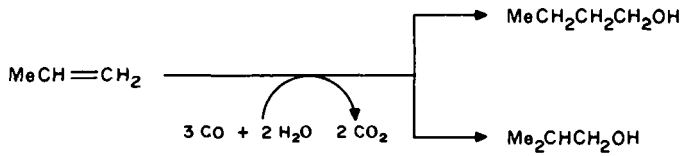
$$PhNO_2 + 2CO + H_2 \longrightarrow PhNH_2 + 2CO_2 \quad (57)$$

In contrast to this reduction, nitrobenzene is reduced by synthesis gas to give phenylformamide if a catalytic system composed of $[Ru_3(CO)_{12}]$ and NaOMe is used (thf, 60 °C, 1 bar, 12 h, 29% yield, catalytic turnover 4 (equation 58)[335]. $[Fe_3(CO)_{12}]$ in the place of $[Ru_3(CO)_{12}]$ gave predominantly *N*-phenyl-*O*-methylurethane (61% yield, catalytic turnover 8).

$$PhNO_2 + 3CO + H_2 \longrightarrow PhNHCHO + 2CO_2 \quad (58)$$

b. Reactions involving CO–H_2O.

(*i*) Hydrohydroxymethylation reactions including hydroformylation using the water gas shift equilibrium. Hydrogen can be generated from water with carbon monoxide by the water gas shift reaction (cf. Section III.A.2.d). Therefore, water can be used in the place of molecular hydrogen for the oxo synthesis; this modification, which converts olefins predominantly into alcohols, is generally called 'hydrohydroxymethylation' (equation 59). The only industrial application, the synthesis of butanol from propene (Reppe synthesis), was not very successful[336]. This reaction is catalysed by iron carbonyls in the presence of tertiary ammonium salts; the trinuclear cluster anion $[HFe_3(CO)_{11}]^-$ detected in the reaction mixture has been discussed as the active species[310]. Spectroscopic studies under CO pressure, however, showed the trinuclear anion $[HFe_3(CO)_{11}]^-$ to be converted into the mononuclear species $[HFe(CO)_4]^-$ [315], and this anion is now assumed to be the catalyst in the Reppe reaction[265].



(59)

With some clusters, hydroformylation employing the water gas shift reaction dominates hydrohydroxymethylation (Tables 12 and 13). A catalytic system composed of $[Fe_3(CO)_{12}]$, NEt_3, NaOH, H_2O, and MeOH has been reported to catalyse the hydroformylation and hydrogenation of styrene at 140 °C and 100 bar CO; the products are 2-phenylpropanol (21.9%) and ethylbenzene (24.0%) and the catalytic turnover does not exceed 3[311]. A very active hydroformylation catalyst using water as a solvent and hydrogen source has been reported in which the dinuclear water-soluble rhodium complex $[Rh_2(CO)_2(SBu^t)_2\{P(m\text{-}C_6H_4SO_3Na)_3\}_2]$ converts hex-1-ene at 80 °C in aqueous acetate buffer (pH 4.8) into heptan-1-al with a catalytic turnover frequency of $40\,h^{-1}$ and a selectivity of $n/i = 23$[312].

(*ii*) Reduction of aromatic nitro compounds. Nitroaryls can be reduced to aniline not only with hydrogen (cf. Section III.A.2.b.iv) or synthesis gas (cf Section III.A.3.a.iii), but also with carbon monoxide and water (equation 60). A fairly large number of transition metal clusters have been reported to be active for this conversion (Table 14).

$$PhNO_2 + 3CO + H_2O \longrightarrow PhNH_2 + 3CO_2 \quad (60)$$

TABLE 12. Hydroformylation and hydrohydroxymethylation of propane with CO–H_2O to give butan-1-al, butan-2-al, butan-1-ol, and butan-2-ol

Catalyst	Conditions (bar C_3C_6/bar CO)	Time	*n/i*	al/ol	Catalytic turnover	Remarks	Ref.
$[Co_3(CO)_9(CMe)]$–dppe (1:1)	thf, H_2O, 135 °C, (9/12)	17 h	n.g.	90	5		203
$[Rh_6(CO)_{16}]$–NEt_3	thf, H_2O, 125 °C, (10/24)	10 h	1.4	40	300	[a,b]	265
$[Ru_3(CO)_{12}]$	thf, H_2O, 100 °C, (10/24)	10 h	11.5	43	47	[a]	265
$[H_4Ru_4(CO)_{12}]$	thf, H_2O, 100 °C, (10/24)	10 h	11.0	37	79	[a]	265
$[Os_3(CO)_{12}]$	thf, H_2O, 180 °C, (10/24)	10 h	1.9	6.6	13	[a,b]	265
$[H_2Os_3(CO)_{10}]$	thf, H_2O, 180 °C, (10/24)	10 h	1.2	300	6	[a,b]	265
$[H_4Os_4(CO)_{12}]$	thf, H_2O, 180 °C, (10/24)	10 h	1.4	300	9	[a,b]	265
$[Ir_4(CO)_{12}]$	thf, H_2O, 125 °C, (10/24)	10 h	1.8	300	250	[a,b]	265
$[HNEt_3][HFe_3(CO)_{11}]$	dmf, H_2O, 150 °C, (8/20)	6 h	2	10	4.5		305–308

[a]Absolute yields not given.
[b]Propane as side product.

TABLE 13. Hydroformylation and hydrohydroxymethylation with $CO-H_2O$ of pent-1-ene to give hexan-1-al, hexan-2-al, hexan-1-ol, and hexan-2-ol

Catalyst	Conditions (bar CO)	Time	*n/i*	al/ol	Catalytic turnover	Remarks	Ref.
$[Fe_3(CO)_{12}]$	MeOH, H_2O, KOH, 150 °C, (55)	0.5 h	1.7	11.4	1.1	[a]	304
$[Ru_3(CO)_{12}]$	MeOH, H_2O, KOH, 150 °C, (55)	0.5 h	48	∞	1.1	[b]	304
$[H_4Ru_4(CO)_{12}]$	MeOH, H_2O, KOH, 150 °C, (55)	0.5 h	48	∞	n.g.		304
$[HRu_3(CO)_9(CCBu^t)]$	MeOH, H_2O, KOH, 150 °C, (55)	0.5 h	48	∞	n.g.		304
$[Rh_6(CO)_{16}]$	MeOH, H_2O, KOH, 150 °C, (55)	0.5	2.8	2.2	2.7	[c]	304

[a]Catalytic turnover 52 after 24 h.
[b]Catalytic turnover 55 after 24 h.
[c]Catalytic turnover 130 after 24 h.

(*iii*) Other reductions using carbon monoxide and water. Some reports concern selective catalytic hydrogenations using CO and H_2O in the presence of catalytically active metal clusters. α,β-Unsaturated aldehydes, ketones, and nitriles are selectively reduced at the C=C double bond with $[Rh_6(CO)_{16}]$. As a typical example, β-phenylacrolein is converted into β-phenylpropionaldehyde in thf at 130 °C and 100 bar; after 20 h the yield is 74% with 100% selectivity (catalytic turnover 1190) (equation 61)[337]. In contrast, with CO and H_2O the aldehyde function of acrolein is selectively reduced to the alcohol function without reducing the C=C double bond by a catalytic system composed of $[Rh_6(CO)_{16}]$ and 1,3-(dimethylamino)propane (80 °C, 10 bar, 24 h, yield 94%, catalytic turnover 56) (equation 62)[338].

$$PhCH{=}CHCH{=}O + CO + H_2O \longrightarrow PhCH_2CH_2CH{=}O + CO_2 \qquad (61)$$

$$CH_2{=}CHCH{=}O + CO + H_2O \longrightarrow CH_2{=}CHCH_2OH + CO_2 \qquad (62)$$

Cobalt clusters in the presence of 1,2-bis(diphenylphosphino)ethane catalyse the hydrocarbonylation of propene with $CO-H_2O$ to give a mixture of the isomeric dipropyl ketones (equation 63). With $[Co_3(CO)_9(CMe)]$ (dioxane, 165 °C, 100 bar) the yield is 53%, the catalytic turnover being 12[339]. The cyclohydrocarbonylation of acetylene to give hydroquinone has also been performed with $CO-H_2O$ using $[Ru_3(CO)_{12}]$ as the catalyst (thf, 190 °C, 175 bar, conversion 60.2%, catalytic turnover 435) (equation 64)[327].

$$2\ MeCH{=}CH_2 + 2\ CO + H_2O \longrightarrow Pr_2C{=}O + CO_2 \qquad (63)$$

$$2\ HC{\equiv}CH + 3\ CO + H_2O \longrightarrow HO\text{-}C_6H_4\text{-}OH + CO_2 \qquad (64)$$

Anthracene has been reported to react with CO and H_2O to give 9,10-dihydroanthracene; the reaction is catalysed by the dinuclear cluster $[Mn_2(CO)_8(PBu_3)_2]$ (thf, KOH, 200 °C, 24 bar, 13% yield, catalytic turnover 2.3)[340]. Accordingly, the N-analogue acridine is hydrogenated to 9,10-dihydroacridine with $CO-H_2$ using the same catalyst (thf, KOH, 200 °C, 24 bar, 2 h, yield 38%, catalytic turnover 3.8)[341].

TABLE 14. Reduction of nitrobenzene to aniline

Catalyst	Conditions (bar H_2)	Time	Conversion (%)	Catalytic turnover	Remarks	Ref.
$[Ru_3(CO)_{12}]$	100 °C, (35)	2 h	71	710	Et_3N–H_2O	329, 330
$[H_4Ru_4(CO)_{12}]$	100 °C, (35)	2 h	73	730	Et_3N–H_2O	329, 330
$[Os_3(CO)_{12}]$	180 °C, (35)	1 h	100	1000	Et_3N–H_2O	329, 330
$[H_2Os_3(CO)_{10}]$	180 °C, (35)	1 h	100	1000	Et_3N–H_2O	329, 330
$[H_4Os_4(CO)_{12}]$	180 °C, (35)	1 h	100	1000	Et_3N–H_2O	329, 330
$[Ir_4(CO)_{12}]$	125 °C, (35)	1 h	100	1000	Et_3N–H_2O	329, 330
$[NBu_4]_2[Pt_3(CO)_6]_5$	125 °C, (35)	10 h	18	180	Et_3N–H_2O	329, 330
$[Mn_2(CO)_{10}]$	180 °C, (35)	2 h	20	200	Et_3N–H_2O	329, 330
$[Re_2(CO)_{10}]$	180 °C, (35)	2 h	10	100	Et_3N–H_2O	329, 330
$[Rh_6(CO)_{16}]$	125 °C, (35)	1 h	100	1000	Et_3N–H_2O	329, 330
$[Rh_6(CO)_{16}]$	80 °C, (0.9)	4 h	100	30	H_2O–$Me_2N(CH_2)_2NMe_2$	331
$[Rh_6(CO)_{16}]$	80 °C, (0.9)	10 h	34	10	H_2O–$H_2N(CH_2)_2NH_2$	331
$[Rh_6(CO)_{16}]$	120 °C, (24)	8 h	90	315	thf, H_2O, $Me_2NC_6H_4CH_2NH_2$	332
$[Rh_6(CO)_{16}]$	165 °C, (30)	2 h	100	6000	EtOH, H_2O, 3,4,7,8-tetramethylphenanthroline	333

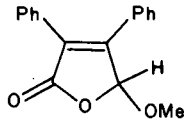
The cluster $[Rh_6(CO)_{16}]$ catalyses the reaction of pyridine with carbon monoxide and water (150 °C, 55 bar, 20 h) to give a series of products, among which the dominant species are 1,5-di(*N*-piperidyl)pentane (55%) and *N*-piperidyl aldehyde (14%). The total catalytic turnover is about 330, but the reaction is not very clear[313].

c. Reactions involving CO and alcohols. The catalytic addition of carbon monoxide and an alcohol to an olefin yields carboxylic esters (hydroesterification). Thus the synthesis of methyl propionate from ethylene, CO, and methanol has been reported using a catalytic system composed of $[Ru_3(CO)_{12}]$ and $[PPh_4]I$ (190 °C, $p_{C_2H_4} = 20$ bar, $p_{CO} = 45$ bar, 2.5 h, yield 74%, catalytic turnover 1000) (equation 65)[342]. The reaction works also with $Ru_3(CO)_{12}$ alone, but the yield and catalytic turnover are considerably lower; the iodide promoter seems to generate the two anionic species $[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$, and a combination of these anions increases activity and selectivity of the reaction[342].

$$CH_2{=}CH_2 + CO + MeOH \longrightarrow CH_3CH_2C(=O)OMe \qquad (65)$$

In a similar reaction internal acetylenes can be converted with CO and alcohols into furanones using $[Rh_4(CO)_{12}]$ as the catalyst in combination with a sodium acetate promoter; 3-ethoxy-3,4-diphenylfuran-2(5*H*)-one (**106**) can be obtained in 87% yield (catalytic turnover 348) from diphenylacetylene, CO, and methanol (125 °C, 50 bar, 6 h) (equation 66)[343,344]. The tetranuclear rhodium cluster $[Rh_4(CO)_{12}]$ has also been reported to catalyse the hydrocarbonylation of acrylic acid derivatives with isopropanol as hydrogen donor. As a typical example ethyl acrylate reacts with CO and isopropanol (equation 67) to give diethyl γ-ketopimelate (**107**) in 60% yield (catalytic turnover 2400) and acetone (180 °C, 95 bar, 6 h); ethyl propionate is formed as a side-product[345].

$$PhC{\equiv}CPh + 2\,CO + MeOH \longrightarrow \qquad (66)$$



(106)

$$2CH_2{=}CHCOOEt + CO \longrightarrow O{=}C(CH_2CH_2COOEt)_2 \qquad (67)$$

Me_2CHOH Me_2CO

(107)

Allene can be carbonylated in alcohols to give methacrylic esters in the presence of $[Ru_2(CO)_9]$ as the catalyst (equation 68). The procedure gives a yield of 50%, corresponding to a catalytic turnover of 114, at a temperature of 140 °C, a pressure of 700–900 bar, and a reaction time of 12 h. Under certain conditions a dimer, α,α-dimethyl-α′-methylene glutarate, is obtained[346].

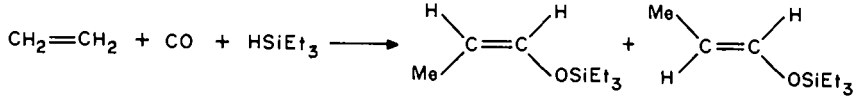
$$CH_2{=}C{=}CH_2 + CO + MeOH \longrightarrow CH_2{=}C(Me)COOMe \qquad (68)$$

The trinuclear $[Ru_3(CO)_{12}]$ can be used in combination with $[NEt_4]Cl$ to catalyse the selective reductive carbonylation of aromatic nitro compounds to carbamates; thus nitrobenzene reacts in toluene with CO and methanol (160–170 °C, 82 bar, 5 h) to give

methyl *N*-phenylcarbamate in 92.7% yield, the catalytic turnover being 92 (equation 69); a small amount of aniline (6.5%) was formed[347].

$$PhNO_2 + 3CO + MeOH \longrightarrow PhNHCOOMe + 2CO_2 \qquad (69)$$

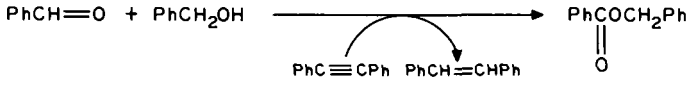
d. Miscellaneous. The cluster anion $[HRu_3(CO)_{10}(SiEt_3)_2]^-$ (or $[HRu_3(CO)_{11}]^-$) catalyses the silacarbonylation of ethylene and propene; ethylene is converted with CO and Et_3SiH at 100 °C in thf into the *Z*- (29%) and *E*-isomers (21%) of 1-(triethylsiloxy)prop-1-ene, the catalytic turnover being 280 after 20 h (equation 70)[277].



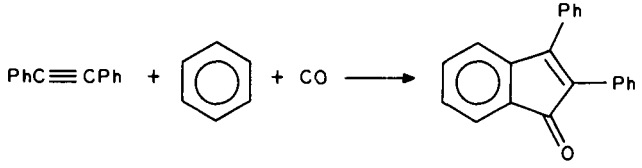
(70)

The analogous reaction of hex-1-ene with CO and $HSiEt_2Me$ has been studied with various catalysts. With $[Ru_3(CO)_{12}]$ the reaction in benzene (140 °C, 50 bar, 20 h) yields 40% of the four expected silacarbonylation products (catalytic turnover 10); with $[Co_2(CO)_8]$ the yield is 57%, corresponding to a catalytic turnover of 14. The product distributions are different, the respective compositions of the mixture being (*Z*)-1-diethylmethylsiloxyhept-1-ene 44% (43%), (*E*)-1-diethylmethylsiloxyhept-1-ene 45% (25%), (*Z*)-1-diethylmethylsiloxy-2-methylhex-1-ene 4% (16%), and (*E*)-1-diethylmethylsiloxy-2-methylhex-1-ene 7% (16%)[314].

The selective formation of carboxylic esters from aldehydes and alcohols in the presence of a hydrogen acceptor such as diphenylacetylene is catalysed by $[Ru_3(CO)_{12}]$. For instance, benzyl benzoate is obtained from benzaldehyde and benzyl alcohol in 72% yield (catalytic turnover 54) after 2 h when the reaction is carried out without solvent at 147 °C (equation 71)[348]. Rhodium carbonyl, $[Rh_4(CO)_{12}]$, catalyses the cyclocarbonylation of acetylenes with benzene to give indenones, e.g. 2,3-diphenylindenone is obtained from diphenyl acetylene and benzene in 10% yield, corresponding to a catalytic turnover of 11 (220 °C, 25 bar, 7 h) (equation 72). The reaction is not very selective, however; triphenylethyene (45%), 1-benzylidene-2,3-diphenylindene (8%), *trans*-stilbene (12%), and 2,3,4,5-tetraphenylcyclopentenone (16%) are further reaction products[349]. In a similar fashion, benzene and CO can be added to diphenylketene in the presence of $[Rh_4(CO)_{12}]$ to give small amounts of 1-diphenylmethylene-3-phenylindene (3% yield, catalytic turnover 6). The main product of the reaction (200 °C, 30 bar, 5 h), however, is 2,2-diphenylacetophenone (68%)[350].



(71)



(72)

Several catalytic reactions involving carbon dioxide have been performed with transition metal clusters. The reaction of CO_2 with hydrogen and methanol to give methyl

formate (equation 73) is catalysed by either $[N(PPh_3)_2][HFe_3(CO)_{11}]$ (175 °C, 41 bar, 4 days, catalytic turnover 5.8)[351] or $[N(PPh_3)_2]$ $[HRu_3(CO)_{11}]$ (125 °C, 17 bar, 24 h, catalytic turnover 4.1)[352]. Another reaction using CO_2 as a building block is the synthesis of vinyl carbamates from carbon dioxide, diethylamine, and alkynes catalysed by $[Ru_3(CO)_{12}]$; as a typical example phenylacetylene, CO_2, and Et_2NH are converted into the isomeric phenylvinyl carbamates (toluene, 140 °C, 50 bar, 20 h, yield 36%, catalytic turnover 18) (equation 74)[353].

$$CO_2 + H_2 + MeOH \longrightarrow HCOOMe + H_2O \tag{73}$$

$$PhC{\equiv}CH + Et_2NH + CO_2 \longrightarrow PhCH{=}CHOOCNEt_2 \; (+ CH_2{=}CHPhCOONEt_2) \tag{74}$$

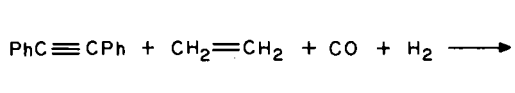
There is also a report, unfortunately lacking clarity, on the oxidation of ketones to carboxylic acids by oxygen and carbon monoxide which is catalysed by $[Rh_6(CO)_{16}]$. Thus cyclohexanone gives adipic acid at 100 °C (34 bar, $O_2/(O_2/CO)CO = 3,24$ h) (equation 75); the catalytic turnover claimed is 1000[355].

$$+ 2O_2 + CO \longrightarrow HOOC(CH_2)_4COOH + CO_2 \tag{75}$$

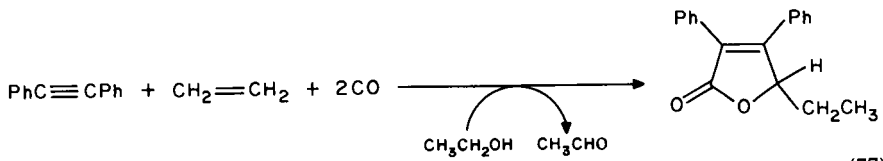
4. Four-component reactions

Few reactions are known in which four components are reacted together in the presence of a transition metal cluster as the catalyst. These reactions involve an acetylene, an olefin, CO, and hydrogen or a hydrogen donor, and are catalysed by the rhodium cluster $[Rh_4(CO)_{12}]$.

In a typical experiment, an acetone solution of diphenylacetylene is pressurized with ethylene (25 bar), CO (30 bar), and H_2 (5 bar) at 150 °C for 6 h; the reaction gives 1,2-diphenylpent-1-en-3-one in 60% yield, the catalytic turnover being 120 (equation 76)[356]. In contrast, 5-ethyl-3,4-diphenylfuran-2(5*H*)-one was obtained from an ethanol solution of diphenylacetylene pressurized with ethylene (20 bar) and CO (30 bar) at 180 °C for 6 h, the yield being 73% (catalytic turnover 292) (equation 77)[357,344].



(76)



(77)

B. Cooperative Effects: Catalytic Reactions Using Cluster Mixtures or Mixed-metal Clusters

The concept of cluster catalysis is based on the idea that catalytic transformations of a substrate may require coordination to several metal atoms of the cluster framework. Hence, in principle, mixed-metal clusters provide the possibility of making a catalytic site

to measure for a given process. A serious drawback, however, is the lack of knowledge of catalytic mechanisms, so that catalytic reactions involving mixed-metal clusters have been found more or less by chance or by a trial-and-error procedure.

Furthermore, disintegration of mixed-metal clusters during a catalytic reaction has to be considered. There are also many examples of catalytic systems consisting of two cluster components with different metals. In general, it is not known whether or not a mixed-metal cluster is formed *in situ* from these mixtures, or if the two different cluster systems cooperate in some way. One of the best studied synergistic effects has been reported for the two ruthenium anions $[HRu_3(CO)_{11}]^-$ and $[Ru(CO)_3I_3]^-$, usually formed from $[Ru_3(CO)_{12}]$ and I^- under catalytic conditions in a 2:1 ratio. This synergism operates in the hydrogenation of carbon monoxide to ethylene glycol[227,238] and in the hydroesterification of ethylene[342]. Based on kinetic and model studies, cluster breakdown to mononuclear species has been proposed[338]; however, the reaction is too complex for a complete understanding of this phenomenon.

In view of these general difficulties, no distruction will be made here between mixed-metal clusters and cluster mixtures as catalyst precursors. The discussion of the reactions reported follows the same criteria as used for monometallic clusters in Section III.A, but the systematization will be less strict.

1. *Hydrogenation reactions*

Several mixed-metal clusters have been reported for the hydrogenation of unsaturated hydrocarbons (Table 15). Particularly noteworthy is the fact that $[Co_2Rh_2(CO)_{12}]$ and $[Co_3Rh(CO)_{12}]$ catalyse the hydrogenation of styrene, whereas $[Co_4(CO)_{12}]$ is inactive[358]. This finding has been interpreted in terms of the hydrogenation occurring on the rhodium centre; the importance of the metal core is demonstrated by the observation that the initial hydrogenation rate of the Co_2Rh_2 cluster is roughly twice as high as that of the Co_3Rh cluster[358]. The mixed-metal clusters reported have been especially used for the partial hydrogenation of diolefins and acetylenes; the selectivity problem arises from the fact that they also catalyse the isomerization of the olefins formed.

2. *Syngas reactions*

The catalytic hydrogenation of carbon monoxide generally leads to a broad range of products of both hydrocarbons and oxygenates. In view of the particular interest focused on the synthesis of ethylene glycol from syngas (cf. Section III.A.2.c), efforts have been made in order to modify the catalysts for an increased ethylene glycol selectivity. In this context mixed-metal clusters and in particular, mixtures of clusters have been applied (Table 16). Especially favourable for ethylene glycol seems to be the cluster anion $[PtRh_5(CO)_{15}]^-$, which requires very high pressures[371]; a binary system of ruthenium and rhodium complexes in acetic acid generates preferentially glycol esters[372]. Noteworthy are also the bimetallic systems employed in molten quaternary phosphonium salts, which direct the synthesis either to methanol, ethanol, or acetic acid[368–370,373]. The most active system for both ethylene glycol and methanol synthesis seems to be the combination of $[Ru_3(CO)_{13}]$, $[Rh(CO)_2(acac)]$ and sodium iodide[365].

3. *Water gas shift reactions*

A very pronounced synergistic effect is found for binary ruthenium–iron carbonyl catalysts in the water gas shift reaction. Both mixed ruthenium–iron clusters and mixtures of ruthenium clusters with iron complexes are considerably more active in basic solutions. Whereas the water gas shift activity (moles of H_2 per mole of complex per day) of alkaline aqueous ethoxyethanol solutions of $[Ru_3(CO)_{12}]$ and $[Fe(CO)_5]$ is reported to be 2.8 and

TABLE 15. Hydrogenation of unsaturated hydrocarbons by mixed-metal clusters

Substrate	Products (%)	Catalyst	Conditions	Time	Catalytic turnover	Ref.
Styrene	Ethylbenzene (100)	$[Co_2Rh_2(CO)_{12}]$[a]	Neat, 27 °C, 2 bar, $P(OPh)_3$	2 h	967	358
Styrene	Ethylbenzene (100)	$[Co_3Rh(CO)_{12}]$[a]	neat, 27 °C, 2 bar, $P(OPh)_3$	2 h	n.g.	258
Cycloocta-1,5-diene	Cyclooctane (17.4), cyclooctene (41.2), cycloocta-1,4-diene, (6.6), cycloocta-1,3-diene (23.7)	$[Cp_2Pt_2W_2(CO)_6(PPh_3)_2]$	thf, 60 °C, 14 bar	5 h	481[b]	359
Cycloocta-1,5-diene	Cyclooctane (6.8), cyclooctene (61.1), cycloocta-1,3-diene (32.1)	$[Cp_2Pt_2Mo_2(CO)_6(PEt_3)_2]$	thf, 60 °C, 14 bar	3 h	557[b]	359
Cycloocta-1,5-diene	Cyclooctane (0.4), cyclooctene (70.4), cycloocta-1,4-diene (3.0), cycloocta-1,3-diene (23.7)	$[Cp_2Pd_2Mo_2(CO)_6(PEt_3)_2]$	thf, 60 °C, 14 bar	3 h	580[b]	359
(*Z*)-Penta-1,3-diene	Pentane (1.4), pent-1-ene (7.3), (*E*)-pent-2-ene (18.4), (*Z*)-pent-2-ene (13.1)	$[CpNiRu_3H_3(CO)_9]$	*n*-Octane, 120 °C, 0.9 bar	0.3 h	226[b]	360
(*Z*)-Penta-1,3-diene	Pentane (0.7), pent-1-ene (14.9), (*E*)-pent-2-ene (27.9), (*Z*)-pent-2-ene (21.5)	$[CpNiOs_3H_3(CO)_9]$	*n*-Octane, 120 °C, 0.9 bar	6 h	247[b]	361, 362
(*Z*)-penta-1,3-diene	Pentane (1.3), pent-1-ene (25), (*E*)-pent-2-ene (27.5), (*Z*)-pent-2-ene (21)	$[CpNiOs_3H_3(CO)_8(PPh_2H)]$	*n*-Octane, 120 °C, 0.9 bar	4 h	337[b]	362, 364
Oct-1-yne	Octane (43), oct-1-ene (55)	$[Pt_2Co_2(CO)_8(PPh_3)_2]$	Toluene, 50 °C, 50 bar	20 h	37[b]	363, 364
Diphenylacetylene	(*Z*)-Stilbene (22), (*E*)-stilbene (1), 1,2-diphenylethane (1)	$[Pt_2Co_2(CO)_8(PPh_3)_2]$	Toluene, 50 °C, 50 bar	20 h	26[b]	363, 364
Diphenylacetylene	(*E*)-Stilbene, (*Z*)-stilbene, 1,2-diphenylethane (12%, rel. ratio 100:18:1030)	$[Cp_2Ni_2Fe_2(CO)_6(C_2Ph_2)]$	Heptane, 120 °C, 0.9 bar	12 h	n.g.	189
Diphenylacetylene	(*E*)-Stilbene, (*Z*)-stilbene, 1,2-diphenylethane (40%, rel. ratio 1400:18.3:830.4)	$[Cp_2Ni_2Fe(CO)_3(C_2Ph_2)]$	Heptane, 120 °C, 0.9 bar	12 h	n.g.	189

[a] $[Co_4(CO)_{12}]$ inactive.
[b] Related to the total of hydrogen products.

TABLE 16. Hydrogenation of carbon monoxide catalysed by bimetallic systems

Catalytst	Products	Conditions (bar H_2/bar CO)	Time	Catalytic turnover[a]	Ref.
$[Ru_3(CO)_{12}]$–$[Rh(CO)_2(acac)]$–NaI (6:1:3)	Methanol, ethylene glycol (1:1)	*N*-Methylpyrrolidine, 230 °C, (43/43)	1 h	1000[b]	365
$[(MeCN)_2Cu_2Ru_6C(CO)_{16}]$	Methanol, methyl formate (84:11)	thf, 275 °C, (600/600)	5 h	680[b]	366
$[Ru_3(CO)_{12}]$–$[Re_2(CO)_{10}]$(1:2)	Methanol, ethylene glycol, ethanol (27:7.9:2.2)	*N*-Methylpyrrolidone, $[N(PPh_3)_2]Cl$, (150/150)	2 h	55[b]	367
$[Ru(acac)_3]$–$[Rh(acac)_3]$ (1:2)	Ethylene glycol, ethylene glycol monomethyl ester, methanol, ethanol (80:40:312:237)	$[PBu_4]I$ melt, 220 °C, (215/215)	18 h	312[b]	368, 369
$[Ru_3(CO)_{12}]$–$[Co_2(CO)_8]$ (1:1)	Ethanol, methanol, propanol, ethyl acetate, propyl acetate, methyl acetate (168:77:56:63:31:25)	$[PBu_4]Br$ melt, 220 °C, (217/217)	6 h	~85[c]	370
$[N(PPh_3)_2][PtRh_5(CO)_{15}]$	Ethylene glycol, methanol, methyl formate, ethanol, ethyl formate (38:13.7:2.5:14.5:2.2)	thf, 230 °C, 2-hydroxypyrrolidine, (1000/1000)	4 h	475[d]	371
$[N(PPh_3)_2][PtRh_4(CO)_{12}]$	Ethylene glycol, methanol, methyl formate, ethanol (13:13:1.2:20.7)	thf, 230 °C, (1000/1000)	4 h	130[d]	371
$[Ru(acac)_3]$–$Rh(CO)_2(acac)]$ (10:1)	Ethylene glycol acetates (mono- and di-), methyl acetate, ethyl acetate (36.5:22.6:4.4)	Acetic acid, 230 °C, (500/500)	2–4 h	~365[e]	372
$[Ru_3(CO)_{12}]$–$[CoI_2]$ (1:3)	Acetic acid, ethyl acetate, propyl acetate, methyl acetate propionic acid (116:34:6:4:5)	$[PBu_4]Br$ melt, 220 °C, (241/241)	18 h	87[f]	373

[a]Based on the minor cluster compound.
[b]Related to methanol.
[c]Related to ethanol.
[d]Related to ethylene glycol.
[e]Related to ethylene glycol esters.
[f]Related to acetic acid.

1.0, respectively, the activity of the mixture $[Ru_3(CO)_{12}]$–$[Fe(CO)_5]$ is 7.4[374,382]; for the mixed-metal cluster $[H_2FeRu_3(CO)_{13}]$ it is even 10.3 (conditions: 100 °C, 0.9 bar CO)[374]. A similar increase is found in piperidine–ethoxyethanol solutions under the same conditions {$[H_4Ru_4(CO)_{12}]$ 8.0, $[Fe(CO)_5]$ 0.9, $[H_4Ru_4(CO)_{12}]$–$[Fe(CO)_5]$ 30.0}[374]. A more dramatic effect has been shown in a different study: a pyridine solution of $[Fe_3(CO)_{12}]$ shows activity 0, the same solution of $[Ru_3(CO)_{12}]$ 15, whereas the activities of the mixed clusters $[FeRu_2(CO)_{12}]$ and $[Fe_2Ru(CO)_{12}]$ were found to be 220 and 250, respectively (conditions: 100 °C, 0.42–0.47 bar CO, activity given in moles of H_2 per mole of cluster per 24 h)[375,376].

4. Hydroformylation reactions

Both mixed-metal clusters and mixtures of clusters have been used as catalysts for the hydroformylation of olefins. No remarkable selectivity has been obseved in comparison with monometallic systems; synergistic effects concern only the activity (Table 17). Of particular interest are the metal-framework transformations observed for mixed iron–ruthenium carbido clusters under hydroformylation conditions; the catalyst precursor $[Fe_5RhC(CO)_{16}]^-$ evolves to a mixture of $[Fe_4Rh_2C(CO)_{16}]$ and $[Fe_4RhC(CO)_{16}]^-$; the latter cluster anion transforms to $[Fe_3Rh_3C(CO)_{15}]^-$ under hydroformylation conditions[379]. Obviously the carbido ligand stabilizes the cluster skeleton, but a redistribution of the metals around the interstitial carbon atom cannot be avoided during the catalysis. In contrast to these findings, suggesting the catalytic reaction to proceed at intact clusters, the synergism observed for $[Ru_3(CO)_{12}]$–$[Co_2(CO)_8]$ mixtures has been explained in terms of a 'hand-to-hand' cooperation of the individual metals; cobalt carbonyl species seem to perform the carbonylation step, whereas the hydrogenation step is assisted by hydridoruthenium species[385].

5. Homologation reactions

Homologation reactions with synthesis gas have attracted much attention; in particular, the transformation of methanol to ethanol with CO–H_2 has a considerable economic potential (cf. Section III.A.3.a.ii). The synergistic effect of two different metals seems to be especially large for reactions with synthesis gas, and therefore mixed-metal clusters and mixtures of clusters represent catalysts particularly favourable for homologation processes using CO–H_2 for the generation of a CH_2 building unit. Hidai *et al.*[386] showed that in a given experiment the mixed-metal clusters $[RuCo_3(CO)_{12}]^-$ and $[Ru_3Co(CO)_{13}]^-$ convert 17.8 and 11.4 mmol of methanol into ethanol, respectively, whereas the conversion with the individual components $[Co_4(CO)_{12}]$ and $[Ru_3(CO)_{12}]$ is only 0.6 and 2.8 mmol, respectively. The cluster anion $[FeCo_3(CO)_{12}]^-$ in the presence of methyl iodide as promoter has been found to convert methanol predominantly into acetaldehyde and its dimethylacetal; at 180 °C and a pressure of 120 bar ($H_2/CO = 2$) the catalytic turnover is 1395 after 2.5 h[386]; under a pressure of 270 bar ($H_2/CO = 1$) a catalytic turnover of 2435 (after 1 h) was reported[388] (Table 18).

Another homologation reaction extensively studied with bimetallic catalysts is the conversion of methyl acetate into ethyl acetate. The most active and also most selective system is composed of $[Ru_3(CO)_{12}]$ and $[Co_2(CO)_8]$ (1:8.9) in acetic acid with lithium acetate–methyltriphenylphosphonium iodide promoters; it yields 71.4% of the product with a catalytic turnover of 2505 in less than 1 h[391].

6. Miscellaneous

There are a number of interesting synthetic applications of bimetallic catalytic systems which mostly use mixtures of $[Ru_3(CO)_{12}]$ and $[Co_2(CO)_8]$. In general it is believed that

TABLE 17. Hydroformylation of olefins catalysed by bimetallic systems

Substrate	Products (%)	Catalyst	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Ref.
Cyclohexene	Cyclohexanal (100)	$[Ru_3(CO)_{12}]$–$[Co_2(CO)_8]$ (10:1)	thf, 110 °C, (40/40)	4 h	400[a,b]	377
Cyclohexene	Cyclohexanal (27)	$[NEt_4][FeCo_3(CO)_{12}]$	thf, 110 °C, (40/40)	4 h	108	377
Pent-1-ene	Hexan-1-al (2.4), hexan-2-al (1.2)	$[Co_2Rh_2(CO)_{12}]$–$[PPh_2H]$ (1:3)	Benzene, 25 °C, (0.5:0.5)	1 h	5.5[c]	378
Pent-1-ene	Hexan-1-al (51), hexan-2-al (19), pent-2-ene (30)	$[N(PPh_3)_2][Fe_5RhC(CO)_{10}]$	CH_2Cl_2, 100 °C, (30:30)	24 h	n.g.	379
Pent-1-ene	Hexan-1-al (50), hexan-2-al (50), pentane (traces)	$[Fe_4Rh_2C(CO)_{16}]$	CH_2Cl_2, 100 °C, (30:30)	6 h	608[d]	379
Pent-1-ene	Hexan-1-al (47), hexan-2-al (18), pent-1-ene + pent-2-ene (35)	$[PPh_4][Fe_4RhC(CO)_{14}]$	CH_2Cl_2, 100 °C, (30:30)	24 h	395[d]	379
Pent-1-ene	Hexan-1-al (50), hexan-2-al (50), pentane (traces)	$[PPh_4][Fe_3Rh_3C(CO)_{15}]$	CH_2Cl_2, 100 °C, (30:30)	5 h	608[d]	379
Pent-1-ene	Hexan-1-al (47), hexan-2-al (23)	$[HFe_3Rh(CO)_{11}(CCHPh)]$	Benzene, 60 °C, (10:10)	5 h	175[d]	380
Pent-1-ene	Hexan-1-al (63.5), hexan-2-al (14.6), hexan-1-ol (7.3)	$[Pt_2Co_2(CO)_8(PPh_3)_2]$	Benzene, 100 °C, (28/28)	17 h	703[d]	359
Pent-1-ene	Hexan-1-al (26.3), hexan-2-al (4.3), hexan-1-ol (1.3), hexan-2-ol (traces)	$[Fe_3(CO)_{12}]$–$[Ru_3(CO)_{12}]$ (1:1)	MeOH, KOH, H_2O, 150 °C, (0/55)	0.5 h	110[d]	382, 383
Pent-1-ene	Hexan-1-al (11.7), hexan-2-al (6.3), hexan-1-ol (8.0), hexan-2-ol (1.7)	$[Rh_6(CO)_{16}]$–$[Fe_3(CO)_{12}]$ (1:1)	MeOH, KOH, H_2O, 150 °C, (0/55)	0.5 h	65[d]	382
Hex-1-ene	Heptan-1-al (39), heptan-2-al (17)	$[Cp_2Zr(CH_2PPh_2)_2RhH(PPh_3)]$	thf, 80 °C, (10:10)	0.58 h	224[d]	381
Hex-1-ene	Heptan-1-al (37.8), heptan-2-al (12.2)	$[Ru_3(CO)_{12}]$–$[Co_2(CO)_8]$ (0.67:1)	Benzene, 110 °C, (40/40)	1.5 h	579[a]	384

[a]Based on the minor cluster compound.
[b]Includes trimer.
[c]No side-products measured.
[d]Related to aldehydes formed.

TABLE 18. Homologation of alcohols and esters catalysed by bimetallic systems

Substrate	Products (%)	Catalyst	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Ref.
Methanol	Ethanol (18.7), methoxymethane (16.3), methoxyethane (7.6), methyl acetate (4.2), ethoxyethane (1.2), acetaldehyde (1.1), 1,1-dimethoxyethane (0.9)	$[PPh_4][RuCo_3(CO)_{12}]$	Neat, 180 °C, MeI promoter, (80/40)	2.5 h	144[a]	386
Methanol	Ethanol (14.5), methoxymethane (23.4), methoxyethane (9.1), methyl acetate (3.4), ethoxyethane (1.1), acetaldehyde (1.6), 1,1-dimethoxyethane (1.0)	$[HRuCo_3(CO)_{12}]$	Neat, 180 °C, MeI promoter, (80/40)	2.5 h	116[a]	386
Methanol	Ethanol (11.4), methoxymethane (14.0), methoxyethane (9.5), methyl acetate (2.7), ethoxyethane (1.0)	$[NEt_4][Ru_3Co(CO)_{13}]$	Neat, 180 °C, MeI promoter, (80/40)	2.5 h	88[a]	386, 387
Methanol	Acetaldehyde (39.5)[b], methyl acetate (6), ethanol (1)	$[NBu_4][FeCo_3(CO)_{12}]$	Neat, 180 °C, MeI promoter, (135/135)	1 h	2435[c]	388
Methyl formate	Ethyl formate (10), methanol[d] (14), ethanol (2)	$[Co(OOCMe)_2]\cdot 4H_2O$–$[Ru(acac)_3]$(1:2.5)	Neat, 200 °C, LiI promoter, (193/97)	5 h	107[e,h]	389

(continued)

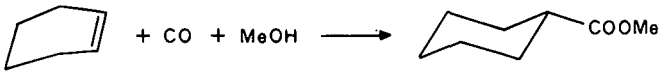
TABLE 18. (*continued*)

Substrate	Products (%)	Catalyst	Conditions (bar H_2/bar CO)	Time	Catalytic turnover	Ref.
Methyl acetate	Ethyl acetate (27.8), acetic acid (29.2), ethanol (8.6), acetaldehyde (1.2), ethers[f] (13.3)	$[Co_2(CO)_8]$–$[Ru(acac)_3]$ (1:2)	Neat, 180 °C, MeI promoter, (60:60)	18 h	178[g]	390
Methyl acetate	Ethyl acetate (21.2), acetic acid (22.1), ethanol (8.5), ethers[f] (7.1)	$[NEt_4][RuCo_3(CO)_{12}]$	Neat, 180 °C, MeI promoter, (60:60)	18 h	265[g]	390
Methyl acetate	Ethyl acetate (33.1), acetic acid (26.0), ethanol (9.6), acetaldehyde (0.9), ethers[f] (15.9)	$[NEt_4][Ru_3Co(CO)_{13}]$	Neat, 180 °C, MeI promoter, (60:60)	18 h	285[g]	390
Methyl acetate	Ethyl acetate (71.4), methanol (15.0), ethanol (11.0), acetaldehyde (2.6)	$[Ru_3(CO)_{12}]$–$[Co_2(CO)_8]$ (1:8.9)	Acetic acid, 215 °C, $LiOOCCH_3$, $[PPh_3Me]I$ promoters, (93/47)	0.66 h	2505[g,h]	391

[a]Related to ethanol.
[b]Including the corresponding dimethylacetal.
[c]Related to ethanol.
[d]CO_2 and methane formed as decarboxylation products.
[e]Related to ethyl formate.
[f]Methoxymethane, methoxyethane.
[g]Related to ethyl acetate.
[h]Based on the minor complex.

cobalt and ruthenium species formed under the catalytic conditions cooperate as individuals. However, the formation of mixed cobalt–ruthenium clusters as active species cannot be excluded. γ-Keto acids can be obtained from terminal alkynes, methyl iodide, carbon monoxide, and water using a 1:1 mixture of $[Co_2(CO)_8]$ and $[Ru_3(CO)_{12}]$ under phase-transfer conditions in a benzene–sodium hydroxide solution with dodecyltrimethylammonium chloride (200 °C, 1 bar; the yield and catalytic turnover were not reported) (equation 78)[392]. In contrast, no carbonyl-containing products are formed using $[Ru_3(CO)_{12}]$ alone[392]; with $[Co_2(CO)_8]$ alone the reaction leads to but-2-enolides[393]. The mixture $[Co_2(CO)_8]$–$[Ru_3(CO)_{12}]$ (1:0.67) also catalyses the hydroesterification of cyclohexene with carbon monoxide and methanol (150 °C, 50 bar, 24 h, 53% yield, catalytic turnover 633) (equation 79)[384].

$$PhC{\equiv}CH + 2\,CO + H_2O + MeI \longrightarrow PhCHCH_2CMe \quad (78)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad COOH \quad O$$



(79)

Alkyl halides react with carbon monoxide and lithium hydroxide to give carboxylic acids (carbonylation) and α-keto carboxylic acids (biscarbonylation) (equations 80 and 81). With $[Co_2(CO)_8]$ as the catalyst 80% of the α-keto acid and only 7% of the acid are formed from 1-bromo-3-phenylethane; using $[HFeCo_3(CO)_{12}]$ the ratio of α-keto acid to acid is inverted to 16:33 (*tert*-butanol, 80 °C, 36 bar, 2 h). With $[Co_2(CO)_8]$ the total conversion is 88%, corresponding to a catalytic turnover of 53; with $[HFeCo_3(CO)_{12}]$ these values are 69 and 41[394]. Substituted allylic alcohols such as 3-methylbut-2-en-1-ol undergo amidocarbonylation with acetamide and CO in the presence of a $[Co_2(CO)_8]$–$[HRh(CO)(PPh_3)_3]$ catalyst (equation 82); *N*-acetylleucine methyl ester is obtained in 20% yield, the catalytic turnover being 109 (conditions: dioxane, 120 °C, 100 bar, 16 h)[395].

$$PhCH_2CH_2Br + CO + 2LiOH \longrightarrow PhCH_2CH_2\underset{\underset{O}{\|}}{C}OLi + LiBr + H_2O \quad (80)$$

$$PhCH_2CH_2Br + 2CO + 2LiOH \longrightarrow PhCH_2CH_2\underset{\underset{O}{\|}}{C}\underset{\underset{O}{\|}}{C}OLi + LiBr + H_2O \quad (81)$$

$$Me_2C{=}CHCH_2OH + CO + MeCNH_2 \longrightarrow Me_2CHCH_2\underset{\underset{HOO}{|}}{C}NH{-}\underset{\underset{O}{\|}}{C}Me \quad (82)$$
$$\qquad\qquad\qquad\qquad\quad \underset{\underset{O}{\|}}{} \qquad\qquad\qquad\qquad\qquad\quad \underset{\underset{O}{\|}}{}$$

A mixture of $[Ru_3(CO)_{12}]$ and $[Fe(CO)_5]$ (1:3) has been reported to catalyse the *trans*-alkylation of 1,2-(dimethylamino)ethane to give predominantly *N*,*N*′-dimethylpiperazine and trimethylamine (equation 83). The reaction proceeds in ethanol at 160 °C under a CO pressure of 34.5 bar over 120 h; the conversion is 53%, corresponding to a catalytic turnover of 70[396].

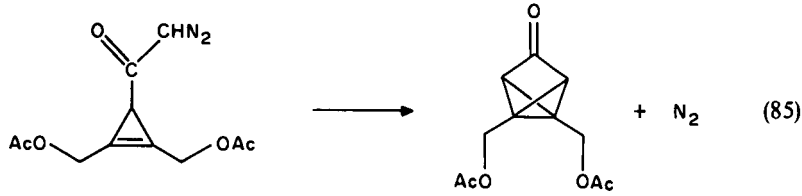
$$2Me_2NCH_2CH_2NMe_2 \longrightarrow MeN\langle\rangle NMe + 2Me_3N \quad (83)$$

C. Unique Applications: Novel Catalytic Reactions Leading to New Organic Compounds

One of the most promising prospects offered by mixed-metal clusters is the possibility of performing unique catalytic reactions. A scientific aim put forward by Muetterties and Krause[29] was the discovery of catalytic reactions 'that either cannot be effected or are very difficult to effect at single metal atom centres'. A particular challenge is to find catalytic applications of transition metal clusters leading to organic compounds which become accessible only by this method, that is, organic compounds which were previously unknown.

Probably the first example of a new organic molecule catalytically generated by a transition metal cluster is *endo,endo*-heptacyclo[5.3.1.$1^{2,6}$, $1^{4,12}$, $1^{9,11}$, $0^{3,5}$, $0^{8,10}$]tetradecane (Binor-S) (**108**). This compound is accessible by the stereospecific fusion of two norbornadiene molecules (equation 84); the process is catalysed by either $Zn[Co(CO)_4]_2$[132] or by a number of cobalt and rhodium clusters[133]. Anionic clusters such as $[FeCo_3(CO)_{12}]^-$ and $[Co_6(CO)_{15}]^-$ show greater catalytic activity than would be expected from neutral clusters of the same size[133]. With $Zn[Co(CO)_4]_2$ and Et_2OBF_3 in toluene, the reaction proceeds at 70–80 °C, giving 76% Binor-S within 3 h (catalytic turnover 472). Another catalytic application of transition metal clusters leading to a new organic compound is the intramolecular cyclisation of the unsaturated diazoketone **109**, which proceeds with elimination of nitrogen to give the tricyclic diacetate **110** (equation 85). The reaction is catalysed by $[Rh_2(OAc)_4$ (50–60 °C, 300% yield, catalytic turnover 50)[134].

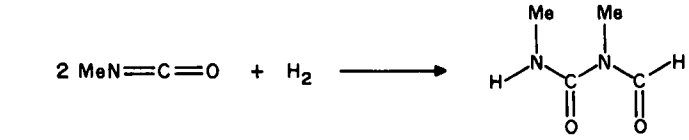
(108) (84)



(109) (110) (85)

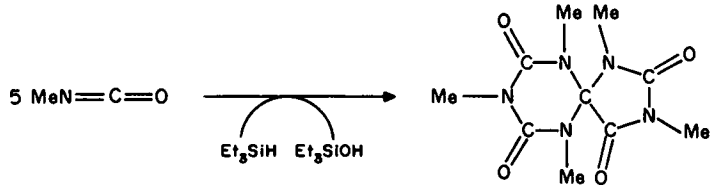
Several examples of novel catalytic reactions resulting in the formation of hitherto unreported organic compounds involve anionic ruthenium clusters as catalysts. The tetranuclear cluster anion $[H_3Ru_4(CO)_{12}]^-$ has been found to catalyse a reaction termed 'hydro-coupling of alkyl isocyanates': two isocyanate molecules are coupled together with uptake of hydrogen and C—N bond formation; the dialkyl carbamylformamides of the type **111** astonishingly had not been made by conventional methods before. The reaction of methyl isocyanate is carried out in thf at 120 °C under a hydrogen pressure of 40 bar, the yield of **111** after 200 h is 46% corresponding to a catalytic turnover of 230 (equation 86)[397]. The trinuclear cluster anion $[HRu_3(CO)_{10}(SiEt_3)_2]^-$ catalyses a process best described as 'silane-assisted spirocyclization of alkyl isocyanates, giving a surprisingly simple access to a new series of [4,5]-spiroheterocycles. No less than five isocyanate molecules are coupled together, one of them losing its oxygen

atom to provide the spiro-carbon atom of the product. The methyl derivative **112** is obtained in 40% yield (catalytic turnover 400) in thf on heating at 150 °C for 25 h (equation 87)[398]. The formation of some new (*E*)- and (*Z*)-benzylidenehydantoins such as **113** from alkyl isocyanates and phenylacetylene (equation 88) is catalysed by the cluster dianion $[Ru_3(CO)_{11}]^{2-}$, generated from various precursors [thf, 120 °C, 224 h, yield of (*Z*)-**113** 8.8% and of (*E*)-**113** 1.0%, catalytic turnover 49][221,399].



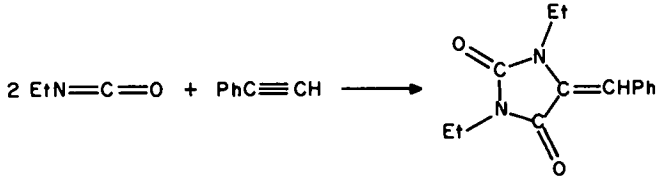
(86)

(**111**)



(87)

(**112**)



(88)

(**113**)

Several ruthenium clusters catalyse the synthesis of some new *N*,*N*′,*N*″-trialkylguanidines from the corresponding carbodiimides and hydrogen. For the isopropyl derivative **114** (equation 89) the best results are obtained with the cluster anion $[H_3Ru_4(CO)_{12}]^-$ as the catalyst (thf, 120 °C, 40 bar H_2, 29 h, yield 13.6%, catalytic turnover 136)[400]. With terminal alkynes, diisopropyl carbodiimide reacts in the presence of various ruthenium clusters to give *N*,*N*′-diisopropylamidines; for the phenyl derivative **115** (equation 90) the most active catalyst is a binary system composed of $[H_4Ru_4(CO)_{12}]$ and $[Co_2(CO)_8]$ (thf, 120 °C, 24 h, yield 9.3%, catalytic turnover 9)[400].

$$2Pr^iN{=}C{=}NPr^i + 3H_2 \longrightarrow Pr^iNC(=NHPr^i)(NHPr^i) + H_3CNHPr^i \qquad (89)$$

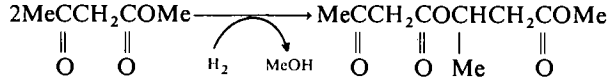
(**114**)

$$PhC{\equiv}CH + Pr^iN{=}C{=}NPr^i \longrightarrow PhC{\equiv}C{-}C(=NPr^i)(NHPr^i) \qquad (90)$$

(**115**)

Apart from the above-mentioned C—N and C—C coupling reactions of isocyanates and carbodiimides, C—O coupling of β-keto esters is observed with the cluster anion $[H_3Ru_4(CO)_{11}]^-$ under hydrogenation conditions. The new ester **116** is obtained from

methyl acetoacetate in thf at 120 °C under a hydrogen pressure of 40 bars (equation 91); after 20 h the yield is 4.5%, corresponding to a catalytic turnover of 45[401].



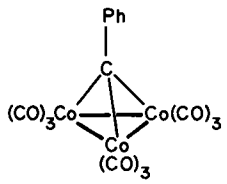
(116) (91)

D. Mechanistic Aspects: Indications for the Intermediacy of Intact Clusters in Catalytic Processes

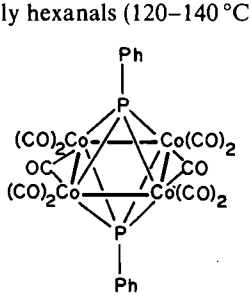
Since the precise nature of the active species involved in a catalytic cycle has not been established in the reactions using transition metal clusters as catalyst precursors, the role of the intact cluster framework for the catalytic process remains controversial. Five criteria have been proposed for identifying cluster catalysis in contrast to catalysis by species generated from a cluster precursor[402]:

(i) Catalyst concentration studies in which the turnover frequency increases with increasing catalyst concentration are indicative of cluster catalysis.
(ii) If, in a given catalytic reaction, the product selectivities obtained using cluster catalyst precursors or the products themselves cannot be reconciled with mechanisms that involve only mononuclear species, then cluster catalysis is indicated.
(iii) If a specific combination of two or more different transition metals can be used to enhance significantly the catalytic rates or change the product selectivity of a given reaction normally catalysed by one of the metals, or if the combination allows the catalyst of a reaction not catalysed independently by one of these metals, then a mixed-metal cluster is suggested.
(iv) If, for a given reaction, it is possible to modify the catalyst or the reaction conditions to favour metal–metal bond formation and the modification results in increased catalytic activity, then metal cluster catalysis must be expected.
(v) Catalytic asymmetric induction with chiral metal clusters in which the asymmetry resides in the metal framework or is a basic skeletal property of the cluster is indicative of cluster catalysis.

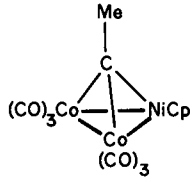
An approach to verify catalysis by intact clusters uses transition metal clusters containing stable, non-fluxional μ_3- or μ_4-ligands. It is assumed that these clusters cannot easily dissociate to mononuclear species or, if they do, the subsequent recombination is improbable. Hence, the fact that such clusters can be recovered after having performed a catalytic reaction is suggestive of cluster catalysis. In this fashion, the clusters **117–119** containing carbon or phosphorus clamps catalyse the hydroformylation of pent-1-ene to yield mainly hexanals (120–140 °C, 17–100 bar, $H_2/CO = 1$); the



(117)



(118)



(119)

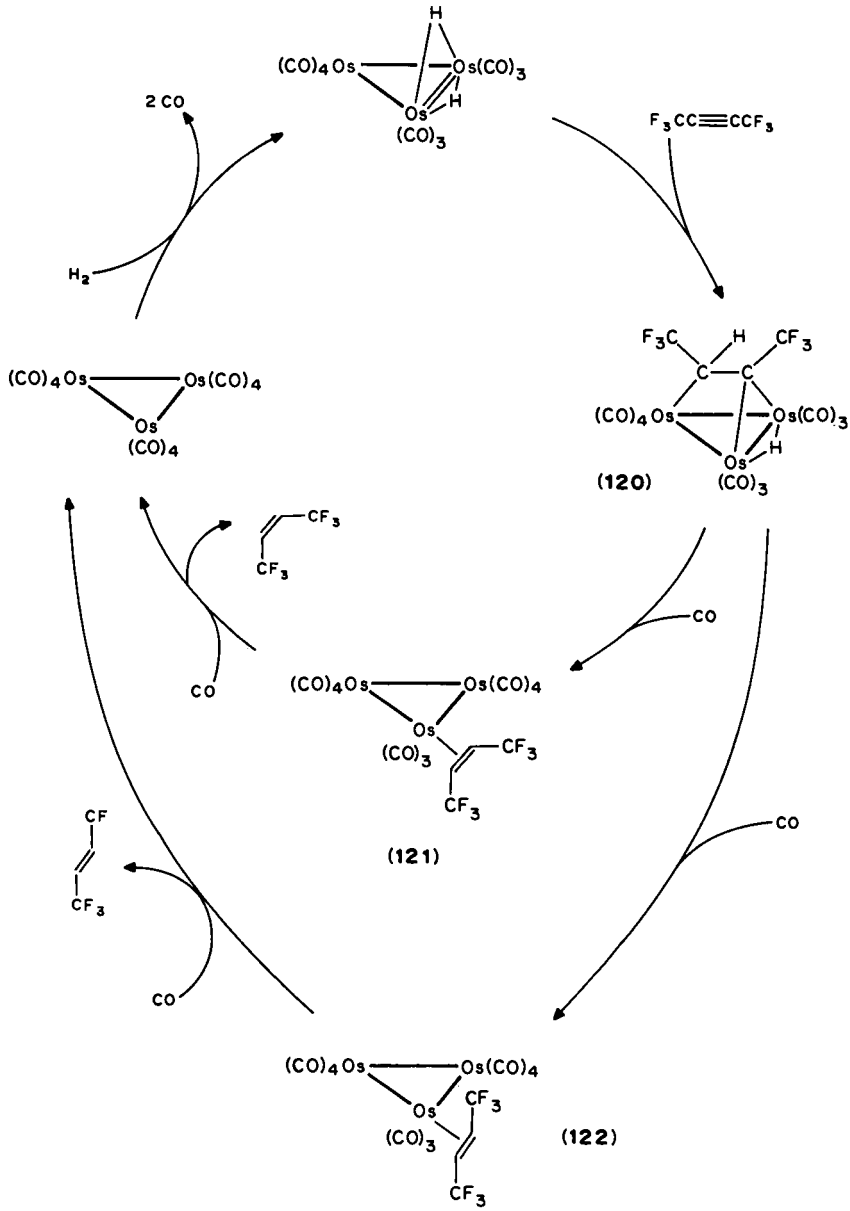
clusters were recovered unchanged in yields of more than 90%[403-405]. Similar arguments have been used in the interpretation of the hydrogenation of styrene catalysed by various tetrahedral M_3E clusters (E=S, PR, CR)[419].

The most fruitful concept in cluster catalysis is to find models for the catalytic mechanism which are based on the isolation and characterization of possible intermediates. A complete catalytic cycle for the hydrogenation of an alkyne to an alkene by a trinuclear osmium cluster has been proposed[406], demonstrated by a trifluoromethyl-substituted substrate (Scheme 23). The hydrido cluster $[H_2Os_3(CO)_{10}]$ adds bis-(trifluoromethyl)acetylene to give the cluster **120**, which itself takes up carbon monoxide (CH_2Cl_2, reflux) to give a 1:1 mixture of the alkene complexes **121** and **122**. These complexes can be react separately with CO (octane, reflux) to generate $[Os_3(CO)_{12}]$ quantitatively with loss of the corresponding (*E*)- and (*Z*)-alkene. The cycle is completed by the known[408] hydrogenation of $[Os_3(CO)_{12}]$ to $[H_2Os_3(CO)_{10}]$ in refluxing octane. All these clusters are isolated compounds; **120**[407] and **122**[406] are fully characterised; the structure of **121** has been established by a single-crystal X-ray structure analysis.

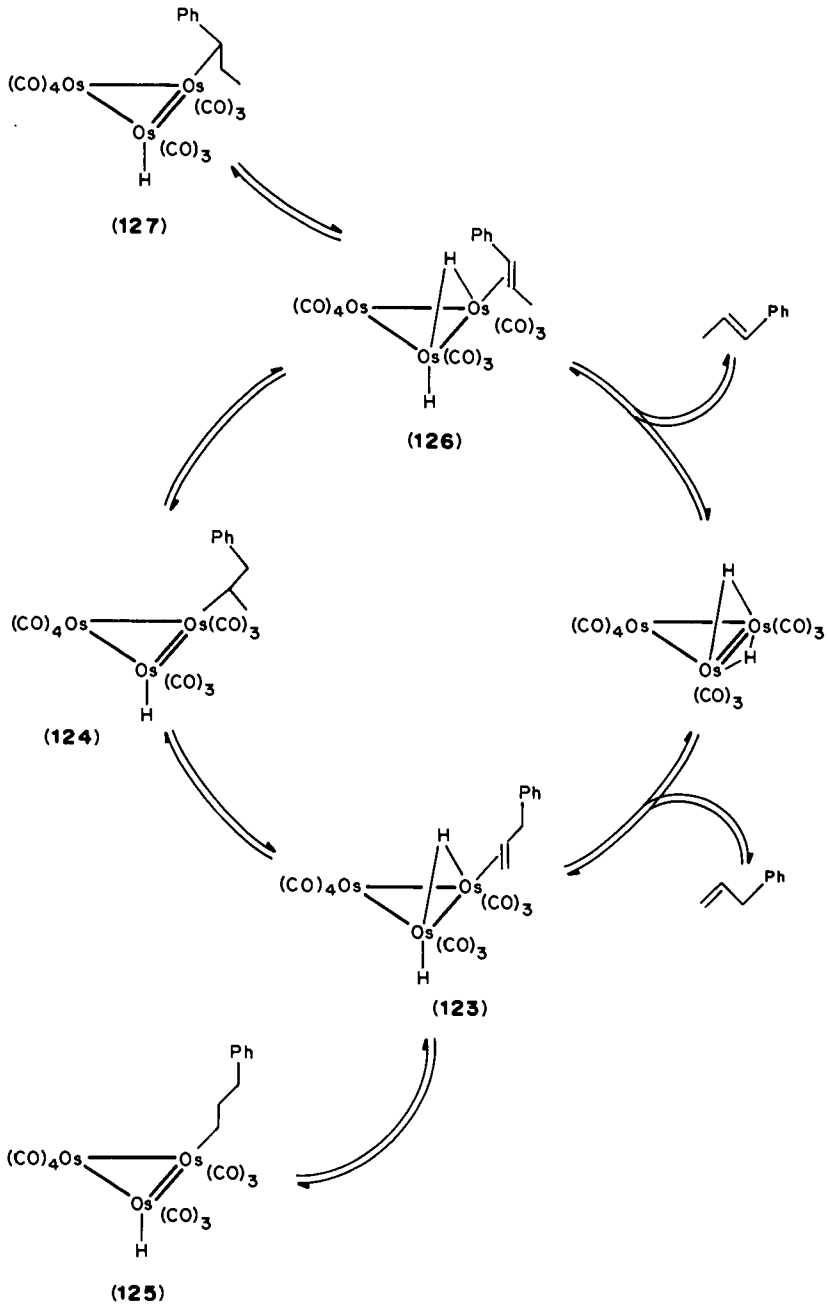
Another catalytic cyclic involving $[H_2Os_3(CO)_{10}]$ has been proposed for the isomerization[409] and hydrogenation[410] of alkenes; both mechanisms involve hydridoalkyl clusters (Scheme 24). The unsaturated cluster $[H_2Os_3(CO)_{10}]$ is assumed to add the alkene to give the η^2-alkene complex **123**, phosphine analogues of which have been synthesized and characterized[409]. Complex **123** can react with hydrogen transfer from the metal framework to the coordinated olefin to give the hydridoalkyl complexes **124** or **125**; with diethyl fumarate or diethyl maleate a hydridoalkyl cluster of this type, $[HOs_3(CO)_{10}\{CH(CH_2COOEt)COOEt]\}$, in which the ester function helps to stabilize the system, could be characterized[410]. The reverse hydrogen transfer gives **126**, from which the isomerized alkene can be eliminated.

Another strategy for the eludication of a catalytic cycle has been successfully applied; since no intermediates could be isolated from the $[Ru_3(CO)_{12}]$–$[NCO]^-$ system active for alkene hydrogenation[163], the corresponding osmium system was examined; in this case the homolgues intermediates were stable[411]. After having established that the anionic ruthenium cluster $[Ru_3(CO)_{11}(NCO)]^-$ was the active catalyst[412], the osmium anion $[Os_3(CO)_{11}(NCO)]^-$ (**128**) was prepared from $[Os_3(CO)_{12}]$ and $[N(PPh_3)_2][N_3]$ (Scheme 25). In refluxing thf **128** loses CO to give **129**, the analogue of $[Ru_3(CO)_{11}(NCO)]^-$, characterized by i.r. spectroscopy. Molecular hydrogen reacts with **129** (52 °C, 3.5 bar) to give **130**, isolated as the bis(triphenylphosphine)iminium salt[411]. Reaction with maleic anhydride at 25 °C gives **132** in quantitative yield; the intermediate is presumably **131**. Cluster **132** was structurally characterized, and it represents the first characterization of a terminally bonded alkyl ligand on a metal carbonyl cluster[411]. The final step is the reductive elimination of the C—H bond: heating **132** under CO pressure (thf, 3.4 bar, 75 °C) gives succinic anhydride and **128**; the cluster **133** is a possible intermediate.

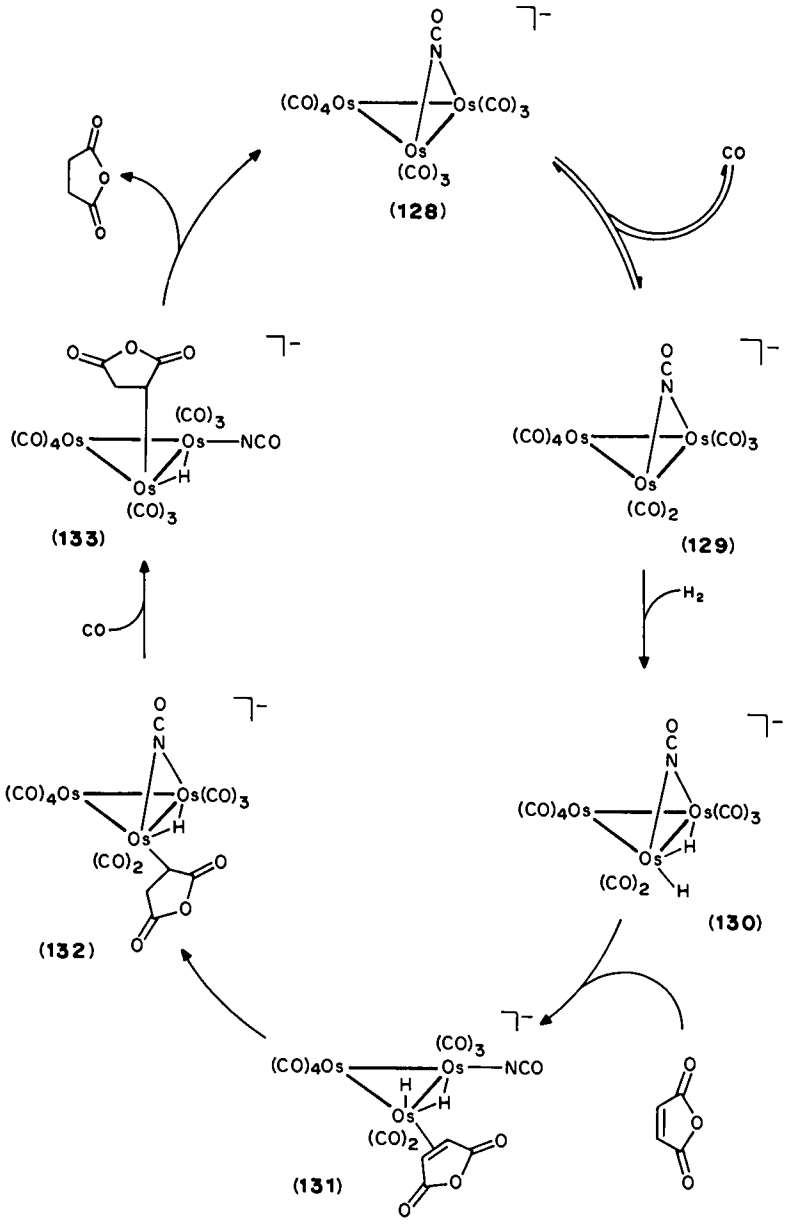
In some cases trapping of intermediates by a consecutive reaction can be successful. The catalytic cycle proposed for the hydroformylation of ethylene by the cluster anion $[HRu_3(CO)_{11}]^-$ (**134**) is based on the isolation of the protonation product of the intermediates **135** in addition to isotope labeling studies[413] (Scheme 26). It is assumed that **134** is attacked by ethylene at the bridging carbon atom, possibly via an intermediary η^2-ethylene complex, to give the μ_2–η^2(C,O)-propionyl complex **135**. Acidification of the reaction solution with CF_3COOH produces the known[414] neutral cluster $[HRu_3(CO)_{10}(OCCH_2Me]$, the crystal structure of which proves the presence of the μ_2–η^2-propionyl ligand. The transfer of the hydrido ligand from the metal skeleton in **135** was demonstrated by acidification with CF_3COOD; the resulting deuterated cluster $[DRu_3(CO)_{10}(OCCH_2Me)]$ was isolated and characterized[413]. Whereas the intermediate **136** could not be trapped by protonation, the mechanism of Scheme 26 is further


H
(CO)4Os
Os(CO)3
Os
H
(CO)3
2 CO
H2
F3CC≡CCF3
F3C
H
CF3
C
C
(CO)4Os
Os(CO)3
Os
H
(CO)3
(120)
(CO)4Os
Os(CO)4
Os
(CO)4
CF3
CF3
CO
CO
(CO)4Os
Os(CO)4
Os
(CO)3
CF3
CF3
(121)
CF
CF3
CO
CO
(CO)4Os
Os(CO)4
Os
CF3
(CO)3
CF3
(122)

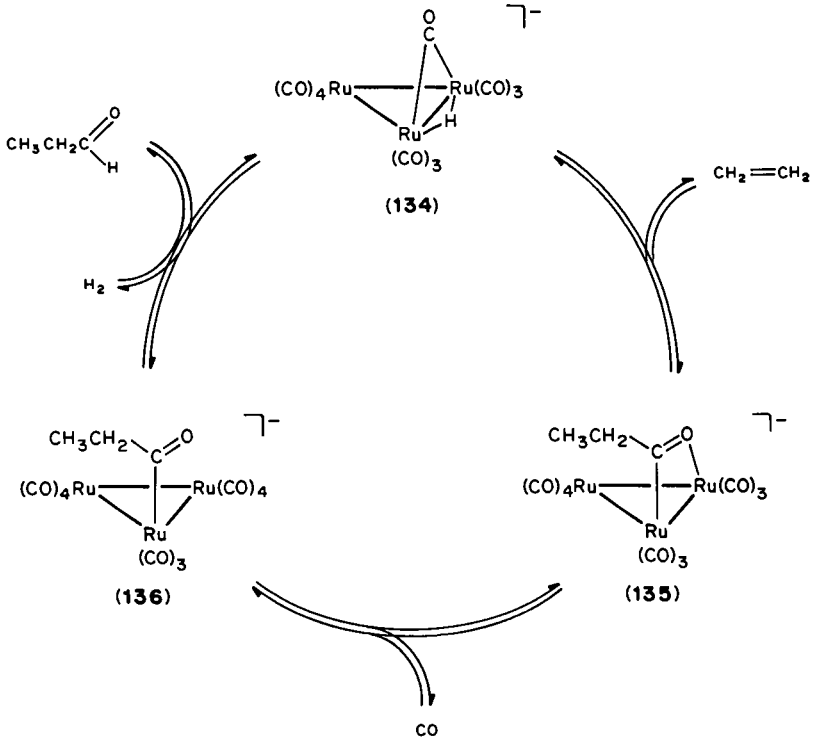
SCHEME 23


Ph
(CO)4Os
Os
(CO)3
Os
(CO)3
H
(127)
Ph
H
(CO)4Os
Os
(CO)3
Os(CO)3
H
(126)
Ph
Ph
(CO)4Os
Os(CO)3
Os
(CO)3
H
(124)
H
(CO)4Os
Os(CO)3
Os
H
(CO)3
Ph
H
(CO)4Os
Os
(CO)3
Os
(CO)3
H
(123)
Ph
(CO)4Os
Os
(CO)3
Os
(CO)3
H
(125)

SCHEME 24



SCHEME 25

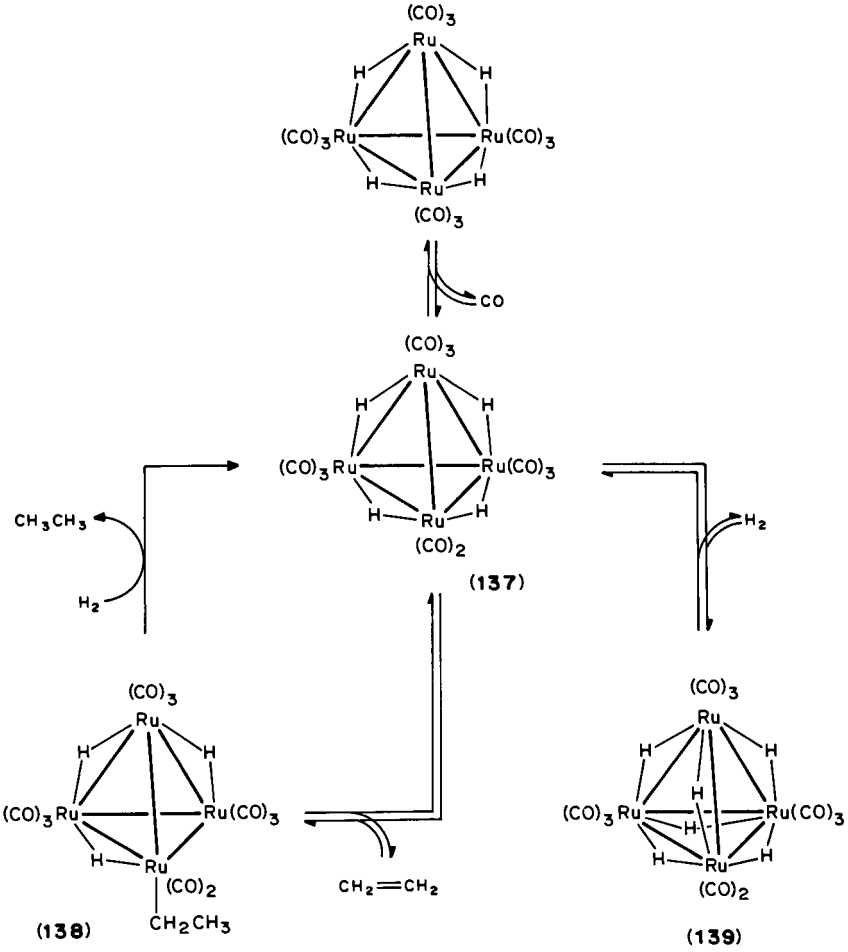


SCHEME 26

supported by the deuteroformylation of ethylene, giving the expected deuterium distribution in the catalytic product[413].

Kinetic data were also employed for the mechanistic interpretation of cluster catalysed reactions. The kinetics of the catalytic ethylene hydrogenation by $[H_4Ru_4(CO)_{12}]$ (heptane, 72 °C, $p_{H_2} = 0.13$ bar, $p_{C_2H_4} = 0.13$ bar) have been studied[415] (Scheme 27). The data are consistent with the formation of the unsaturated cluster **137** by loss of CO in an initial equilibrium; the further reaction is assumed to involve an ethyl cluster **138** (the ethyl ligand could also be bridging), which on reaction with hydrogen eliminates ethylene, regenerating **137**. The rapid H–D exchange between H_2 and $[D_4Ru_4(CO)_{12}]$ was rationalized in terms of an equilibrium between **137** and **139**[415].

Although the implication of intact transition metal clusters in the catalytic process seems to be highly probable in view of these results, in particular comprising isolation or trapping of intermediates or their homologues, isotope labelling experiments, and kinetic studies, there is no direct evidence for the intermediacy for intact clusters. The only definite proof for a catalytic reaction being performed by a cluster framework would consist in an asymmetric catalytic synthesis by a transition metal cluster containing an intrinsic chiral metal skeleton[416]. Since chiral clusters of this type are known, mainly thanks to the work of Vahrenkamp and coworkers[419], efforts have been made to use such clusters as catalysts with prochiral substrates. If it is possible to induce an enantiometric excess in the product distribution by the intrinsic framework chirality, the catalytic reaction must without doubt proceed through the intermediacy of the intact cluster. However, none of these experiments has been unequivocal so far.



SCHEME 27

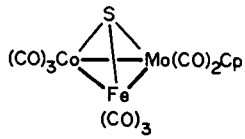
One of the test reactions[417] is the hydrosilylation of the prochiral acetophenone, which under photocatalytic conditions gives the chiral product **140**, the major product being the unsaturated compound **141** (equations 92 and 93). The chiral cluster (+)-**142** was employed for this reaction. An enantioselective effect would have been proven the integrity of the chiral FeCoMoS tetrahedron during the catalysis; however, the reaction gave only a racemic mixture of **140** (16% yield) and 48% of **141**. On the other hand, it was also found that the cluster (+)-**142** had racemized during the photocatalytic process[418]. This means that this result is not conclusive, either for the catalysis by intact clusters or for catalysis by achiral cluster fragments.

$$\underset{\underset{\|}{O}}{PhCMe} + HSiEt_3 \longrightarrow \underset{\underset{OSiEt_3}{|}}{Ph\overset{*}{C}HMe} \qquad (92)$$

(140)

$$\underset{\underset{\|}{O}}{PhCMe} + HSiEt_3 \longrightarrow \underset{\underset{OSiEt_3}{|}}{PhC{=}CH_2} + H_2 \qquad (93)$$

(141)



[(+)-142]

Arguments have been launched against this approach from studies of the hydroformylation activity of three tetrahedral Co_2MoS clusters containing chiral bidentate ligand clamps[420] (the exact nature of these clusters cannot be extracted from the paper cited); the results are said to be more likely to be in agreement with the concept of clusters acting as storehouses for the release of catalytically active fragments.

E. Heterogenized Systems: Catalytic Reactions Using Supported Transition Metal Clusters

A rapidly growing area of research is concerned with supported transition metal clusters which can function as heterogeneous catalysts. this is described more fully in Chapter 14 of Volume 4 of this series. Thanks to the availability of spectroscopic techniques, the characterization of these materials has improved a great deal, leading to a better understanding of the nature of the cluster species on the support. Therefore, the investigation of supported metal clusters derives from the expectation that catalysts with new activities and new selectivities may be discovered. The prospects and up-to-date results of this research have been reviewed in detail recently, so that an extensive discussion here would be superfluous. The chemistry of metal clusters hosted in zeolites is summarized in two papers[421,422]; two other reviews[423,424] concern metal clusters on polymers and on functionalized inorganic oxides, respectively. The catalytic activity of supported metal clusters has been reviewed in general[122,123,127]; particular attention has been paid to alkene conversion[124] and catalytic CO hydrogenation[126] by supported metal clusters. The relationships between metal clusters and metal surfaces have been critically discussed[425].

IV. FUTURE DEVELOPMENTS

The catalytic potential of transition metal clusters has had an enormous impact on the progress of cluster chemistry. The present state of catalytic applications of these systems still suffers from the lack of understanding of the basic mechanistic features. In spite of the vast number of well established fundamental transformations on cluster frameworks, the implication of these reactions in a catalytic process has not been proved so far. In particular, conclusive evidence for the intermediacy of intact clusters in catalysis is still awaited. Hence mechanistic studies on catalytic reactions with transition metal clusters are urgently needed.

One of the most rewarding goals in cluster chemistry is possibly the search for novel catalytic processes, making use of the unique polymetallic coordination sites in soluble organometallic molecules. New compounds and high selectivities should be expected from these investigations.

Another perspective deserving enhanced attention is opened up by studying the synergistic effects found in mixed-metal clusters and bimetallic cluster mixtures; further progress in this area requires a deeper insight into these cooperative effects of two different metal centres in a cluster; therefore, organometallic model reactions with bimetallic clusters, in particular site-selectivity studies, would certainly be of great value.

V. REFERENCES

1. F. A. Cotton, *Q. Rev. Chem. Soc.*, **20**, 389 (1966).
2. B. F. G. Johnson, in *Transition Metal Clusters* (Ed. B. F. G. Johnson), Wiley, Chichester, 1980, p. 2.
3. J. Dewar and H. O. Jones, *Proc. R. Soc. London Ser. A*, **76**, 558 (1905); 79, 66 (1907), *Chem. News*, **97**, 108 (1907).
4. C. H. Wei and L. F. Dahl, *J. Am. Chem. Soc.*, **91**, 1351 (1961).
5. K. Wade, *J. Chem. Soc., Chem. Commun.*, **729** (1971); *Inorg. Nucl. Chem. Lett.*, **8**, 559, 563 (1972); *Chem. Br.*, **11**, 177 (1975); *Adv. Inorg. Chem. Radiochem.*, **18**, 1 (1976).
6. R. W. Rudolph and W. R. Pretzer, *Inorg. Chem.*, **11**, 1972 (1978); *Acc. Chem. Res.*, 9, 446 (1976).
7. R. E. Williams, *Inorg. Chem.*, **10**, 210 (1971).
8. D. M. P. Mingos, *Nature (London)*, *Phys. Sci.*, **236**, 99 (1972); R. Mason, K. M. Thomas, and D. M. P. Mingos, *J. Am. Chem. Soc.*, **95**, 3802 (1973).
9. R. B. King and D. H. Rouvray, *J. Am. Chem. Soc.*, **99**, 7834 (1977).
10. R. B. King, *Inorg. Chim. Acta*, **116**, 99, 109, 119, 125 (1986).
11. A. J. Stone, *Inorg. Chem.*, **20**, 563 (1981).
12. M. Elian, M. M. L. Chen, D. M. P. Mingos, and R. Hoffmann, *Inorg. Chem.*, **15**, 1148 (1976); R. Hoffmann, *Science*, **211**, 995 (1981); B. E. R. Schilling and R. Hoffmann, *J. Am. Chem. Soc.*, **101**, 3456 (1979); R. Hoffmann, B. E. R. Schilling, R. Bau, H. D. Kaesz, and D. M. P. Mingos, *J. Am. Chem. Soc.*, **100**, 6088 (1978).
13. J. E. Ellis, *J. Chem. Educ.*, **53**, 2 (1976); F. G. A. Stone, *Acc. Chem. Res.*, **14**, 318 (1981).
14. J. W. Lauher, *J. Am. Chem. Soc.*, **100**, 5305 (1978); **101**, 2604 (1979); *J. Organomet. Chem.*, **213**, 25 (1981).
15. G. Ciani and A. Sironi, *J. Organomet. Chem.*, **197**, 233 (1980).
16. D. M. P. Mingos, *J. Chem. Soc., Dalton Trans.*, 133 (1974); 1163 (1976); D. M. P. Mingos and M. J. Forsyth, *J. Chem. Soc., Dalton Trans.*, 610 (1977); K. G. Evans and D. M. P. Mingos, *Organometallics*, **2**, 435 (1983).
17. M. B. Hall and R. F. Fenske, *Inorg. Chem.*, **11**, 768 (1972); N. M. Kostic and R. F. Fenske, *Inorg. Chem.*, **22**, 666 (1983); A. B. Rives, X.-Z. You, and R. F. Fenske, *Inorg. Chem.*, **21**, 2286 (1982).
18. B. K. Teo, M. B. Hall, R. F. Fenske, and L. F. Dahl, *J. Organomet. Chem.*, **70**, 413 (1974); B. K. Teo, M. B. Hall, R. F. Fenske, and L. F. Dahl, *Inorg. Chem.*, **14**, 3103 (1975).
19. D. E. Sherwood, Jr, and M. B. Hall, *Inorg. Chem.*, **21**, 3458 (1982); *Organometallics*, **1**, 1519 (1982); P. T. Chesky and M. B. Hall, *Inorg. Chem.*, **20**, 4419 (1981).
20. F. A. Cotton and G. G. Stanley, *Chem. Phys. Lett.*, **58**, 450 (1978); B. E. Bursten, F. A. Cotton, and G. G. Stanley, *Isr. J. Chem.*, **19**, 132 (1980).
21. B. F. G. Johnson, *J. Chem. Soc., Chem. Commun.*, 211 (1986); B. F. G. Johnson and R. E. Benfield, in *Topics in Inorganic and Organometallic Stereochemistry* (Ed. G. L. Geoffroy), Wiley, New York, 1981, p. 253.
22. B. K. Teo, *Inorg. Chem.*, **23**, 1251 (1984); B. K. Teo, G. Longoni, and F. R. K. Chung, *Inorg. Chem.*, **23**, 1257 (1984).
23. P. Chini, *Inorg. Chim. Acta Rev.*, **2**, 31 (1968).
24. J. Lewis and B. F. G. Johnson, *Pure Appl. Chem.*, **44**, 43 (1975).
25. R. Ugo, *Catal. Rev. Sci. Eng.*, **11**, 225 (1975).
26. E. L. Muetterties, *Bull. Soc. Chim. Belg.*, **84**, 959 (1975); **85**, 451 (1976).
27. E. L. Muetterties, *Science*, **196**, 839 (1977).
28. B. F. G. Johnson and J. Lewis, *Colloq. Int. CNRS*, **281**, 101 (1977).
29. E. L. Muetterties and H. J. Krause, *Angew. Chem.*, **95**, 135 (1983); *Angew. Chem., Int. Ed. Engl.*, **22**, 135 (1983).
30. A. P. Humphries and H. D. Kaesz, *Prog. Inorg. Chem.*, **25**, 145 (1979).

31. A. J. Deeming, in *Transition Metal Clusters* (Ed. B. F. G. Johnson), Wiley, Chichester, 1980, pp. 391–469.
32. H. Vahrenkamp, *Adv. Organomet. Chem.*, **22**, 169 (1983).
33. R. D. Adams and J. Horvath, *Prog. Inorg. Chem.*, **33**, 127 (1985).
34. E. L. Muetterties, R. R. Burch, and A. M. Stolzenberg, *Annu. Rev. Phys. Chem.*, **33**, 89 (1982).
35. H. Vahrenkamp, *Angew. Chem., Int. Ed. Engl.*, **17**, 379 (1978).
36. E. L. Muetterties, *Chem. Soc. Rev.*, **11**, 283 (1982).
37. K. Burgess, *Polyhedron*, **3**, 1175 (1984).
38. J. S. Bradley, in *Metal Clusters* (Ed. M. Moskovits), Wiley, Chichester, 1986, p. 105.
39. G. Lavigne and H. D. Kaesz, in *Metal Clusters in Catalysis* (Eds. B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 43.
40. K. Whitmire and D. F. Shriver, *J. Am. Chem. Soc.*, **102**, 1456 (1980).
41. E. M. Holt, K. H. Whitmire, and D. F. Shriver, *J. Organomet. Chem.*, **213**, 125 (1981).
42. M. Tachikawa and E. L. Muetterties, *J. Am. Chem. Soc.*, **102**, 4541 (1980).
43. M. A. Bino, J. M. Williams, M. Tachikawa, and E. L. Muetterties, *J. Am. Chem. Soc.*, **102**, 4542 (1980).
44. M. A. Bino, J. M. Williams, M. Tachikawa, and E. L. Muetterties, *J. Am. Chem. Soc.*, **103**, 1485 (1981).
45. J. S. Bradley, *Philos. Trans. R. Soc. London, Ser. A*, **308**, 103 (1982).
46. W. A. Herrmann, *Angew. Chem.*, **94**, 118 (1982); *Angew. Chem., Int. Ed. Engl.*, **21**, 117 (1982).
47. J. S. Bradley, G. B. Ansell, M. E. Leonowicz, and E. W. Hill, *J. Am. Chem. Soc.*, **103**, 4968 (1981).
48. J. S. Bradley, G. B. Ansell, and E. W. Hill, *J. Am. Chem. Soc.*, **101**, 7417 (1979).
49. M. A. Andrews and H. D. Kaesz, *J. Am. Chem. Soc.*, **99**, 6763 (1977).
50. M. A. Andrews and H. D. Kaesz, *J. Am. Chem. Soc.*, **101**, 7238 (1979).
51. M. A. Andrews, G. van Buskirk, C. B. Knobler, and H. D. Kaesz, *J. Am. Chem. Soc.*, **101**, 7245 (1979).
52. M. A. Andrews, C. B. Knobler, and H. D. Kaesz, *J. Am. Chem. Soc.*, **101**, 7260 (1979).
53. J. B. Keister, *J. Chem. Soc., Chem. Commun.*, 214 (1979).
54. M. A. Andrews and H. D. Kaesz, *J. Am. Chem. Soc.*, **101**, 7255 (1979).
55. B. F. G. Johnson, J. Lewis, A. G. Orpen, P. R. Raithby, and G. Süss-Fink, *J. Organomet. Chem.*, **173**, 187 (1979).
56. J. B. Keister, M. W. Payne, and M. J. Muscatella, *Organometallics*, **2**, 219 (1983).
57. L. R. Beanan and J. B. Keister, *Organometallics*, **4**, 1713 (1985).
58. L. R. Beanan, Z. A. Rahman, and J. B. Keister, *Organometallics*, **2**, 1062 (1983).
59. M. R. Churchill, J. C. Fettinger, J. B. Keister, R. F. Lee, and J. W. Ziller, *Organometallics*, **4**, 2112 (1985).
60. D. A. Roberts and G. L. Geoffroy, in *Comprehensive Organometallic Chemistry* (Eds G. Willinson and E. W. Abel), Pergamon Press, Oxford, 1982, Chapt. 40, p. 766.
61. G. D. Williams, R. R. Whittle, G. L. Geoffroy, and A. L. Rheingold, *J. Am. Chem. Soc.*, **109**, 3936 (1987).
62. S.-H. Han, G. L. Geoffroy, and A. L. Rheingold, *Organometallics*, **6**, 2380 (1987).
63. S.-H. Han, G. L. Geoffroy, and A. L. Rheingold, *Organometallics*, **5**, 2561 (1986).
64. H. Hoberg and B. W. Oster, *Synthesis*, 324 (1982); *J. Organomet. Chem.*, **234**, C35 (1982).
65. I. U. Khand, G. R. Knox, P. L. Pauson, and W. E. Watts, *J. Chem. Soc., Chem. Commun.*, 36 (1971).
66. I. U. Khand, G. R. Knox, P. L. Pauson, and W. E. Watts, *J. Chem. Soc., Perkin Trans. 1*, 975 (1973).
67. I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, and M. J. Foreman, *J. Chem. Soc., Perkin Trans. 1*, 977 (1973).
68. P. Bladon, I. U. Khand, and P. L. Pauson, *J. Chem. Res. (S)*, 8 (1977); *J. Chem. Res. (M)*, 153 (1977).
69. P. L. Pauson and I. U. Khand, *Ann. N. Y. Acad. Sci.*, **295**, 2 (1977).
70. P. L. Pauson, *Tetrahedron*, **41**, 5855 (1985).
71. P. L. Pauson, in *Organometallics in Organic Synthesis* (Eds A. de Meijere and H. tom Dieck), Springer, Heidelberg, 1987, p. 233.
72. K. Krohn, *Nachr. Chem. Tech. Lab.*, **35**, 606 (1987).
73. R. F. Newton, P. L. Pauson, and G. R. Taylor, *J. Chem. Res. (S)*, 277 (1980); *J. Chem. Res. (M)*, 3501 (1980).

74. C. Exon and P. Magnus, *J. Am. Chem. Soc.*, **105**, 2477 (1983).
75. P. Magnus, C. Exon, and P. Allbaugh-Robertson, *Tetrahedron*, **41**, 5869 (1985).
76. K. M. Nicholas and R. Pettit, *Tetrahedron Lett.*, **37**, 3475 (1971).
77. A. A. Schegolev, W. A. Smit, Y. B. Kalyan, M. Z. Krimer, and R. Caple, *Tetrahedron Lett.*, **23**, 4419 (1982).
78. K. M. Nicholas, *J. Am. Chem. Soc.*, **107**, 4999 (1985).
79. R. E. Connor and K. M. Nicholas, *J. Organomet. Chem.*, **125**, C45 (1977).
80. R. F. Lockwood and K. M. Nicholas, *Tetrahedron Lett.*, **48**, 4163 (1977).
81. R. E. Conner and K. M. Nicholas, *J. Organomet. Chem.*, **125**, C45 (1977).
82. C. Descoins and D. Samain, *Tetrahedron Lett.*, **10**, 745 (1976).
83. U. Krüerke and W. Hübel, *Chem. Ber.*, **94**, 2829 (1961).
84. R. S. Dickson and P. J. Fraser, *Aust. J. Chem.*, **23**, 475 (1970).
85. R. S. Dickson, P. J. Fraser, and B. M. Gatehouse, *J. Chem. Soc., Dalton Trans.*, 2278 (1972).
86. U. Krüerke, C. Hoogzand, and W. Hübel, *Chem. Ber.*, **94**, 2817 (1961).
87. R. Markby, J. Wender, R. A. Friedel, F. A. Cotton, and H. W. Sternberg, *J. Am. Chem. Soc.*, **80**, 6529 (1958).
88. P. W. Sutton and L. F. Dahl, *J. Am. Chem. Soc.*, **89**, 261 (1967).
89. W. T. Dent, L. A. Duncanson, R. G. Guy, H. W. B. Reed, and B. L. Shaw, *Proc. Chem. Soc.*, **80**, 6529 (1958).
90. R. Ercoli, E. Santambrogio, and G. Tettamanti-Casagrande, *Chim. Ind. (Milan)*, **44**, 1344 (1962).
91. G. Bor, L. Markó, and B. Markó, *Acta Chim. Acad. Sci. Hung.*, **27**, 395 (1961); *Chem. Ber.*, **95**, 333 (1962).
92. D. Seyferth, J. E. Hallgreen, R. J. Spohn, A. T. Wehman, and G. H. Williams, *Spec. Lect., 23rd Int. Congr. Pure Appl. Chem.*, **6**, 133 (1971).
93. D. Seyferth, *Adv. Organomet. Chem.*, **14**, 98 (1976).
94. G. Pályi, F. Piacenti, and L. Markó, *Inorg. Chim. Acta Rev.*, **4**, 109 (1970).
95. B. R. Penfold and B. H. Robinson, *Acc. Chem. Res.*, **6**, 73 (1973).
96. G. Schmidt, *Angew. Chem.*, **90**, 417 (1978); *Angew. Chem., Int. Ed. Engl.*, **17**, 392 (1978).
97. I. U. Khand, G. R. Knox, P. L. Pauson, and W. E. Watts, *J. Org. Chem.*, **73**, 383 (1974).
98. D. Seyferth and A. T. Wehman, *J. Am. Chem. Soc.*, **92**, 5520 (1970).
99. D. Seyferth, J. E. Hallgreen, R. J. Spohn, G. H. Williams, M. O. Nestle, and P. L. K. Hung, *J. Organomet. Chem.*, **65**, 99 (1974).
100. K. Tominaga, N. Yamagami, and H. Wakamatzu, *Tetrahedron Lett.*, **25**, 2217 (1970).
101. U. Krüerke and W. Hübel, *Chem. Ind. (London)*, 1264 (1960).
102. J. Lewis and B. F. G. Johnson, *Gazz. Chim. Ital.*, **109**, 271 (1979).
103. J. M. Landesberg, L. Katz, and C. C. Olson, *J. Org. Chem.*, **37**, 930 (1972).
104. H. des Abbayes and H. Alper, *J. Am. Chem. Soc.*, **99**, 98 (1977).
105. H. Alper and Hang-Nam Paik, *Nouv. J. Chim.*, **2**, 245 (1978).
106. H. Alper, *J. Org. Chem.*, **37**, 3972 (1972).
107. B. M. Trost and S. D. Ziman, *J. Org. Chem.*, **38**, 932 (1973).
108. I. Rhee, M. Ryang, and S. Tsutzumi, *J. Organomet. Chem.*, **9**, 361 (1967).
109. A. L. Robinson, *Science*, **194**, 1150 (1976).
110. C. U. Pittman, Jr, and R. C. Ryan, *ChemTech*, **8**, 170 (1978).
111. J. R. Shapley, *Strem Chem.*, **4**, 3 (1978).
112. G. Huttner, *Nachr. Chem. Tech. Lab.*, **27**, 261 (1979).
113. P. Braunstein, *Nouv. J. Chim.*, **10**, 366 (1986).
114. A. K. Smith and J. M. Basset, *J. Mol. Catal.*, **2**, 229 (1977).
115. R. Whyman, in *Transition Metal Clusters* (Ed. B. F. G. Johnson), Wiley, Chichester, 1980, p. 545.
116. L. Markó and A. Vizi-Orosz, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knötzinger), Elsevier, Amsterdam, 1986, p. 89.
117. J. Zwart and R. Snel, *J. Mol. Catal.*, **30**, 305 (1985).
118. M. Castiglioni, R. Giordano, and E. Sappa, *J. Organomet. Chem.*, **258**, 217 (1983).
119. R. Ugo and R. Psaro, *J. Mol. Catal.*, **20**, 53 (1983).
120. R. D. Adams, *Acc. Chem. Res.*, **16**, 67 (1983).
121. J. S. Bradley, E. Hill, M. E. Lenowicz, and H. Witzke, *J. Mol. Catal.*, **41**, 59 (1987).
122. A. Brenner, in *Metal Clusters* (Ed. M. Moskovits), Wiley, New York, 1986, p. 249.
123. B. C. Gates, in *Metal Clusters* (Ed. M. Moskovits), Wiley, New York, 1986, p. 283.

124. B. C. Gates, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 497.
125. G. Maire, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 509.
126. B. C. Gates and H. Knözinger, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 531.
127. L. Guczi, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 547.
128. W. Hübel and C. Hoogzand, *Chem. Ber.*, **93**, 103 (1960).
129. H. R. Allcock, R. A. Nissan, P. J. Harris, and R. R. Whittle, *Organometallics*, **3**, 432 (1984).
130. C. Choo Yin and A. J. Deeming, *J. Organomet. Chem.*, **144**, 351 (1978).
131. V. W. Day, R. O. Day, J. S. Kristoff, F. J. Hirsekorn, and E. L. Muetterties, *J. Am. Chem. Soc.*, **97**, 2571 (1975).
132. G. N. Schrauzer, B. N. Bastian, and G. N. Fosselius, *J. Am. Chem. Soc.*, **88**, 4890 (1966).
133. G. A. Catton, G. F. C. Jones, M. J. Mays, and J. A. S. Howell, *Inorg. Chim. Acta*, **20**, L41 (1976).
134. H. Irngartinger and A. Goldmann, *J. Chem. Soc., Chem. Commun.*, 455 (1981).
135. M. Castiglioni, L. Milone, D. Osella, G. A. Vaglio and M. Valle, *Inorg. Chem.*, **15**, 394 (1976).
136. M. Valle, D. Osella, and G. A. Vaglio, *Inorg. Chim. Acta*, **20**, 213 (1976).
137. G. A. Vaglio and M. Valle, *Inorg. Chim. Acta*, **30**, 161 (1978).
138. P. M. Lausarot, G. A. Vaglio, and M. Valle, *Trans. Met. Chem.*, **4**, 39 (1979).
139. G. A. Vaglio, D. Osella, and M. Valle, *Trans. Met. Chem.*, **2**, 94 (1977).
140. R. P. Ferrari and G. A. Vaglio, *Inorg. Chim. Acta*, **20**, 141 (1976).
141. D. Bingham, B. Hudson, D. E. Webster, and P. B. Wells, *J. Chem. Soc., Dalton Trans.*, 1521 (1974).
142. G. Pregaglia, A. Andreetta, G. Ferrari, and R. Ugo, *J. Organomet. Chem.*, **33**, 73 (1971).
143. A. J. Deeming and S. Hasso, *J. Organomet. Chem.*, **114**, 313 (1976).
144. G. Süss-Fink, *Habilitationsschrift*, Universität Bayreuth, 1984.
145. J. L. Graff, R. D. Sanner, and M. S. Wrighton, *J. Am. Chem. Soc.*, **101**, 273 (1979).
146. J. L. Graff and M. S. Wrighton, *J. Am. Chem. Soc.*, **102**, 2123 (1980).
147. A. Basu and K. R. Sharma, *J. Mol. Catal.*, **38**, 315 (1986).
148. A. Basu, S. Bhaduri and K. R. Sharma, *Adv. Catal., Proc. Natl. Symp. Catal.*, **8**, 669 (1985).
149. U. Matteoli, M. Bianchi, P. Frediani, G. Menchi, C. Botteghi, and M. Marchetti, *J. Organomet. Chem.*, **263**, 243 (1984).
150. T. Kitamura, N. Sakamoto, and T. Joh, *Chem. Lett.*, 379 (1973).
151. G. Albanesi and M. Tovaglieri, *Chim. Ind. (Milan)*, **41**, 189 (1959).
152. J. C. Sauer, R. D. Cramer, V. A. Engelhardt, T. A. Ford, H. E. Holmquist, and B. W. Howk, *J. Am. Chem. Soc.*, **81**, 3677 (1959).
153. O. S. Mills and G. Robinson, *Inorg. Chim. Acta*, **1**, 61 (1967).
154. D. J. S. Guthrie, I. U. Khand, G. R. Knox, J. Kollmeier, P. L. Pauson, and W. E. Watts, *J. Organomet. Chem.*, **90**, 93 (1975).
155. S. A. Sánchez-Delgado, J. Puga, and M. Rosales, *J. Mol. Catal.*, **24**, 221 (1984).
156. A. Basu, S. Bhaduri, H. Khwaja, P. G. Jones, T. Schroeder, and G. M. Sheldrick, *J. Organomet. Chem.*, **290**, C19 (1985).
157. C. Bergounhou, J.-J. Bonnet, P. Fompeyrine, G. Lavigne, N. Lugun, and Mansilla, *Organometallics*, **5**, 60 (1986).
158. Y. Blum, D. Czarkie, Y. Rahamim, and Y. Shvo, *Organometallics*, **4**, 1459 (1985).
159. W. Abbout, Y. Ben Taarit, and J. M. Basset, *J. Organomet. Chem.*, **220**, C15 (1981).
160. R. A. Sánchez-Delgado, A. Audriollo, J. Puga, and G. Martín, *Inorg. Chem.*, **26**, 1867 (1987).
161. B. C. Hui and G. L. Rempel, *J. Chem. Soc., Chem. Commun.*, 1195 (1970).
162. J. Müller, B. Passon, and S. Schmitt, *J. Chem. Soc., Chem. Commun.*, **195**, C21 (1980).
163. J. L. Zuffa, M. L. Blohm, and W. L. Gladfelter, *J. Am. Chem. Soc.*, **108**, 552 (1986).
164. S. A. Fouda and G. L. Rempel, *Inorg. Chem.*, **18**, 1 (1979).
165. G. F. Pregaglia, A. Andreetta, G. F. Ferrari, G. Montrasi, and R. Ugo, *J. Organomet. Chem.*, **33**, 73 (1971).
166. H. Inoue and M. Sato, *J. Chem. Soc., Chem. Commun.*, 983 (1983).
167. K. G. Caulton, M. G. Thomas, B. A. Sosinski, and E. L. Muetterties, *Proc. Natl. Acad. Sci. USA*, **73**, 474 (1976).
168. Y. Doi, S. Tamura, and K. Koshizuka, *Inorg. Chim. Acta*, **65**, L63 (1982).

169. Y. Doi, S. Tamura, and K. Koshizuka, *J. Mol. Catal.*, **19**, 213 (1983).
170. J. Fischler, R. Wagner, and E. A. Koerner von Gustdorf, *J. Organomet. Chem.*, **112**, 155 (1976).
171. W. Reimann, W. Abboud, J. M. Basset, R. Mutin, G. L. Rempel, and A. K. Smith, *J. Mol. Catal.*, **9**, 349 (1980).
172. G. Süss-Fink, unpublished results; cf. G. Süss-Fink, *Habilitationsschrift*, Universität Bayreuth, 1983.
173. M. Bianchi, F. Piacenti, P. Frediani, U. Matteoli, C. Botteghi, S. Gladiali, and E. Benedetti, *J. Organomet. Chem.*, **141**, 107 (1977).
174. M. Bianchi, F. Piacenti, G. Menchi, P. Frediani, U. Matteoli, C. Botteghi, S. Gladiali, and R. Benedetti, *Chim. Ind. (Milan)*, **60**, 588 (1978).
175. C. Botteghi, M. Bianchi, E. Benedetti, and U. Matteoli, *Chimica*, **29**, 256 (1975).
176. M. Bianchi, U. Matteoli, P. Frediani, G. Menchi, F. Piacenti, C. Botteghi, and M. Marchetti, *J. Organomet. Chem.*, **252**, 317 (1983).
177. C. Botteghi, S. Gladiali, M. Bianchi, U. Matteoli, P. Frediani, P. G. Vergamini, and E. Benedetti, *J. Organomet. Chem.*, **140**, 221 (1977).
178. U. Matteoli, G. Menchi, P. Frediani, M. Bianchi, and F. Piacenti, *J. Organomet. Chem.*, **285**, 281 (1985).
179. T. H. Johnson, L. A. Siegle, and V. J. K. Chaffin, *J. Mol. Catal.*, **9**, 307 (1980).
180. R. Mutin, W. Abbout, J. M. Basset, and D. Sinou, *J. Mol. Catal.*, **33**, 47 (1985).
181. G. Balavoine, T. Dang, C. Eskenzai, and H. B. Kagan, *J. Mol. Catal.*, 7, 531 (1980).
182. Tuan-Phat Dang, P. Aviron-Violet, Y. Colleuille, and J. Varagnat, *J. Mol. Catal.*, **16**, 51 (1982).
183. C. U. Pittmann, Jr, R. C. Ryan, J. McGee, and J. P. O'Conner, *J. Organomet. Chem.*, **178**, C43 (1979).
184. P. M. Lausarot, G. A. Vaglio, and M. Valle, *Inorg. Chim. Acta*, **36**, 213 (1979).
185. P. M. Lausarot, G. A. Vaglio, and M. Valle, *Inorg. Chim. Acta*, **25**, L105 (1977).
186. P. M. Lausarot, G. A. Vaglio, and M. Valle, *J. Organomet. Chem.*, **204**, 249 (1981).
187. E. L. Muetterties, E. Band, A. Kokorin, W. R. Pretzer, and M. G. Thomas, *Inorg. Chem.*, **19**, 1552 (1980).
188. M. G. Tomas, W. R. Pretzer, B. F. Beier, F. J. Hirsekorn, and E. L. Muetterties, *J. Am. Chem. Soc.*, **99**, 743 (1977).
189. M. Castiglioni, R. Giordano, and E. Sappa, *J. Organomet. Chem.*, **258**, 217 (1983).
190. J. P. Collman, R. G. Finke, P. L. Matlock, R. Wahren, and J. I. Brauman, *J. Am. Chem. Soc.*, **98**, 4685 (1976).
191. Bong Rae Cho and R. M. Laine, *J. Mol. Catal.*, **15**, 383 (1982).
192. B. Heil and L. Markó, *Acta Chim. Acad. Sci. Hung.*, **55**, 107 (1968).
193. P. Frediani, U. Matteoli, M. Bianchi, F. Piacenti, and G. Menchi, *J. Organomet. Chem.*, **150**, 273 (1978).
194. U. Matteoli, M. Bianchi, G. Menchi, F. Frediani, and F. Piacenti, *J. Mol. Catal.*, **29**, 269 (1985).
195. U. Matteoli, G. Menchi, M. Bianchi, and F. Piacenti, *J. Organomet. Chem.*, **299**, 233 (1986).
196. U. Matteoli, M. Bianchi, G. Menchi, F. Frediani, and F. Piacenti, *J. Mol. Catal.*, **22**, 353 (1984).
197. U. Matteoli, G. Menchi, M. Bianchi, P. Frediani, and F. Piacenti, *Gazz. Chim. Ital.*, **115**, 603 (1985).
198. M. Bianchi, G. Menchi, F. Francalanci, F. Piacenti, U. Matteoli, P. Frediani, and C. Botteghi, *J. Organomet. Chem.*, **188**, 109 (1980).
199. T. Yoshida, T. Okano, and S. Otsuka, *J. Chem. Soc., Chem. Commun.*, 870 (1979).
200. E. Band, W. Pretzer, M. G. Thomas, and E. L. Muetterties, *J. Am. Chem. Soc.*, **99**, 7380 (1977).
201. C. M. Giandomenico, A. Elsenstadt, M. F. Fredericks, A. S. Hirschon, and R. M. Laine, in *Catalysis of Organic Reactions* (Ed. R. L. Augustine), Marcel Dekker, New York, 1985, p. 73.
202. R. M. Laine, *Nouv. J. Chim.*, **11**, 543 (1987).
203. A. Eisenstadt, G. M. Giandomenico, M. F. Fredericks, A. S. Hirschon, and R. M. Laine, *Organometallics*, **4**, 2033 (1985).
204. J. Kašpar, R. Spogliarich, and M. Graziani, *J. Organomet. Chem.*, **281**, 299 (1985).
205. K. Jothimony, S. Vancheesan, and J. C. Kuriacose, *J. Mol. Catal.*, **32**, 11 (1985).
206. T. A. Smith and P. M. Maitlis, *J. Organomet. Chem.*, **289**, 385 (1985).
207. Y. Blum, D. Reshef, and Y. Shvo, *Tetrahedron Lett.*, **22**, 1541 (1981).
208. Y. Blum and Y. Shvo, *J. Organomet. Chem.*, **263**, 93 (1984).
209. Y. Blum and Y. Shvo, *J. Organomet. Chem.*, **282**, C7 (1985).
210. Y. Shvo, Y. Blum, D. Reshef, and M. Menzin, *J. Organomet. Chem.*, **226**, C21 (1982).

211. S. Bhaduri and K. R. Sharma, *J. Chem. Soc., Chem. Commun.*, 1412 (1983).
212. A. Basu, S. Bhaduri, and K. R. Sharma, *J. Chem. Soc., Dalton Trans.*, 2315 (1984).
213. M. Bianchi, U. Matteoli, P. Frediani, G. Menchi, and F. Piacenti, *J. Organomet. Chem.*, **236**, 375 (1982).
214. M. Bianchi, U. Matteoli, G. Menchi, P. Frediani, S. Pratesi, F. Piacenti, and C. Botteghi, *J. Organomet. Chem.*, **198**, 73 (1980).
215. M. Bianchi, U. Matteoli, G. Menchi, P. Frediani, F. Piacenti, and C. Botteghi, *J. Organomet. Chem.*, **195**, 337 (1980).
216. K. Ohkubo, K. Sugahara, I. Terada, and K. Yoshinaga, *Inorg. Nucl. Chem. Lett.*, **14**, 297 (1978).
217. K. Ohkubo, J. Terada, and K. Yoshinaga, *Inorg. Nucl. Chem. Lett.*, **15**, 421 (1979).
218. K. Ohkubo, I. Terada, K. Sugahara, and K. Yoshinaga, *J. Mol. Catal.*, **7**, 421 (1980).
219. M. Bianchi, U. Matteoli, G. Menchi, P. Frediani, and F. Piacenti, *J. Organomet. Chem.*, **240**, 65 (1982).
220. B. D. Dombek, *Adv. Catal.*, **32**, 325 (1983).
221. G. A. Süss-Fink, G. Hermann, and G. F. Schmidt, in *Rep. Int. Sem. Heteronucl. Clust. Multimet. Catal.* (Eds R. D. Adams and W. A. Herrmann), 1987; to be published in *Polyhedron* (1988).
222. R. Whyman, *Philos. Trans. R. Soc. London, Ser. A*, **308**, 131 (1982).
223. R. L. Pruett and W. E. Walker, *US Pat.*, 3957857 (1976).
224. R. L. Pruett and W. E. Walker, *US Pat.*, 4133776 (1979).
225. R. L. Pruett and W. E. Walker, *US Pat.*, 3833634 (1974).
226. R. L. Pruett, *Ann. N. Y. Acad. Sci.*, **295**, 239 (1977).
227. M. G. Tomas, B. F. Beier, and E. L. Muetterties, *J. Am. Chem. Soc.*, **98**, 1296 (1976).
228. G. C. Demitras and E. L. Mutterties, *J. Am. Chem. Soc.*, **99**, 2796 (1977).
229. W. Keim, H. Berger, and J. Schlupp, *J. Mol. Catal.*, **61**, 359 (1980).
230. R. B. King, A. D. King, Jr, and K. Tanaka, *J. Mol. Catal.*, **10**, 75 (1980).
231. W. Keim, M. Berger, A. Eisenbeis, J. Kadelka, and J. Schlupp, *J. Mol. Catal.*, **13**, 95 (1981).
232. C. Masters and J. A. van Doorn, *Ger. Offen.*, 2644185 (1975).
233. J. S. Bradley, *J. Am. Chem. Soc.*, **101**, 7419 (1979).
234. J. S. Bradley, in *Fundamental Research in Homogeneous Catalysis* (Ed. M. Tsutsui), Plenum Press, New York, 1979, p. 165.
235. R. J. Daroda, J. R. Blackborow, and G. Wilkinson, *J. Chem. Soc., Chem. Commun.*, 1101 (1980).
236. B. D. Dombek, *J. Am. Chem. Soc.*, **102**, 6855 (1980).
237. B. D. Dombek, *J. Am. Chem. Soc.*, **103**, 6510 (1981).
238. B. D. Dombek, *J. Organomet. Chem.*, **250**, 457 (1983).
239. B. K. Warren and B. D. Dombek, *J. Catal.*, **79**, 334 (1983).
240. Y. Kiso and K. Saeki, *J. Organomet. Chem.*, **309**, C26 (1986).
241. Y. Kiso and K. Saeki, *J. Organomet. Chem.*, **303**, C17 (1986).
242. Y. Kiso and K. Saeki, *Bull. Chem. Soc. Jpn.*, **60**, 617 (1987).
243. S.-I. Yoshida, S. Mori, H. Kinochita, and Y. Watanabe, *J. Mol. Catal.*, **42**, 215 (1987).
244. J. Knifton, *J. Am. Chem. Soc.*, **103**, 3959 (1981).
245. J. Knifton, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **31**, 26 (1986).
246. L. Kaplan, *US Pat.*, 3944588 (1976).
247. P. Chini and S. Martinengo, *Inorg. Chim. Acta*, **3**, 299 (1969).
248. S. Martinengo and P. Chini, *Gazz. Chim. Ital.*, **102**, 344 (1972).
249. P. Chini, G. Longoni, and V. G. Albani, *Adv. Organomet. Chem.*, **14**, 285 (1976).
250. J. L. Vidal and W. E. Walker, *Inorg. Chem.*, **19**, 896 (1980).
251. B. T. Heaton, J. Jones, T. Eguchi, and G. A. Hoffman, *J. Chem. Soc., Chem. Commun.*, 331 (1981).
252. A. Fumagalli, T. F. Koetzle, F. Takusagawa, P. Chini, S. Martinengo, and B. T. Heaton, *J. Am. Chem. Soc.*, **102**, 1740 (1980).
253. R. L. Pruett, *Science*, **211**, 11 (1981).
254. L. Kaplan, *US Pat.*, 4162216 (1979).
255. R. M. Laine, R. G. Rinker, and P. C. Ford, *J. Am. Chem. Soc.*, **99**, 252 (1977).
256. C. Ungermann, V. Landis, S. A. Moya, H. Cohen, H. Walker, R. G. Pearson, R. C. Rinker, and P. C. Ford, *J. Am. Chem. Soc.*, **101**, 5922 (1979).
257. P. C. Ford, *Acc. Chem. Res.*, **14**, 31 (1981).
258. P. C. Ford, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **29**, 567 (1984).
259. P. C. Ford, C. Ungermann, V. Landis, S. A. Moya, R. C. Rinker, and R. M. Laine, *Adv. Chem. Ser.*, No. **173**, 81 (1979).

260. J. R. Moss and W. A. G. Graham, *J. Chem. Soc., Dalton Trans.*, 89 (1977).
261. J. C. Bricker, C. C. Nagel, and S. G. Shore, *J. Am. Chem. Soc.*, **104**, 1444 (1982).
262. P. Yarrow, H. Cohen, C. Ungermann, D. Vandenberg, P. C. Ford, and R. G. Rinker, *J. Mol. Catal.*, **22**, 239 (1983).
263. A. D. King, R. B. King, and D. B. Yang, *J. Chem. Soc., Chem. Commun.*, 529 (1980).
264. T. Venäläinen, T. A. Pakkanen, T. T. Pakkanen, and E. Iiskola, *J. Organomet. Chem.*, **314**, C49 (1986).
265. Hi Chung Kang, C. H. Mauldin, T. Cole, W. Slegeir, K. Cann, and R. Pettit, *J. Am. Chem. Soc.*, **99**, 8323 (1977).
266. Chien-Hong Cheng, D. E. Hendriksen, and R. Eisenberg, *J. Am. Chem. Soc.*, **99**, 2791 (1977).
267. K. Kaneda, M. Hiraki, K. Sano, T. Imanaka, and S. Teranishi, *J. Mol. Catal.*, **9**, 227 (1980).
268. R. M. Laine, D. W. Thomas, L. W. Cary, and S. E. Buttrill, *J. Am. Chem. Soc.*, **100**, 6527 (1978).
269. R. M. Laine, *J. Am. Chem. Soc.*, **100**, 6451 (1978).
270. A. Basu, S. Bhaduri, and H. Khwaja, *J. Organomet. Chem.*, **319**, C28 (1987).
271. H. Yamazaki, and P. Hong, *J. Mol. Catal.*, **21**, 133 (1983).
272. P. Hong, Bo-Re Cho, and H. Yamazaki, *Chem. Lett.*, 507 (1980).
273. A. J. Cornish, M. F. Lappert, G. L. Filators, and T. A. Nile, *J. Organomet. Chem.*, **172**, 153 (1979).
274. Y. Seki, K. Takeshita, K. Kuwamoto, S. Murai, and N. Sonoda, *Angew. Chem.*, **92**, 974 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 928 (1980).
275. Y. Seki, K. Takeshita, K. Kuwamoto, S. Murai, and N. Sonoda, *J. Org. Chem.*, **51**, 3890 (1986).
276. J. Ojima, T. Fuchikami, and M. Yatabe, *J. Organomet. Chem.*, **260**, 335 (1984).
277. G. Süss-Fink and J. Reiner, *J. Mol. Catal.*, **16**, 231 (1982).
278. M. P. Doyle, W. H. Tamblyn, W. E. Buhro, and R. L. Dorow, *Tetrahedron Lett.*, **22**, 1783 (1981).
279. M. P. Doyle, D. van Leusen, and W. H. Tamblyn, *Synthesis*, 787 (1981).
280. A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, and P. Teyssié, *J. Org. Chem.*, **45**, 695 (1980).
281. N. Petiniot, A. J. Anciaux, A. F. Noels, A. J. Hubert, and P. Teyssié, *Tetrahedron Lett.*, **14**, 1239 (1978).
282. Y. Shvo and R. M. Laine, *J. Chem. Soc., Chem. Commun.*, 756 (1980).
283. R. M. Laine, *Ann. N. Y. Acad. Sci.*, **415**, 271 (1983).
284. R. M. Laine, *J. Mol. Catal.*, **2**, 119 (1983).
285. R. M. Laine, D. W. Thomas, and L. W. Cary, *J. Am. Chem. Soc.*, **104**, 1763 (1982).
286. R. D. Adams, Hoon-Sik Kim, and S. Wang, *J. Am. Chem. Soc.*, **107**, 6107 (1985).
287. C. Masters, *Adv. Organomet. Chem.*, **17**, 61 (1979).
288. B. Cornils, in *New Syntheses with Carbon Monoxide* (Ed. J. Falbe), Springer, Berlin, 1980, p. 1.
289. K. Weissermel and H. J. Arpe, *Industrielle Organische Chemie*, 2. Aufl., Verlag Chemie, Weinheim, 1978, p. 34.
290. G. Braca, G. Sbrana, F. Piacenti, and P. Pino, *Chim. Ind. (Milan)*, **52**, 1091 (1970).
291. G. Süss-Fink, *J. Organomet. Chem.*, **193**, C20 (1980).
292. G. Süss-Fink and G. Schmidt, *J. Mol. Catal.*, **42**, 361 (1987).
293. A. Ceriotti, L. Garlaschelli, G. Longoni, M. C. Maletesta, D. Strumolo, A. Fumagalli, and S. Martinengo, *J. Mol. Catal.*, **24**, 309 (1984).
294. Bian-Hung Chang, *Inorg. Chim. Acta*, **65**, L189 (1982).
295. H. P. Withers, Jr, and D. Seyferth, *Inorg. Chem.*, **22**, 2931 (1983).
296. P. Kalck, J.-M. Frances, P.-M. Pfister, T. G. Southern, and A. Thorez, *J. Chem. Soc., Chem. Commun.*, 510 (1983).
297. B. Heil, and L. Markó, *Chem. Ber.*, **101**, 2209 (1968).
298. G. Csontos, B. Heil, and L. Marko, *Ann. N. Y. Acad. Sci.*, **239**, 47 (1974).
299. N. S. Imyanitov, and D. M. Rudkovskii, *Zh. Prikl. Khim.*, **39**, 1948 (1967).
300. P. Chini, S. Martinengo, and G. Garlaschelli, *J. Chem. Soc., Chem. Commun.*, 709 (1982).
301. F. Piacenti, G. Menchi, P. Frediani, and U. Matteoli, *Chim. Ind. (Milan)*, **60**, 808 (1978).
302. C. Botteghi, M. Branca, G. Micera, F. Piacenti, and G. Menchi, *Chim. Ind. (Milan)*, **60**, 16 (1978).
303. K. Murata, A. Matsuda, K.-I. Bando, and Y. Sugi, *J. Chem. Soc., Chem. Commun.*, 785 (1979).
304. R. M. Laine, *Ann. N. Y. Acad. Sci.*, **333**, 124 (1980).
305. E. Z. Gil'denberg and A. L. Lapidus, *Kinet. Katal.*, **18**, 124 (1977).
306. E. Z. Gil'denberg, V. P. Gul'myai, L. N. Valueva, and A. L. Lapidus, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **2**, 332 (1979).
307. Ya. T. Éidus, A. L. Lapidus, and E. Z. Gil'denberg, *Kinet. Katal.*, **14**, 598 (1973).

308. A. L. Lapidus, E. Z. Gil'denberg, and Ya. T. Éidus, *Kinet. Katal.*, **16**, 252 (1975).
309. M. Marchionna and G. Longoni, *Organometallics*, **6**, 606 (1987).
310. N. Kutepow and H. Kindler, *Angew. Chem.*, **72**, 802 (1960).
311. J. Palágyi and L. Markó, *J. Organomet. Chem.*, **236**, 343 (1982).
312. P. Escaffre, A. Thorez, and P. Kalck, *J. Chem. Soc., Chem. Commun.*, 146 (1987).
313. R. M. Laine, D. W. Thomas, and L. W. Carey, *J. Org. Chem.*, **44**, 4964 (1979).
314. Y. Seki, S. Murai, A. Hidaka, and N. Sonoda, *Angew. Chem.*, **89**, 919 (1977); *Angew. Chem., Int. Ed. Engl.*, **16**, 881 (1977).
315. F. Wada and T. Matsuda, *J. Organomet. Chem.*, **64**, 365 (1973).
316. H. Bahrmann and B. Cornils, in *New Syntheses with Carbon Monoxide* (Ed. J. Falbe), Springer, Berlin, 1980, p. 266.
317. M. J. Chen, H. M. Feder, and J. W. Rathke, *J. Mol. Catal.*, **17**, 331 (1982).
318. M. J. Chen, H. M. Feder, and J. W. Rathke, *J. Am. Chem. Soc.*, **104**, 7346 (1982).
319. J. F. Knifton, *J. Chem. Soc., Chem. Commun.*, 41 (1981).
320. J. F. Knifton, *J. Mol. Catal.*, **11**, 91 (1981).
321. J. F. Knifton, *J. Catal.*, **76**, 101 (1982).
322. J. R. Zoeller, *J. Mol. Catal.*, **37**, 117 (1986).
323. J. F. Knifton and J. J. Lin, *C_1 Mol. Chem.*, **1**, 387 (1986).
324. J. F. Knifton, *J. Chem. Soc., Chem. Commun.*, 1412 (1985).
325. J. F. Knifton and D. C. Alexander, *Isr. J. Chem.*, **27**, 255 (1986).
326. J. A. Marsella, and G. P. Pez, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **31**, 22 (1986).
327. P. Pino, G. Bracca, G. Sbrana, and A. Cuccuru, *Chem. Ind. (London)*, 1732 (1968).
328. B. W. Howk and J. C. Sauer, *US Pat.*, 3055949 (1958).
329. K. Cann, T. Cole, W. Slegeir, and R. Pettit, *J. Am. Chem. Soc.*, **100**, 3969 (1978).
330. R. Pettit, J. Cann, T. Cole, C. H. Mauldin, and W. Slegeir, *Adv. Chem. Ser.*, No. **173**, 121 (1979).
331. K. Kaneda, M. Hiraki, T. Imanaka, and S. Teranishi, *J. Mol. Catal.*, **12**, 385 (1981).
332. R. C. Ryan, G. M. Wilemon, M. P. Dalsanto, and C. U. Pittman, Jr, *J. Mol. Catal.*, **5**, 319 (1979).
333. E. Alessio, G. Zassinovich, and G. Mestroni, *J. Mol. Catal.*, **18**, 113 (1983).
334. F. L'Eplattenier, P. Matthys, and F. Calderazzo, *Inorg. Chem.*, **9**, 343 (1970).
335. H. Alper and K. E. Hashem, *J. Am. Chem. Soc.*, **103**, 6514 (1981).
336. J. Falbe, *J. Organomet. Chem.*, **94**, 213 (1975).
337. T. Kitamura, N. Sakamoto, and T. Joh, *Chem. Lett.*, 379 (1972).
338. K. Kaneda, T. Imanaka, and S. Teranishi, *Proc. Int. Congr. Catal.*, **8**, V15 (1984).
339. K. Murata and A. Matsuda, *Chem. Lett.*, 11 (1980).
340. R. H. Fish, *Ann. N. Y. Acad. Sci.*, **415**, 292 (1983).
341. R. H. Fish, A. D. Thormodsen, and G. A. Cremer, *J. Am. Chem. Soc.*, **104**, 5234 (1982).
342. M. Hidai, Y. Koyasu, K. Chikanari, and Y. Uchida, *J. Mol. Catal.*, **40**, 243 (1987).
343. T. Mise, P. Hong, and H. Yamazaki, *Chem. Lett.*, 993 (1981).
344. T. Mise, P. Hong, and H. Yamazaki, *J. Org. Chem.*, **48**, 238 (1983).
345. P. Hong, T. Mise, and H. Yamazaki, *Chem. Lett.*, 361 (1982).
346. T. J. Kealy and R. E. Benson, *J. Org. Chem.*, **26**, 3126 (1961).
347. S. Cenini, M. Pizzotti, C. Crotti, F. Porta, and G. La Monica, *J. Chem. Soc., Chem. Commun.*, 1286 (1984).
348. Y. Blum, D. Reshef, and Y. Shvo, *Tetrahedron Lett.*, **22**, 1541 (1981).
349. P. Hong, Bo-Re Cho, and H. Yamazaki, *Chem. Lett.*, 339 (1979).
350. P. Hong, H. Yamazaki, K. Sonogashira, and N. Hagihara, *Chem. Lett.*, 535 (1978).
351. G. O. Evans and C. J. Newell, *Inorg. Chim. Acta*, **31**, L387 (1978).
352. D. J. Darensbourg, C. Ovalles, and M. Pala, *J. Am. Chem. Soc.*, **105**, 5937 (1983).
353. Y. Sasaki and P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, 790 (1986).
354. G. Süss-Fink and J. Reiner, *J. Organomet. Chem.*, **221**, C36 (1981).
355. G. D. Mercer, J. Shing Shu, T. B. Rauchfuss, and D. M. Roundhill, *J. Am. Chem. Soc.*, **97**, 1967 (1975).
356. T. Mise, P. Hong, and H. Yamazaki, *Chem. Lett.*, 401 (1982).
357. P. Hong, T. Mise, and H. Yamazaki, *Chem. Lett.*, 989 (1981).
358. D. Labroue and R. Poilblanc, *J. Mol. Catal.*, **2**, 329 (1979).
359. C. U. Pittman, Jr, W. Honnick, M. Absi-Halabi, M. G. Richmond, R. Bender, and P. Braunstein, *J. Mol. Catal.*, **32**, 177 (1985).

360. M. Castiglioni, R. Giordano, and E. Sappa, *J. Organomet. Chem.*, **319**, 167 (1987).
361. M. Castiglioni, R. Giordano, E. Sappa, G. Predieri, and A. Tiripicchio, *J. Organomet. Chem.*, **270**, C7 (1984).
362. M. Castiglioni, R. Giordano, E. Sappa, A. Tiripicchio, and M. Tiripicchio Camellini, *J. Chem. Soc., Dalton Trans.*, 23 (1986).
363. A. Fusi, R. Ugo, R. Psaro, P. Braunstein, and J. Dehand, *J. Mol. Catal.*, **16**, 217 (1982).
364. A. Fusi, R. Ugo, R. Psaro, P. Braunstein, and J. Dehand, *Phil. Trans. R. Soc. London, Ser. A*, **308**, 125 (1982).
365. B. D. Dombek, *Organometallics*, **4**, 1707 (1985).
366. R. L. Pruett and J. S. Bradley, *Eur. Pat.*, 0037700 (1981).
367. M. Tanaka, Y. Kiso, and K. Saeki, *J. Organomet. Chem.*, **329**, 99 (1987).
368. J. F. Knifton, *J. Chem. Soc., Chem. Commun.*, 729 (1983).
369. J. F. Knifton, *Platinium Met. Rev.*, **29**, 63 (1985).
370. J. F. Knifton, R. A. Grigsby, Jr, and J. J. Lin, *Organometallics*, **3**, 62 (1984).
371. M. Röper, M. Schieren, and A. Fumagalli, *J. Mol. Catal.*, **34**, 173 (1986).
372. R. Whyman, *J. Chem. Soc., Chem. Commun.*, 1439 (1983).
373. J. F. Knifton, *J. Catal.*, **96**, 439 (1985).
374. P. C. Ford, R. G. Rinker, C. Ungermann, R. M. Laine, V. Landis, and S. A. Moya, *J. Am. Chem. Soc.*, **100**, 4595 (1978).
375. T. Venäläinen, *Ann. Acad. Sci. Fenn., Ser. A2*, **211**, 1 (1987).
376. T. Venäläinen, E. Iiskola, J. Pursiainen, T. A. Pakkanen, and T. T. Pakkanen, *J. Mol. Catal.*, **34**, 293 (1986).
377. M. Hidai, A. Fukuoda, Y. Koyasu, and Y. Uchida, *J. Chem. Soc., Chem. Commun.*, 516 (1984).
378. A. Ceriotti, L. Garlaschelli, G. Longoni, M. C. Malatesta, D. Strumolo, A. Fumagalli, and S. Martinengo, *J. Mol. Catal.*, **24**, 323 (1984).
379. M. K. Alami, F. Dahan, and R. Mathieu, *J. Chem. Soc., Dalton Trans.*, 1983 (1987).
380. S. Attali and R. Matthieu, *J. Organomet. Chem.*, **291**, 205 (1985).
381. R. Choukroun, A. Iraqi, and D. Gervais, *J. Organomet. Chem.*, **311**, C60 (1986).
382. R. M. Laine, *J. Org. Chem.*, **45**, 3370 (1980).
383. R. M. Laine, *US Pat.*, 4226845 (1980).
384. M. Hidai, A. Fukuoka, Y. Koyasu, and Y. Uchida, *J. Mol. Catal.*, **35**, 29 (1986).
385. M. Hidai, in *Rep. Int. Sem. Heteronucl. Clust. Multimet. Catal.* (Eds R. D. Adams, and W. A. Herrmann), 1987; to be published in *Polyhedron* (1988).
386. M. Hidai, M. Orisaku, M. Ue, Y. Koyasu, T. Kodama, and Y. Uchida, *Organometallics*, **2**, 292 (1983).
387. M. Hidai, M. Orisaku, M. Ue, Y. Uchida, K. Yasufuku, and H. Yamazaki, *Chem. Lett.*, 143 (1981).
388. G. Doyle, *J. Mol. Catal.*, **13**, 237 (1981).
389. H. Kheradmand, A. Kiennemann, and G. Jenner, *J. Organomet. Chem.*, **251**, 339 (1983).
390. M. Hidai, Y. Koyasu, M. Yokota, M. Orisaku, and Y. Uchida, *Bull. Chem. Soc. Jpn.*, **55**, 3951 (1982).
391. J. Gauthier-Lafaye and R. Perron, *Eur. Pat.*, 0031784 (1981).
392. H. Alper and J.-F. Petrignani, *J. Chem. Soc., Chem. Commun.*, 1154 (1983).
393. H. Alper, J. K. Currie, and H. des Abbayes, *J. Chem. Soc., Chem. Commun.*, 311 (1978).
394. B. Fell, H. Chrobaczek, and W. Kohl, *Chem.-Ztg.*, **100**, 167 (1985).
395. Sun-Shine Yuan and A. M. Ajami, *J. Organomet. Chem.*, **302**, 255 (1986).
396. R. B. Wilson, Jr, and R. M. Laine, *J. Am. Chem. Soc.*, **107**, 361 (1985).
397. G. Süss-Fink and G. Herrmann, *Angew. Chem.*, **98**, 568 (1986); *Angew. Chem., Int. Ed. Engl.*, **25**, 570 (1986).
398. G. Süss-Fink, G. Herrmann, and U. Thewalt, *Angew. Chem.*, **95**, 899 (1983); *Angew. Chem., Int. Ed. Engl.*, **22**, 880 (1983).
399. G. Süss-Fink, G. Schmidt, and G. Herrmann, *Chem. Ber.*, **120**, 1451 (1987).
400. G. F. Schmidt and G. Süss-Fink, *J. Organomet. Chem.*, **356**, 207 (1988).
401. G. F. Schmidt, J. Reiner, and G. Süss-Fink, *J. Organomet. Chem.*, **355**, 379 (1988).
402. R. M. Laine, *J. Mol. Catal.*, **14**, 137 (1982).
403. R. C. Ryan, C. U. Pittman, Jr, and J. P. O'Connor, *J. Am. Chem. Soc.*, **99**, 1986 (1977).
404. C. U. Pittman, Jr, G. M. Wilemon, W. D. Wilson, and R. C. Ryan, *Angew. Chem.*, **92**, 494 (1980); *Angew. Chem., Int. Ed. Engl.*, **19**, 478 (1980).

405. M. G. Richmond, M. Absi-Halabi, and C. U. Pittman, Jr, *J. Mol. Catal.*, **22**, 367 (1982).
406. Z. Dawoodi, K. Henrick, and M. J. Mays, *J. Chem. Soc., Chem. Commun.*, 696 (1982).
407. M. Laing, P. Somerville, Z. Dawoodi, M. J. Mays, and P. Wheatley, *J. Chem. Soc., Chem. Commun.*, 1035 (1978).
408. S. A. R. Knox, J. W. Koepke, M. A. Andrews, and H. D. Kaesz, *J. Am. Chem. Soc.*, **97**, 3942 (1975).
409. A. J. Deeming and S. Hasso, *J. Organomet. Chem.*, **114**, 313 (1976).
410. J. B. Keister and J. R. Shapley, *J. Am. Chem. Soc.*, **98**, 1056 (1976).
411. J. L. Zuffa and W. L. Gladfelter, *J. Am. Chem. Soc.*, **108**, 4669 (1986).
412. D. E. Fjare, J. A. Jensen, and W. L. Gladfelter, *Inorg. Chem.*, **22**, 1774 (1983).
413. G. Süss-Fink and G. Herrmann, *J. Chem. Soc., Chem. Commun.*, 735 (1985).
414. C. E. Kampe, N. M. Boag, and H. D. Kaesz, *J. Am. Chem. Soc.*, **105**, 2896 (1983).
415. Y. Doi, K. Koshizuka, and T. Keii, *Inorg. Chem.*, **21**, 2732 (1982).
416. J. R. Norton, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **21**, 343 (1976).
417. C. U. Pittman, Jr, R. H. Ryan, W. D. Wilson, G. Wilemon, and M. Absi-Halabi, *Am. Chem. Soc. Div. Pet. Chem. Prepr.*, **25**, 417 (1980).
418. C. U. Pittman, Jr, M. G. Richmond, M. Absi-Halabi, H. Beurich, F. Richter, and H. Vahrenkamp, *Angew. Chem.*, **94**, 805 (1982); *Angew. Chem., Int. Ed. Engl.*, **19**, 478 (1980).
419. D. Mani and H. Vahrenkamp, *J. Mol. Catal.*, **29**, 305 (1985).
420. C. Mahe, H. Patin, J.-Y. Le Marouille, and A. Benolt, *Organometallics*, **2**, 1051 (1983).
421. P. Gallezot, in *Metal Clusters* (Ed. M. Moskovits), Wiley, New York, 1986, p. 219.
422. P. A. Jacobs, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 357.
423. B. C. Gates, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 415.
424. R. Psaro and R. Ugo, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 427.
425. G. Ertl, in *Metal Clusters in Catalysis* (Eds B. C. Gates, L. Guczi, and H. Knözinger), Elsevier, Amsterdam, 1986, p. 575.

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 8

Lanthanide reagents in organic synthesis

GARY A. MOLANDER

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215, USA

I. INTRODUCTION

In seeking novel means to accomplish highly selective synthetic transformations, organic chemists have utilized reagents derived from most elements in the Periodic Table. As a natural course of events, Main Group organometallics received immediate attention in the search for suitable synthetic tools. The chemistry of organolithiums, organomagnesiums, organoborons, and many other Main Group organometallics has therefore been relatively well defined for some time, and these reagents are now routinely utilized by virtually every practising synthetic organic chemist. Exponential growth in the use of organotransition metals in organic synthesis has also occurred since the 1960s. Development of organotitanium, organocopper, organonickel, and organopalladium chemistry has more recently revolutionized the manner in which organic molecules are synthesized.

Scant attention was given to the utilization of lanthanide reagents in organic synthesis until the 1980s. In a relatively short time, however, enormous strides have been made in delineating useful applications for a wide range of lanthanide reagents. As evidence of this, several excellent reviews concerning various aspects of lanthanide chemistry applied to organic synthesis have appeared[1]. In addition, excellent surveys on the synthetic and structural aspects of organolanthanide chemistry have been published[2]. This chapter is intended to concentrate on applications of lanthanide reagents in selective organic synthesis. Emphasis is placed on transformations that are unique to the lanthanides, and that therefore complement existing synthetic methods. Carbon—carbon bond-forming reactions are discussed to the near exclusion of simple functional group transformations. With these considerations in mind, five general areas for review have been identified. After a brief presentation of pertinent chemical and physical properties of the lanthanides, the chemistry of cerium reagents and their unique role in organic synthesis is discussed. This is followed by a section on organoytterbium reagents. In the third part, the application of samarium diiodide as a reductive coupling agent for organic substrates is presented. The current role of lanthanide reagents as catalysts in carbon—carbon bond-forming reactions is then outlined. Finally, less highly developed applications of lanthanides to organic synthesis are condensed into the final section.

A. Occurrence and Isolation of the Lanthanides

Lanthanides are often referred to as the 'rare earths', although as depicted in Table 1[3] only one of these elements might be referred to as truly rare. That single exception is promethium, which does not occur naturally.

Although there are many ores containing traces of the lanthanides, three minerals constitute the primary industrial source of these elements; bastnasite, monazite, and xenotime[4]. Bastnasite is a lanthanide fluorocarbonate, and is composed largely of cerium, lanthanum, neodymium, and praseodymium ('light' lanthanides). Monazite is a thorium-containing lanthanide phosphate which occurs in placer deposits and, like bastnasite, contains relatively little of the 'heavy' lanthanides (Sm to Lu). Xenotime also occurs in placer deposits. It is an yttrium phosphate ore and is made up largely of yttrium and the 'heavy' lanthanides, with the 'light' lanthanides making up a much smaller fraction.

The lanthanides are typically separated from other elements occurring in these ores by precipitation of lanthanide oxalates or fluorides from nitric acid solution[5]. Because the lanthanides occur together in ore deposits and are so similar in size and chemical properties, separation from one another is a non-trivial problem. Cerium and europium are generally first removed, since these metals are readily converted to unique, stable oxidation states allowing separation from the other lanthanides. Thus, cerium is typically oxidized to cerium(IV) and separated by precipitation or by solvent extraction. Europium is removed by reduction to europium(II) and precipitation as $EuSO_4$. Counter-current two-phase extraction through a chain of 50–100 cells is then necessary to accomplish clean separation of the remaining lanthanides. Owing largely to their importance in industry, all of the lanthanides are now readily available in very pure form at reasonable cost for use by organic chemists.

B. Toxicity

Unlike many of their Main Group and transition metal counterparts, inorganic lanthanide compounds are generally classified as non-toxic when introduced orally

TABLE 1. Natural abundance of lanthanide elements in the lithosphere relative to some other elements

Lanthanide	Abundance (ppm)	Element	Abundance (ppm)
Cerium	60	Chromium	100
Yttrium	33	Nickel	75
Lanthanum	30	Zinc	70
Neodymium	28	Copper	55
Lutetium	10	Beryllium	28
Praseodymium	8.2	Cobalt	25
Samarium	6	Lithium	20
Gadolinium	5.4	Lead	12.5
Ytterbium	3.0	Boron	10
Dysprosium	3.0	Tin	2
Erbium	2.8	Molybdenum	1.5
Europium	1.2	Tungsten	1.5
Holmium	1.2	Cadmium	0.2
Terbium	0.9	Mercury	0.08
Thulium	0.5	Silver	0.07
Promethium	—	Gold	0.004

TABLE 2. Toxicity of some lanthanide compounds (LD_{50} per oral dose, in mg kg^{-1})

Lanthanide	Nitrate[a]	Chloride[b]	Oxide[c]
Lanthanum	4500	4200[d]	> 10000
Cerium	3600–4200	5277	> 5000
Praseodymium	3500	4500	> 1000
Neodymium	2750	3692–5250	> 1000
Samarium	2900	> 2000	> 1000
Europium	> 5000	5000	> 1000
Gadolinium	3805–5000	> 2000	> 1000
Terbium	> 5000	3631–5100	> 1000
Dysprosium	3100	5443–7650	> 1000
Holmium	3000	5165–7200	> 1000
Erbium	—	4417–6200	> 1000
Thulium	—	4294–6250	> 1000
Ytterbium	3100	4836–6700	—
Lutetium	—	7100	> 1000

[a]Water-soluble salt. Toxicity determined in rats.
[b]Water-soluble salt. Toxicity determined in mice unless noted otherwise.
[c]Water-insoluble. Toxicity determined in rats.
[d]Toxicity determined in rats.

(Table 2)[4,6]. Moderate toxicity is exhibited by lanthanide salts introduced via the intraperitoneal route.

Although toxicity may obviously vary to some extent based on the ligands attached to the metal, in most cases lanthanide complexes are converted to hydroxides immediately on ingestion, and thus have limited absorption through the digestive tract.

C. General Characteristics of the Lanthanides

1. *Oxidation states*

The +3 oxidation state is the most stable oxidation state for all of the lanthanides. Other oxidation states (Ln^{2+} and Ln^{4+}) are accessible for some of these metals, and assume importance in applications to organic synthesis. The most stable alternate oxidation states are formed by elements that can attain empty, half-filled, or filled *f*-shells[3,5]. For example, cerium forms a stable +4 species (f^0) which is highly oxidizing (Table 3)[7], and ammonium cerium(IV) nitrate in particular has been utilized extensively as a useful oxidant of organic substrates[1d,e,8]. The +4 oxidation states of terbium (f^7) and praseodymium (f^1) are much less stable relative to that of cerium.

As indicated above, several lanthanides possess accessible +2 oxidation states. Of particular importance are those of europium (f^7), ytterbium (f^{14}), and samarium (f^6). As expected, Eu^{2+} and Yb^{2+} are the most stable of the dipositive species, whereas Sm^{2+} is a powerful one-electron reducing agent (Table 3). The utility of Sm^{2+} as a reductant in organic synthesis is discussed in detail below, and various aspects of its chemistry have previously been reviewed[1].

It is important to note that none of the individual lanthanide elements have both accessible +4 and +2 oxidation states available to them. As a consequence, the type of two-electron redox chemistry on a single metal centre, typical of several transition elements, is not observed in the lanthanides.

TABLE 3. Selected oxidation potentials of lanthanides in aqueous media

Reaction	E^0(V)[a]
$Ce^{3+} \rightleftharpoons Ce^{4+} + e^-$	+1.74
$Pr^{3+} \rightleftharpoons Pr^{4+} + e^-$	+3.2
$Sm^{2+} \rightleftharpoons Sm^{3+} + e^-$	−1.55
$Eu^{2+} \rightleftharpoons Eu^{3+} + e^-$	−0.35
$Tb^{3+} \rightleftharpoons Tb^{4+} + e^-$	+3.1
$Tm^{2+} \rightleftharpoons Tm^{3+} + e^-$	−2.3
$Yb^{2+} \rightleftharpoons Yb^{3+} + e^-$	−1.15

[a]Relative to the normal hydrogen electrode.

2. *Other properties of the lanthanides*

It is the special combination of inherent physical and chemical properties of the lanthanides that sets them apart from all other elements, and promises to provide a unique niche for these elements and their derivatives in organic synthesis. The lanthanides as a group are fairly electropositive (electronegativities ranging from 1.10 for lanthanum to 1.27 for lutetium on the Pauling scale[3]) and the chemistry of these elements is predominantly ionic. This is a consequence of the fact that the $4f$ electrons do not have significant radial extension beyond the filled $5s^2 5p^6$ orbitals of the xenon inert gas core[2b]. The lanthanides therefore appear like closed-shell inert gases with a tripositive charge, and in general electrostatic and steric interactions play a greater role in the chemistry of the lanthanides than do interactions between the metal and associated ligand orbitals[2b,9].

The f orbitals do play a bonding role in complexes in which the coordination number is higher than 9. Compared with the transition metals, the ionic radii of the lanthanides are large[3]. For example, the ionic radius for a typical eight-coordinate lanthanide species is approximately 1.2 Å. Divalent species are, of course, even larger; eight-coordinate Sm^{2+} has an ionic radius of 1.41 Å, for example. For comparison, most transition metal ionic radii lie in the range 0.6–1.0 Å. The relatively large ionic radii of the lanthanides allows the accommodation of up to 12 ligands in the coordination sphere, and coordinations numbers of 7, 8, and 9 are common. Owing to the well known 'lanthanide contraction', ionic radii decrease steadily as one moves across the row of lanthanides in the Periodic Table (from 1.30 Å for eight-coordinate La^{3+} to 1.117 Å for eight-coordinate Lu^{3+})[3]. The lanthanide contraction is a consequence of poor shielding of the $4f$ electrons, resulting in an increase in effective nuclear charge and a concomitant decrease in ionic radius. As might be expected, higher coordination numbers are most common in the larger, early lanthanides, whereas for lutetium only the fluoride exhibits a coordination number greater than 6.

According to the concept of hard and soft acids and bases (HSAB) established by Pearson[10], lanthanide +3 ions are considered to be hard acids, falling between Mg^{2+} and Ti^{4+} in the established scale. Lanthanides therefore complex preferentially to hard bases such as fluoride and oxygen-donor ligands. This property of the lanthanides has been exploited extensively in terms of their use shift reagents for n.m.r. studies[11], and in effective promotion of Lewis acid-catalysed processes (see Section V).

The strong affinity of lanthanides for oxygen is further evidenced by the bond dissociation energies (D_0^0) for the gas-phase dissociation of diatomic lanthanide oxides (LnO, Table 4)[12].

TABLE 4. Gas-phase dissociation energies of selected lanthanide oxides

Lanthanide oxide	Dissociation energy, D_0^0 (kJ mol^{-1})
LaO	795
CeO	787
PrO	737
SmO	569
EuO	469
YbO	398

As can be seen, most of the values lie between 580 and 795 kJ mol^{-1}, and even the lowest (YbO, 398 kJ mol^{-1}) is higher than that for MgO (362 kJ mol^{-1}). This demonstrated oxophilicity (strong metal—oxygen bonds and hard Lewis acid character) has been used to great advantage in organic synthesis. As described below, these properties have been exploited extensively to enhance carbonyl substrate reactivity, and also to control stereochemistry in carbonyl addition reactions through chelation.

II. CERIUM REAGENTS

The relatively high natural abundance of cerium and the corresponding low cost of the metal and its derivatives have made cerium reagents attractive tools for organic synthesis. The pioneering work of Imamoto and coworkers in particular has enlightened the synthetic organic community to the many advantages of organocerium reagents in carbon—carbon bond-forming processes. Consequently, useful processes have emerged from studies of organocerium(III) compounds derived from corresponding organolithium or organomagnesium reagents and cerium(III) halides. Reductive coupling processes promoted by cerium metal and low-valent cerium compounds have also been examined, and provide promising procedures for inducing carbon—carbon bond formation. Finally, cerium(IV) oxidants have been utilized in oxidative carbon—carbon bond-forming processes. These topics are discussed in the following sections, and provide some insight into the vital role that cerium reagents have assumed in selective organic synthesis.

A. Preparation and Utility of Cerium Reagents Derived from Corresponding Magnesium or Lithium Reagents and Cerium(III) Halides

Although Grignard and organolithium reagents are certainly the most convenient and widely utilized carbon nucleophiles, their basicity and high reactivity towards many electrophiles render them ineffectual for a variety of desirable applications. As described below, the unique characteristics of organocerium reagents have insured a place within the arsenal of synthetic organic chemists for these highly selective nucleophiles.

1. Preparation and use of organoceriums in carbonyl addition reactions

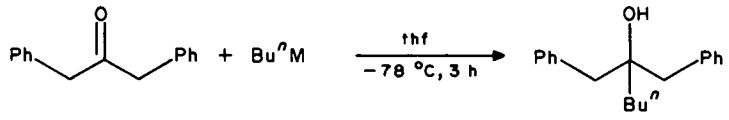
Imamoto and coworkers were the first to recognize that the attenuated basicity and high oxophilicity of organocerium reagents could be utilized to great advantage within the context of selective synthetic organic transformations. Organocerium reagents can be generated by treatment of organolithium reagents with readily available CeI_3 or $CeCl_3$ at

$-65\,°C$ (equation 1)[13].

$$RLi + CeX_3 \xrightarrow[-65\ °C]{thf} 'RCeCl_2' + LiX \quad (1)$$

Alkyl (primary, secondary, and tertiary), alkenyl, alkynyl, allyl, and aryl organocerium compounds can all be prepared by this transmetalation procedure. Reagents prepared in this manner are not isolated, but rather utilized as prepared *in situ*. Little is known of the structure of these molecules or the exact nature of the reactive species. Although they have been denoted as σ-alkyl species ('$RCeX_2$'), certainly other compositions (e.g. 'ate' complexes[2] or species resulting from Schlenk-type equilibria) cannot be ruled out. Regardless of the true nature of the reactive nucleophiles, these reagents react efficiently with aldehydes and ketones, providing the corresponding alcohols in yields that are often superior to those reported utilizing Grignard or organolithium reagents (equation 2)[13].

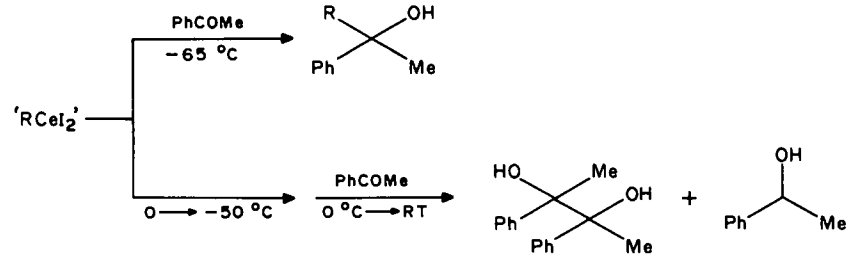
Organoceriums are perhaps not unique among the lanthanides in serving as suitable alternatives to Grignard reagents and organolithiums for certain carbonyl addition reactions (see Section VI)[13]. However, the low cost of cerium compounds and the demonstrated success of organocerium reagents have inhibited investigations into use of other lanthanide salt precursors.



(2)

Bu^nLi–$CeCl_3$	96%
Bu^nLi	33%
Bu^nMgBr	10%

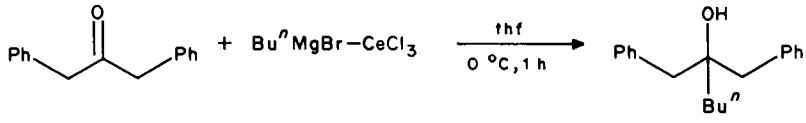
Careful attention must be paid to temperature in reactions utilizing organocerium reagents which possess β-hydrogens. When such reagents prepared from organolithiums are warmed to 0 °C and treated with acetophenone, reductive coupling and/or simple reduction processes predominate (equation 3)[13b]. The pinacol and reduction products observed with alkylceriums apparently arise from low-valent cerium or cerium hydride species which are generated by a β-hydride elimination process. Reagents prepared from methyllithium and phenyllithium, which cannot suffer β-hydride elimination, undergo exclusive 1,2-addition to ketones even at elevated temperatures.



(3)

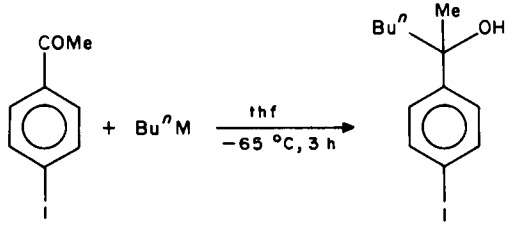
Interestingly, reagents prepared from Grignard reagents and cerium(III) salts actually perform best at elevated temperatures (equation 4), with no formation of by-products from reductive processes[13a,14]. It is clear that the constitution of cerium reagents is much more

complex than indicated by the simple equation for transmetalation from organolithium or corresponding Grignard reagents.



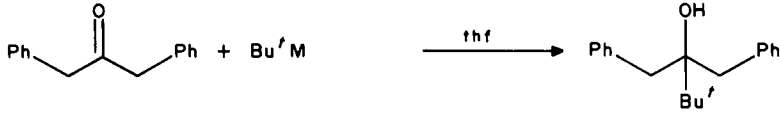
(4)

Unlike their more reactive organolithium precursors, organocerium reagents exhibit excellent chemoselectivity towards a number of functional groups. Addition to aldehydes and ketones can thus be carried out in the presence of halides, esters, epoxides, amines, acetals, amides, and nitriles (equation 5). One of the unique features of organocerium reagents is their ability to provide clean carbonyl addition to substrates which are highly susceptible to enolization with more basic Grignard or organolithium reagents (equations 6 and 7)[13–15].



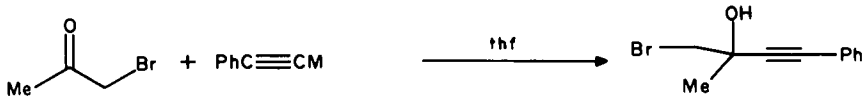
(5)

Bu^{n}Li–CeI$_3$	99%
Bu^{n}Li	<1%



(6)

Bu^{t}Li–CeCl$_3$	(–78 °C, 3 h)	65%
Bu^{t}MgCl	(0 °C, 8 h)	0%



(7)

PhC≡CLi–CeCl$_3$	(–78 °C, 3 h)	95%
PhC≡CMgBr	(–78 °C, 2 h)	7%

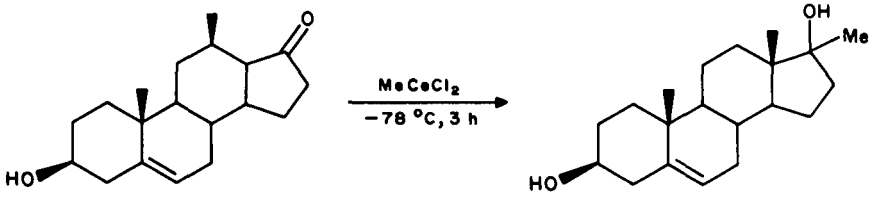
The propensity of organolithium and especially Grignard reagents to undergo competitive reduction and enolization reactions with sterically encumbered ketones inhibits the generation of many tertiary alcohols. Once again, the use of organocerium reagents has been demonstrated to be superior in this regard, allowing the construction of

highly hindered tertiary alcohols in synthetically useful yields (equation 8)[14].

$$Pr^{i}{}_{2}CO + Pr^{i}M \xrightarrow[0\ ^{\circ}C,\,1\ h]{thf} Pr^{i}{}_{3}COH \qquad (8)$$

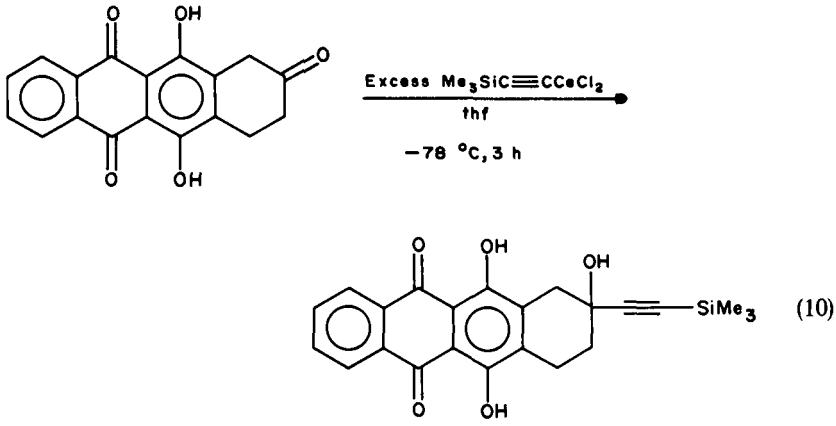
$Pr^{i}MgCl-CeCl_3$	52%
$Pr^{i}MgCl$	3%

The demonstrated success of organocerium reagents in accomplishing clean carbonyl addition with these relatively simple substrates has prompted their application to the synthesis of more complex products. For example, treatment of dehydroisoandrosterone with '$MeCeCl_2$' generates 17-methylandrost-5-ene-3,17-diol in nearly quantitative yield (equation 9)[15]. Use of MeMgI provided the same product in only 65% yield[16].



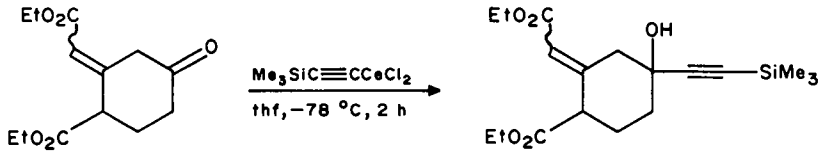
(9)

Organocerium reagents have also recently been applied to the construction of anthracyclinones. Suzuki *et al.*[17] found alkynylcerium reagents to be preferable to organomagnesium reagents in the conversion of a tetracyclic triketone to the corresponding propargyl alcohol en route to (+)-4-demethoxydaunomycinone (equation 10)[17].



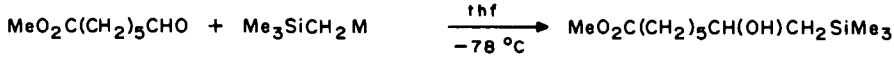
(10)

Utilizing similar chemistry, Tamura *et al.*[18] later found alkynylcerium reagents to be superior to the corresponding alkynyllithium reagents in an alternative approach to the 11-deoxyanthracyclinones (equation 11)[18]. Alkynyllithiums provided only 11% of the desired adduct in this case, together with 73% of recovered starting material. Enolization again predominates to the near exclusion of carbonyl addition. Both examples taken from applications of organocerium chemistry to anthracyclinone chemistry attest to the remarkable chemoselectivity of these organometallic reagents, as clean carbonyl addition is accomplished in the presence of esters, enoates, and even less reactive ketone carbonyls.



82% (11)

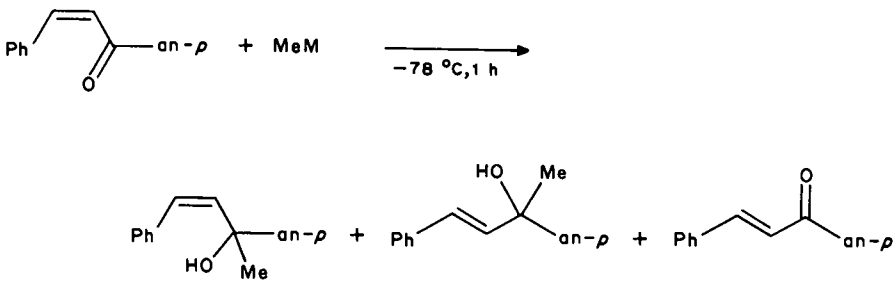
Johnson and Tait[19] reported an important modification of the Peterson reaction which utilizes organocerium reagents in place of the more common organolithium or organomagnesium reagents. In all cases studied involving substrates with enolizable aldehydes or ketones, the Me_3SiCH_2Li–$CeCl_3$ protocol provided higher yields than those of Me_3SiCH_2MgX–$CeCl_3$, Me_3SiCH_2Li, or Me_2SiCH_2MgX (equation 12).



Me_3SiCH_2Li–$CeCl_3$	72%
Me_3SiCH_2Li	36%

(12)

Another prominent feature of organocerium reagents which has been exploited in synthesis is their tendency to provide predominant 1,2-addition in reactions with conjugated aldehydes and ketones (equation 13)[13b,14,20]. The reaction depicted has mechanistic implications. The lack of isomerization in the organocerium 1,2-addition product indicates addition by direct nucleophilic attack as opposed to electron transfer pathways. According to Cohen's *et al.* model describing the role of ion-pairing in 1,2- vs 1,4-addition to enones, the organocerium reagents presumably exist and react through contact ion pairs rather than solvent-separated ion pairs under these reaction conditions[21].

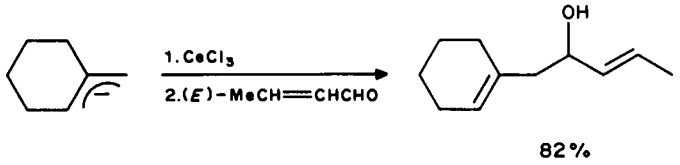


MeLi–$CeCl_3$	(thf–Et_2O)	97%	<1%	<1%
MeLi	(thf–Et_2O)	96%	<1%	<1%
MeMgBr	(thf)	20%	26%	38%

(13)

Allylcerium reagents prepared by transmetalation from the corresponding allyllithium reagents show some of the same characteristics of reactivity toward carbonyl substrates as

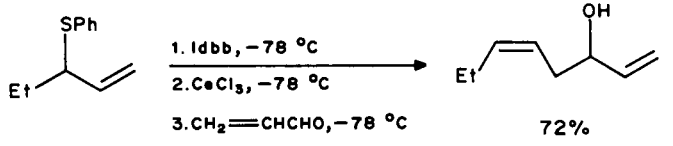
their alkylcerium counterparts, such as exclusive 1,2-addition to unsaturated aldehydes and ketones[22]. Further, they exhibit reactivity patterns unique from those of many other allylmetallic reagents. For example, most allylmetallic nucleophiles add to aldehydes and ketones only at the most substituted terminus of the allyl unit. In contrast, allylcerium reagents react with a variety of carbonyl substrates to provide products resulting from predominant reaction at the least substituted end of the allylmetallic system, regardless of the substitution pattern about the allylcerium starting material (equation 14).



(14)

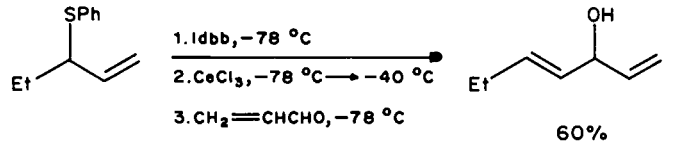
The observation of this unusual regiochemistry has been attributed to the structure of the allylcerium reagents and the high oxophilicity of the metal in these systems. The thermodynamically most favorable isomer of σ-bonded allylmetallics places the metal at the least sterically hindered terminus of the allylic system. Reactions with aldehydes and ketones occurs through a six-membered transition state, with the metal serving as a Lewis acid promoter. This mechanism results in a carbonyl addition in which the most substituted end of the allyl system becomes bonded to the carbonyl substrate. By utilizing allylcerium reagents, which are likely to be trihapto-bonded rather than σ-bonded to the allyl unit, direct 1,2-addition occurs at the least sterically hindered position of the allyl moiety.

The reversal of regiochemistry can be utilized to advantage in generating both *cis* and *trans* homoallylic alcohols with a high degree of stereochemical control. Allyl anions (prepared by reaction of allylic thiophenoxides with lithium *p,p'*-di-*tert*-butylbiphenylide, ldbb) are kinetically generated in the *cis* configuration. By maintaining this geometry in the transmetalation reaction, one can take advantage of the unique regiochemical outcome of the allylcerium carbonyl addition reactions to construct *cis* homoallylic alcohols (equation 15).



(15)

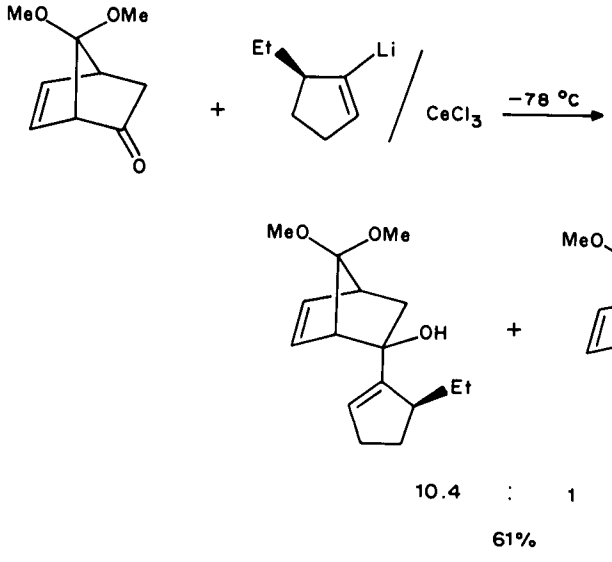
Equilibration of the allylcerium π-complex to the thermodynamically more stable *trans*-allylceriums then allows the generation of the corresponding *trans* isomers (equation 16). This unprecedented display of stereochemical and regiochemical control can be applied iteratively to produce biologically important skipped polyenes.



(16)

Surprisingly, little has been done to determine diastereoselectivity in the addition of organocerium reagents to chiral aldehydes and ketones. In one such study, Paquette and

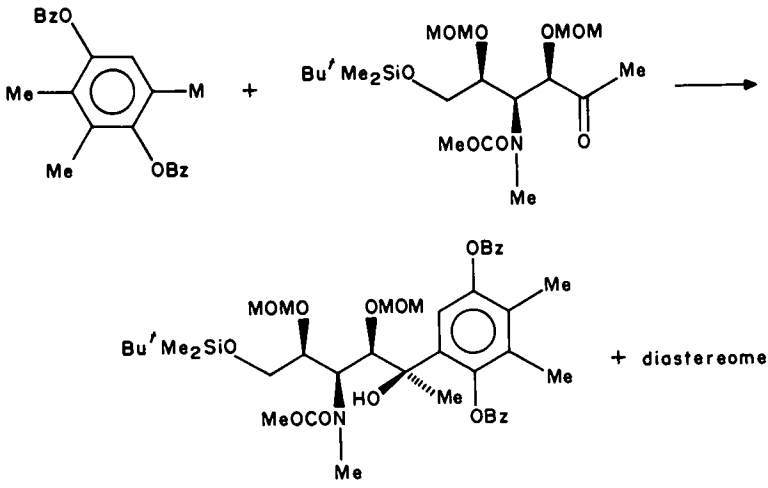
coworkers examined the addition of alkenylcerium reagents to chiral β,γ-unsaturated ketones[23]. Organocerium reagents were chosen because corresponding organolithium reagents proved of little value owing to excessive enolization in attempted carbonyl additions. The extent to which stereochemical control in the organocerium additions can be achieved when the carbonyl group is only remotely perturbed is impressive in these examples (equation 17). The observed diastereoselectivity is attributed to non-bonded steric interactions in transition states leading to the product, although other factors cannot be readily dismissed.



(17)

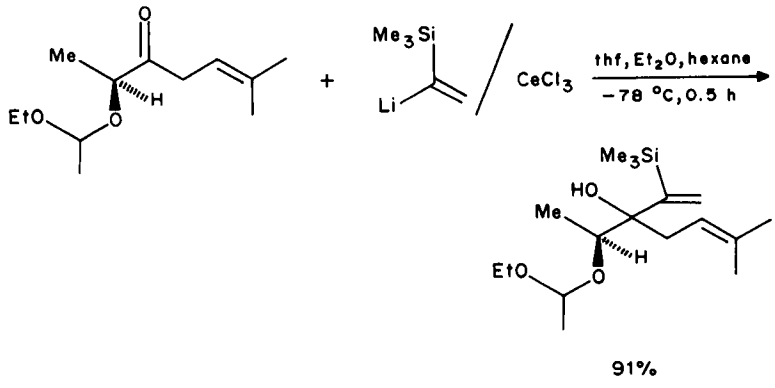
The question of chelation control versus Felkin–Ahn addition of organocerium reagents to α-oxygenated carbonyl substrates has so far been addressed in very few examples. Unexpectedly, in one system the organolithium reagent provides the product resulting from chelation control, whereas the organocerium reagent appears to proceed through a transition state corresponding to the Felkin–Ahn model (equation 18)[24]. Another α-heterosubstituted ketone provides a 1:1 mixture of diastereomers in reaction with an alkenylcerium reagent (equation 19)[25]. Although in this case organolithium and organomagnesium reagents generate the same products in less than 40% yield, the lack of stereoselectivity for the organocerium reaction is still disappointing. A more systematic investigation to determine diastereoselectivity in addition of organoceriums to chiral aldehyde and ketone substrates is clearly warranted.

Two reports have appeared in which the chemistry of cerium enolates is delineated. Imamoto and coworkers have described crossed-aldol reactions which proceed in high yields, even in cases where the substrates are prone to enolization (equation 20)[26]. Presumably, retro-aldol and cross enolization processes are inhibited in these reactions owing to the formation of a tightly chelated cerium aldolate intermediate. Stereoselectivity in the cerium enolate aldol reactions is nearly identical with those of the corresponding lithium enolates. This implies that transmetalation occurs with retention of enolate geometry, and that the aldol reaction itself proceeds through the familiar six-membered ring transition state.



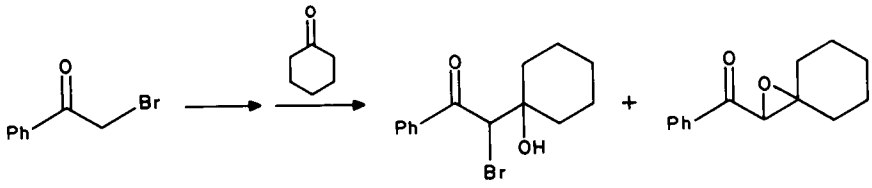
(18)

M=Li	74%	8	:	1
M=Li–$CeCl_3$	95%	1	:	15



(19)

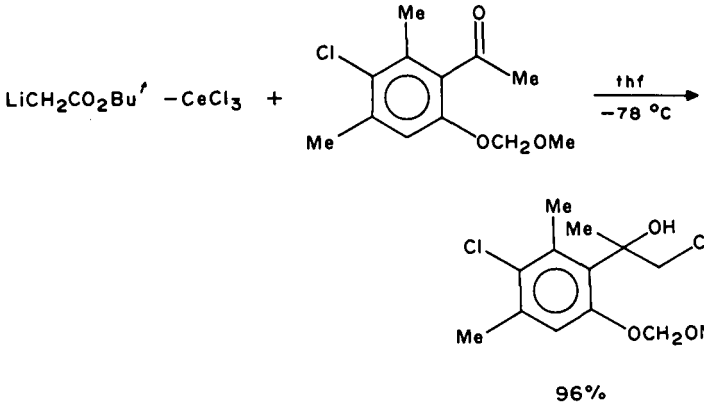
91%



Ihmds–$CeCl_3$	75%	8%
Ihmds	trace	trace

(20)

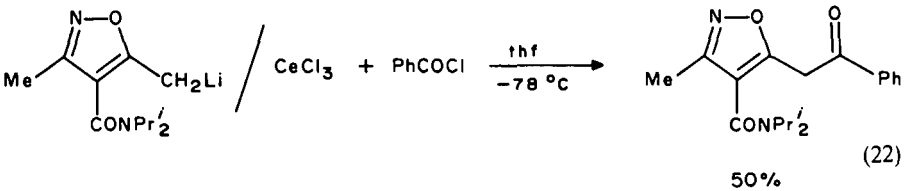
Cerium ester enolates have also found utility in organic synthesis. With carbonyl electrophiles which display high susceptibility to enolization utilizing lithium ester enolate nucleophiles, cerium enolate counterparts are found to produce the desired products in nearly quantitative yields (equation 21)[27].



(21)

2. Reaction of organoceriums with other electrophiles

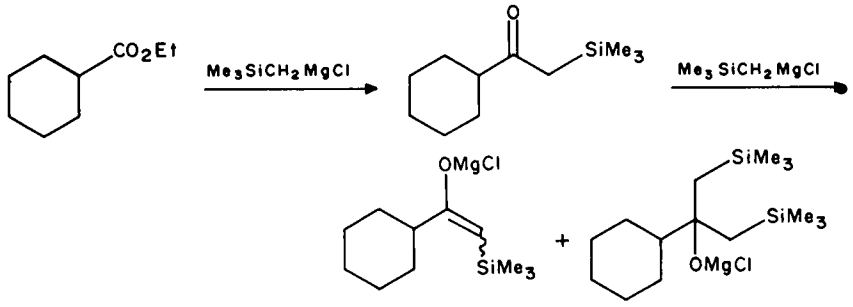
Transformations other than carbonyl addition reactions employing organocerium reagents have been reported. For example, cerium trichloride has been utilized in nucleophilic acyl substitution reactions to moderate the reactivity of organolithium reagents, permitting the chemoselective generation of ketones (equation 22)[28].



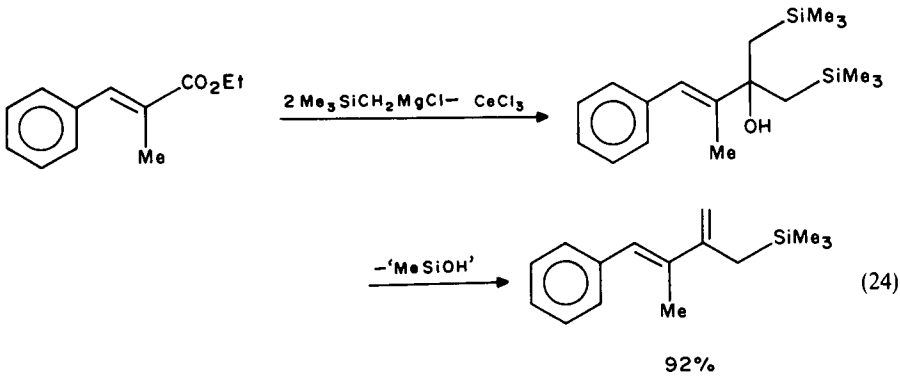
(22)

The ability of organocerium reagents to react with readily enolizable ketones has been exploited to advantage in synthesizing allylsilanes from carboxylic acid derivatives. Nucleophilic acyl substitution, followed by nucleophilic carbonyl addition to the resulting ketone, and finally an elimination of 'Me_3SiOH' is required for the desired transformation. Trimethylsilylmethylmagnesium chloride has been utilized to achieve this transformation; however, the yields are typically low owing to competitive enolization in the second step of the process (equation 23)[29]. The reagent derived from trimethylsilylmethylmagnesium chloride and $CeCl_3$ allows the clean conversion of a variety of esters to the tertiary alcohol, and subsequent elimination provides allylsilanes (equation 24)[30].

Curiously, reagents derived from trimethylsilylmethyllithium and $CeCl_3$ show different properties in this process[31]. Thus, whereas the organolithium-derived reagents react poorly with esters (with unreacted starting material remaining), they provide excellent overall yields in reactions with carboxylic acid chloride substrates (equations 25 and 26). This again demonstrates the dramatic differences displayed in organoceriums prepared from organomagnesium reagents on the one hand and organolithium reagents on the other.

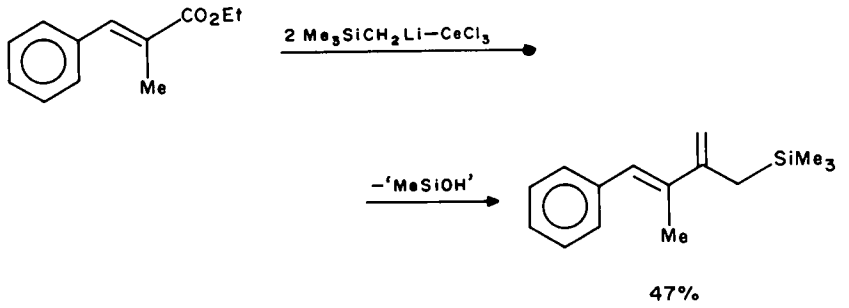


(23)



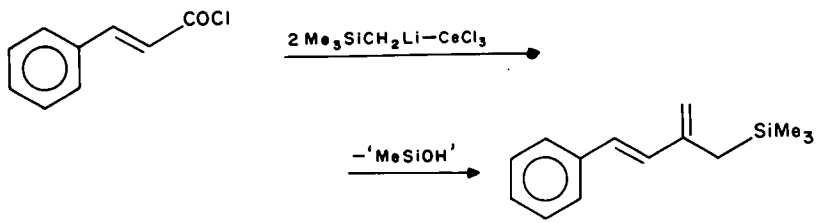
(24)

92%



(25)

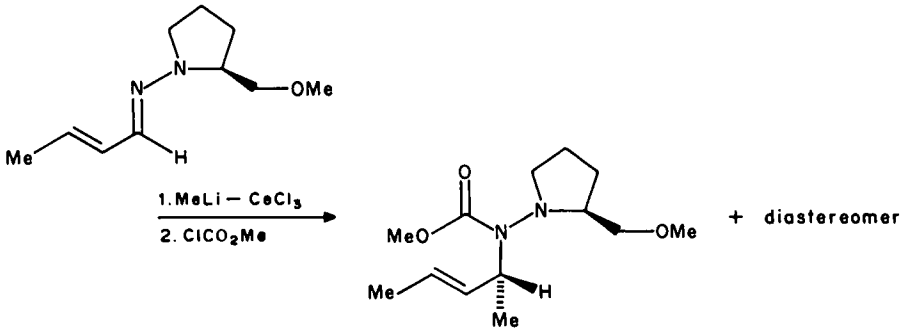
47%



(26)

90%

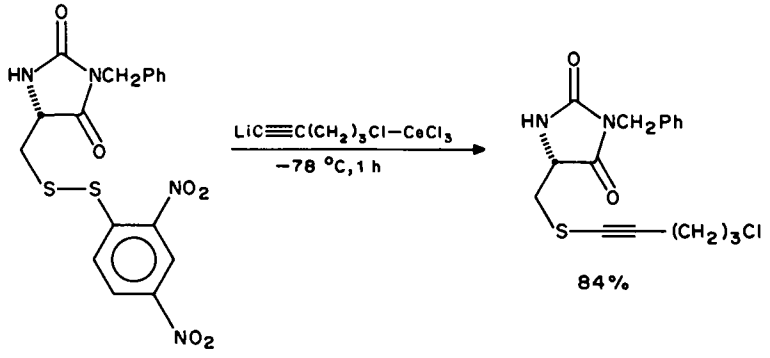
Denmark *et al.*[32] reported a general synthesis of chiral, non-racemic amines utilizing addition of organoceriums to samp hydrazones. These reagents add to chiral hydrazones in good yields and high diastereoselectivities (equation 27). Attempts to utilize other organometallics (e.g. RLi, RMgX, or R_2CuLi) in this process failed, with competitive enolization a major problem in many cases. Subsequent conversions lead to the amines.



(27)

The sense of asymmetric induction is explained by coordination of '$RCeCl_2$' to the methoxymethyl group of the hydrazone, with delivery to the *re* face of the electrophile. Little enolization occurs in systems susceptible to this phenomenon, and exclusive 1,2-addition to conjugated systems is reported. A variety of organoceriums (alkyl, alkenyl, and aryl) ultimately derived from both organomagnesium and organolithium reagents are suitable for the reaction. Of the nucleophiles examined, only an alkynyllithium-derived reagent failed to add to the hydrazone. The involvement of organocerium reagents was indicated by the fact that pre-complexation of one of the hydrazones with $CeCl_3$, followed by addition of MeLi, resulted in poor yields (28%) of the desired product.

Substitution reactions on disulfides have also proved effective when carried out utilizing organocerium reagents. Corey and Mehrotra utilized an alkynylcerium reagent to cleave cleanly a chiral, non-racemic disulfide substrate (equation 28)[33]. The resulting alkynyl sulfide was a key intermediate in the synthesis of (+)-biotin.



(28)

B. Direct Methods for Formation of Carbon—Carbon Bonds Utilizing Cerium Reagents

Whereas transmetalation reactions provide one convenient entry to organocerium reagents, it is often more efficient to utilize cerium metal or cerium salts in conjunction with organic halides or other organic substrates for the purpose of generating nucleophilic species by more direct routes. Indeed, several different approaches have been successfully developed along these lines, providing useful alternatives to current methodologies.

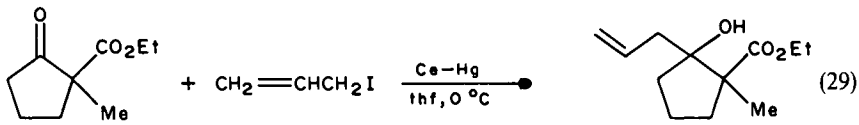
Reductive processes which utilize cerium metal or 'low-valent' cerium salts have been developed to the greatest extent. Cerium metal is reported to be less reactive towards functionalized organic substrates than lithium, magnesium, or many of the other lanthanides. As a consequence, reactive organic substrates (e.g. aldehydes, α-halo esters, and allylic or benzylic halides) and some form of activation of the metal are usually required for successful reaction. Cerium(II) species have been postulated as intermediates in many of these reductive processes. However, no such species have previously been characterized, and the lack of structural and mechanistic work in reported studies makes this assertion highly speculative[34].

Cerium(III) salts have been utilized to generate cerium enolates directly from α-halocarbonyl precursors, and oxidative carbon—carbon bond formation promoted by cerium(IV) salts has been described. The following section provides details of these diverse processes.

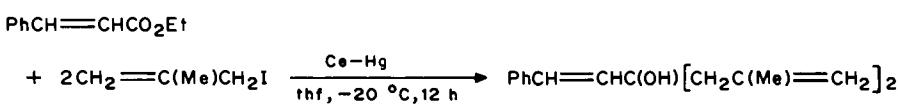
1. Barbier-type coupling reactions

Barbier-type reactions are particularly effective when promoted by cerium amalgam[13b,35]. Nearly all reactions of allylic halides with a variety of aldehydes and ketones proceed smoothly at 0 °C, providing reasonable isolated yields of the corresponding homoallylic alcohols (equation 29). Based on a limited number of examples, it appears that allylic iodide substrates are better than the corresponding allylic bromides in these reactions. A variety of functional groups can be tolerated under the reaction conditions, including esters, nitriles, and aromatic halides. In the absence of more reactive ketone or aldehyde carbonyls, esters can be induced to react under Barbier-type conditions with allylic iodides and cerium amalgam. High yields of the corresponding tertiary alcohols can be obtained (equation 30)[13b].

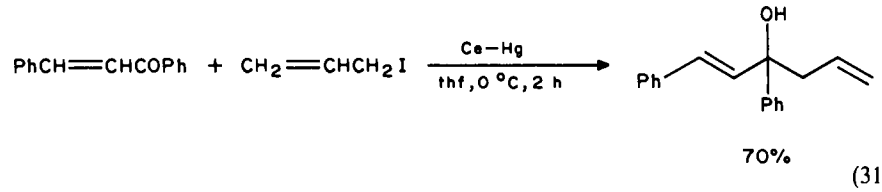
Strict 1,2-addition is realized in reactions of allylic halides with conjugated ketones (equation 31). Mixtures of regioisomeric homoallylic alcohols result when substituted allylic halides are utilized in these reactions (equation 32)[13b,35]. Although direct



(29)

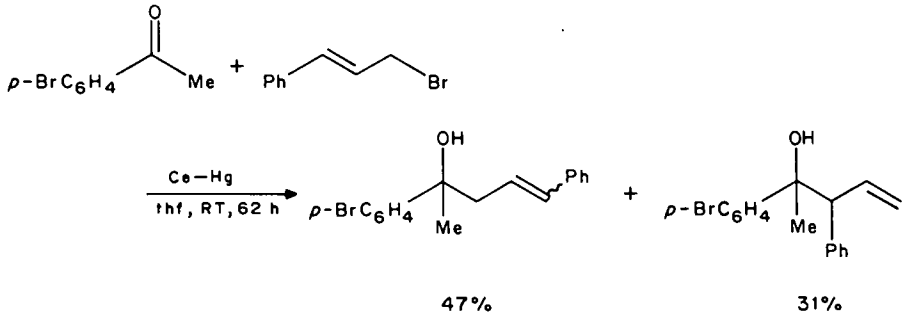


(30)



70%

(31)

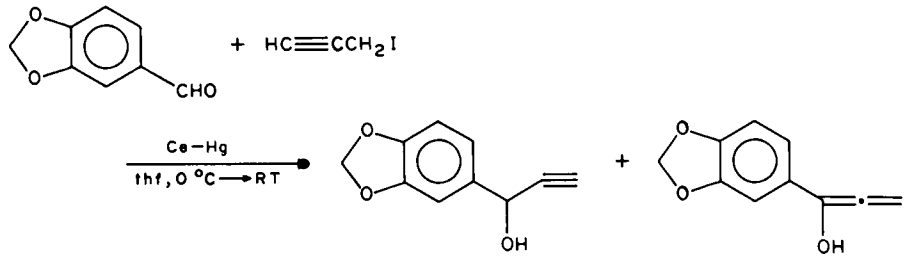


47% 31%

(32)

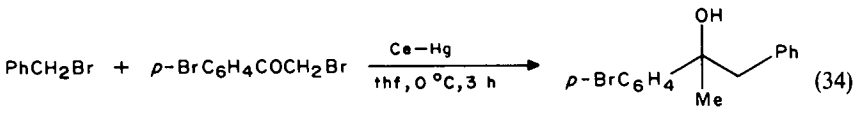
comparison is not possible, it is interesting that the major product is generated as a result of reaction at the least substituted terminus of the allylic system, as in the system described by Guo *et al.*[22]. Propargyl iodides provide mixtures of propargyl alcohol and the allenyl alcohol isomer (equation 33)[13b].

Benzylic halides can also be utilized in various coupling reactions (equations 34–36). Little information is available on the reaction manifold followed in equation 34. In fact, several different pathways to the observed product could be suggested, none of

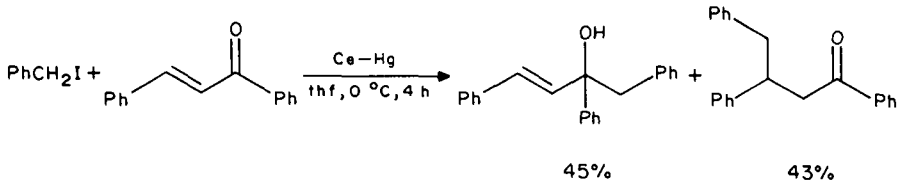


62% 23%

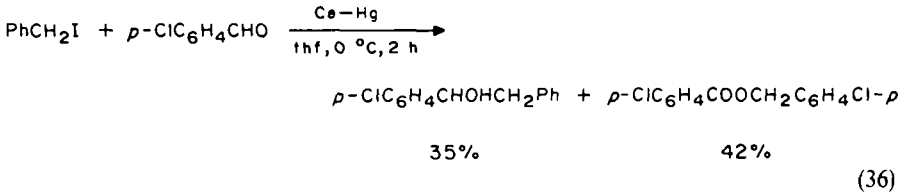
(33)



72% (34)



(35)

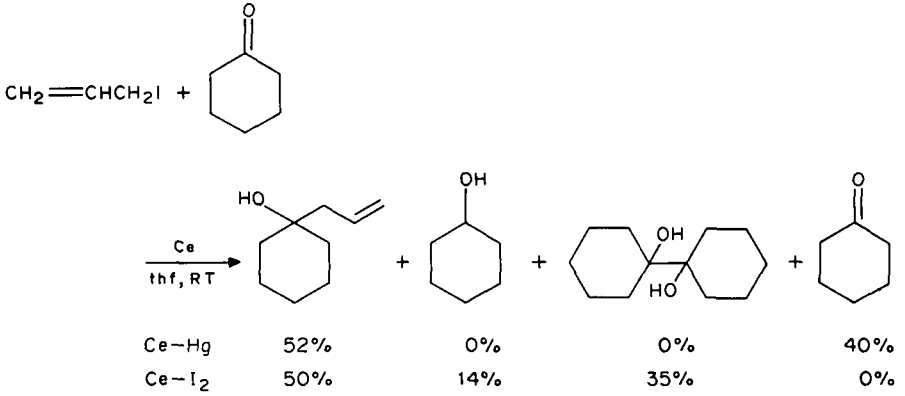


(36)

which can be ruled out based on the information at hand. Both 1,2- and 1,4-addition to conjugated carbonyl substrates are observed in these systems (equation 35), and aromatic aldehydes provide esters as a result of a Tischenko-type reaction with both allylic halide and benzylic halide precursors (equation 36)[13b,22].

The success of cerium-mediated Barbier-type reactions is highly dependent on the method of activation of the cerium metal[36]. For example, cerium amalgam provides very different results to cerium activated by addition of 1 mol% iodine (equation 37). Many by-products were also observed when a two-step procedure was utilized with the iodine-activated cerium[36]. In these latter reactions, where prior formation of a Grignard-type adduct ('RCeI') was postulated, reduction and reductive coupling products were generated in significant amounts, making the reaction of little synthetic value.

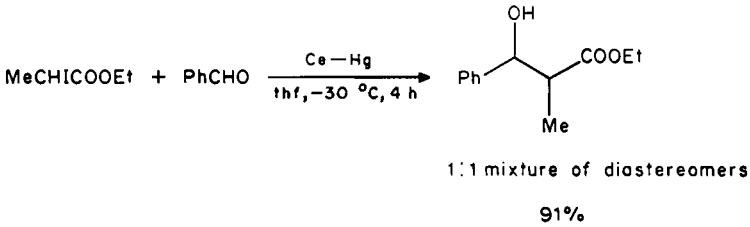
The presence of regioisomers, stereoisomers, and various by-products detracts from the synthetic utility of many of these cerium-mediated Barbier-type reactions.



(37)

2 Reformatsky-type reactions and homoenolate chemistry

The reaction of α-halo esters with ketones or aldehydes in the presence of cerium amalgam generally proceeds at low temperatures, and provides good to excellent yields of the corresponding β-hydroxy esters (equation 38)[13b]. Halide, nitrile, ester, and nitro groups can be tolerated within the ketone or aldehyde electrophiles. Diastereoselectivities in the Reformatsky-type reactions promoted by cerium are poor. In pertinent examples tested to date, the ratio of *erythro* to *threo* diastereomers generated is no greater than 57:43.

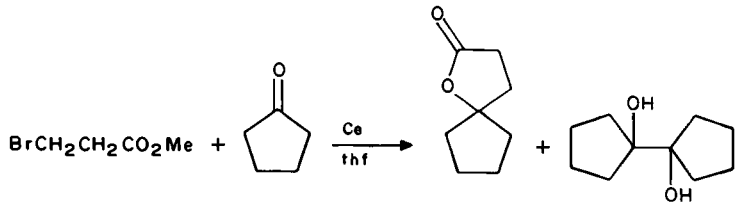


(38)

1:1 mixture of diastereomers

91%

β-Metallo esters have been prepared by direct reaction of corresponding β-halo esters with a variety of lanthanide metals (e.g. La, Ce, Nd, and Sm)[37]. Under the same conditions, use of activated magnesium or zinc metal led to the recovery of the starting materials. Homoenolates generated from β-halo esters and cerium (activated by a trace of iodine) could be coupled to ketones, providing moderate yields of butyrolactones (equation 39). Significant amounts (15–30%) of pinacol by-products were also formed under these conditions. No mention was made of whether cerium amalgam could be utilized to prevent this problem. Nevertheless, the process does provide an alternative to the use of other β-metallo ester nucleophiles.

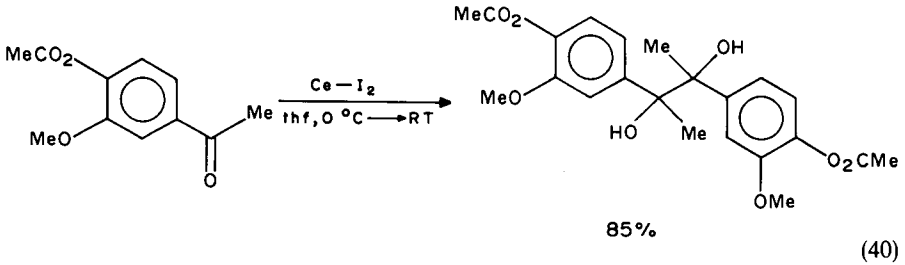


(39)

60% 15%

3. Cerium-promoted pinacolic coupling

Pinacol by-products have been observed in attempted Barbier-type coupling reactions[36] and in Reformatsky-type processes when cerium metal is utilized as the reductant[37]. However, the synthesis of pinacols from ketone or aldehyde precursors utilizing cerium reagents can best be accomplished by utilizing low-valent cerium salts rather than the metal itself[38]. Cerium oxidized with iodine, diiodoethane, or iodobenzene provides excellent yields of pinacol products. Alternatively, CeI_3 reduced with potassium can be utilized as a reductant for the pinacolic coupling. Neither cerium metal nor CeI_3 provides more than a trace of coupled product. A divalent cerium species has been implicated as the active species, although there is little direct evidence to establish this. Utilizing the Ce–I_2 protocol, a variety of aldehydes and ketones have been reductively coupled to provide the desired 1,2-diols (equation 40).

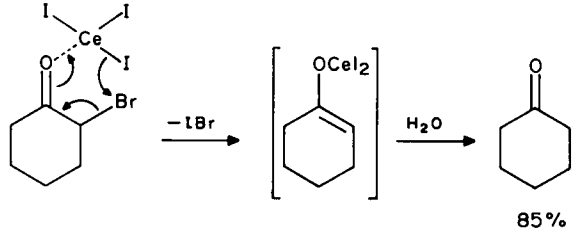


(40)

It is important to note that esters, nitriles, and alkenyl halides can all be tolerated under the reaction conditions, and that both aldehydes and ketones provide excellent yields of the coupled products. Only two exceptions to this general reactivity pattern have been noted so far: benzophenone is unreactive under the conditions utilized and cyclododecanone provides a 70% yield of cyclododecanol rather than undergoing pinacolic coupling.

4. Cerium(III)-promoted enolate chemistry

Treatment of α-halo ketones with cerium(III) salts in aqueous media has been recognized as a convenient method for selective dehalogenation[39]. A cerium enolate is generated and rapidly protonated under these reaction conditions (equation 41). It has



(41)

been determined that the cerium enolate can be trapped by aldehyde electrophiles in an aldol condensation when the reaction is performed under aprotic conditions[40]. The final products are either α,β-unsaturated ketones or β-hydroxy ketones, depending on the nature of the salt utilized. Cerium triiodide provides the unsaturated enones directly in high yields (equation 42).

Treatment of an isolated β-hydroxy ketone with CeI_3 provides the α,β-unsaturated ketone in quantitative yield. This suggests that elimination of the cerium aldolate occurs in the presence of the cerium(III) Lewis acid. Utilizing CeI_3 as the dehalogenating salt, ketones are unreactive as enolate electrophiles. In contrast, $CeCl_3$–NaI mixtures provide aldol products on aqueous work-up, with little or no elimination to unsaturated ketones (equation 43)[40].

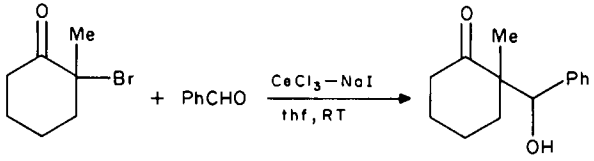
$$PhCOCH_2Br + MeCH{=}CHCHO \xrightarrow[\text{thf, RT, 1 h}]{CeI_3} PhCOCH{=}CHCH{=}CHMe \quad (42)$$

95%

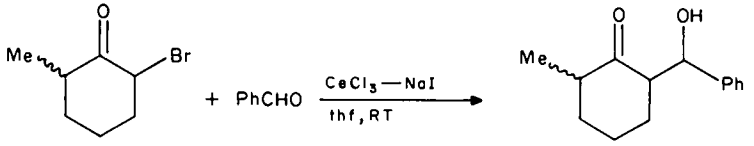
$$PhCOCH_2Br + MeCH{=}CHCHO \xrightarrow[\text{thf, RT}]{CeCl_3\text{–NaI}} PhCOCH_2CH(OH)CH{=}CHMe$$

79% (43)

In instances where diastereomers can be generated in these aldol reactions, little stereoselectivity is observed (*threo*:*erythro* = 1–1.5:1). Ketone electrophiles provide low yields of the desired aldol products (30–50%), and treatment of ethyl bromoacetate and benzaldehyde with $CeCl_3$–NaI gives no Reformatsky-type coupled product. Reactions are regioselective; no aldol products resulting from retro-aldol or cross-enolization processes could be detected (equations 44 and 45).

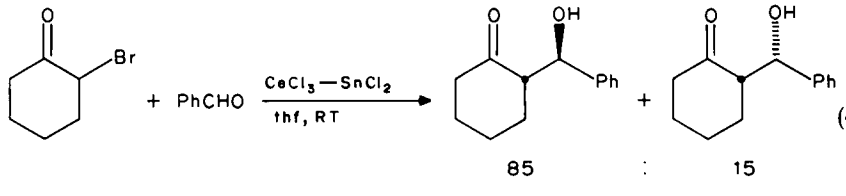


(44)



(45)

Crossed-aldol condensations utilizing $CeCl_3$–$SnCl_2$ provide yet another level of selective reactivity[40]. Improved diastereoselectivity is observed, and a chemoselective aldol condensation to 6-oxoheptanal can be readily achieved utilizing α-bromo ketone precursors (equations 46 and 47). Unfortunately, Reformatsky-type reactions cannot be carried out utilizing this combination of reagents, and α-chloro ketones are also unreactive as cerium enolate precursors under these conditions. A cerium enolate is again implicated by these results since use of $SnCl_2$ alone gives none of the coupled product, and reaction of 2-bromocyclohexanone with benzaldehyde in the presence of low-valent tin ($SnCl_2$–$LiAlH_4$) affords the *erythro*-aldol product in low yields[41].



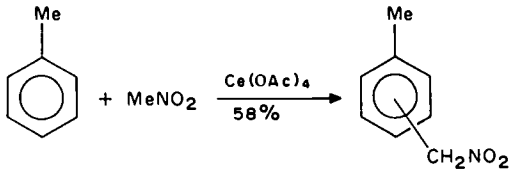
(46)

$$PhCOCH_2Br + MeCO(CH_2)_4CHO \xrightarrow[thf,\ RT]{CeCl_3\text{–}SnCl_2} PhCOCH_2CH(OH)(CH_2)_4COMe \qquad (47)$$

5. *Oxidative carbon—carbon bond formation promoted by cerium(IV) salts*

Although various cerium(IV) complexes have been utilized routinely for the oxidation of a variety of organic substrates[1d,e,8], these salts have been incorporated into few schemes in which carbon—carbon bonds are generated. Several studies have been performed which indicate that cerium(IV) oxidants are superior to the more frequently utilized

manganese(III) salts for such oxidative conversions. In fact, cerium(IV) reagents are more reactive than manganese(III) oxidants in some reactions of interest[42]. Free-radical aromatic nitromethylation is one process which proceeds readily when mediated by cerium(IV) salts (equation 48)[43].

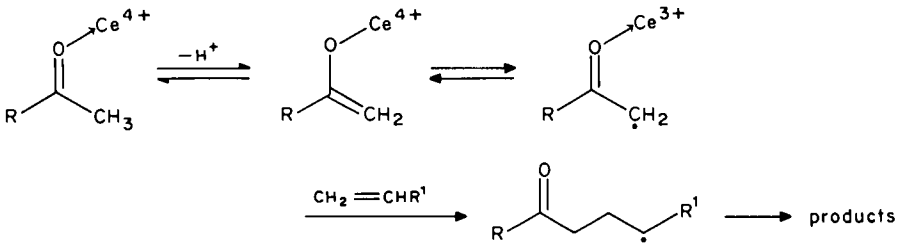


(48)

A number of cerium(IV) salts (as well as other metal salts) were screened as potential replacements for manganese(III) oxidants in this reaction. Ceric(IV) acetate was deemed to be the reagent of choice in these reactions, owing largely to the lack of by-product formation. However, the fact that the light-sensitive $Ce(OAc)_4$ is rather difficult to prepare and store is a drawback. In addition, careful control of the reaction is required in order to prevent oxidation of the initially formed nitromethylation product.

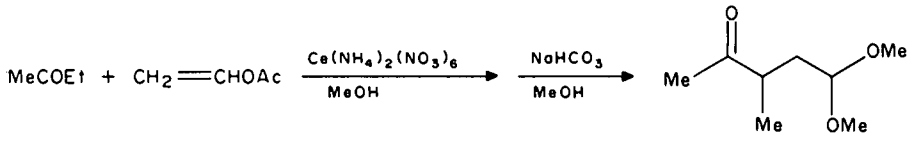
Enolizable ketones can also be readily oxidized by $Ce(OAc)_4$ to a radical which rapidly adds to olefins. The newly generated radical may suffer hydrogen abstraction from the solvent. Alternatively, oxidation to a cation can occur, with subsequent loss of a proton or entrapment by acetate (equation 49)[42]. Owing to the electron-withdrawing nature of the carbonyl, the initially formed radical is not further oxidized, allowing a selective radical process to occur. Radicals generated by interaction of cerium(IV) oxidants with enolizable ketones apparently exist as cerium(III)-coordinated free radicals, in equilibrium with the cerium(IV)–carbonyl complexes (equation 50)[43].

$$\mathrm{MeCOMe + Hex^nCH{=}CH_2 \xrightarrow[AcOH]{Ce(OAc)_4} MeCO(CH_2)_8Me}$$
$$\mathrm{+ MeCOCH_2CH{=}CHHex^n + MeCO(CH_2)_2CH(OAc)Hex^n} \qquad (49)$$



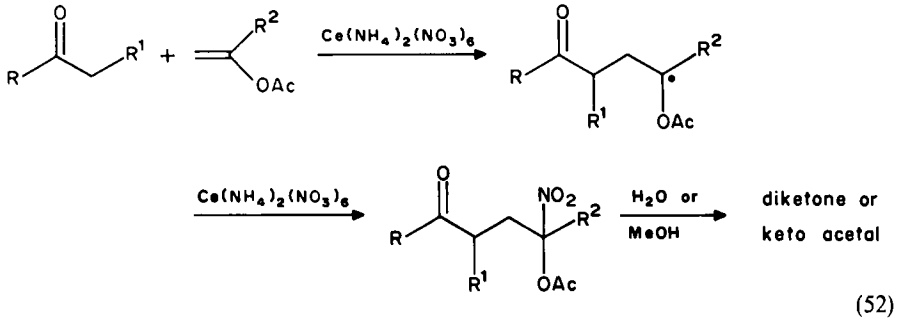
(50)

A version of this olefin oxidative addition process has been adapted to a synthesis of 1,4-dicarbonyl compounds, wherein enol acetates are utilized as the olefin substrates (equation 51)[44]. Unlike $Mn(OAc)_3$-promoted reactions, the major products generated result from oxidation at the more substituted side of the ketone. Furthermore, yields in the ammonium cerium(IV) nitrate-mediated reactions are much higher than those provided by the manganese(III) protocol. The reaction presumably proceeds through an acetoxy nitrate intermediate, which is hydrolysed to the observed product (equation 52).



70%

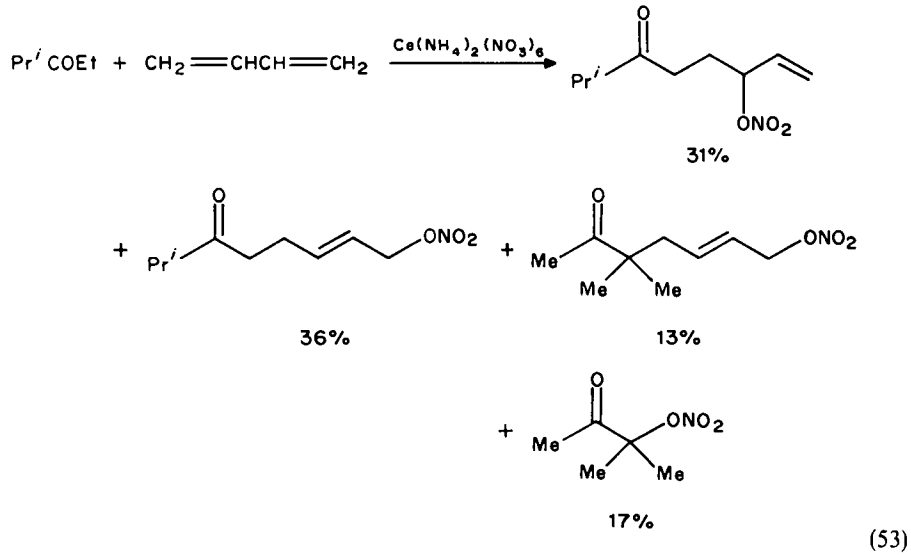
(51)



(52)

Finally, radicals generated by reaction of enolizable ketone substrates with ammonium cerium(IV) nitrate undergo oxidative 1,2- and 1,4-addition to buta-1,3-diene, providing a mixture of unsaturated nitro ketones (equation 53)[43]. Curiously, in this instance the major products result from generation of a radical at the least substituted side of the ketone.

Ammonium cerium(IV) nitrate is very efficient in promoting oxidation of radicals by a ligand transfer mechanism, and thus even in methanol no significant incorporation of the nucleophilic solvent in the reaction products is observed.



(53)

III. ORGANOYTTERBIUM REAGENTS

The chemistry of organocerium reagents applied to organic synthesis is dominated by cerium(III) species, which can be prepared by transmetalation reactions of corresponding organolithium or organomagnesium reagents with cerium(III) halides. Owing to the relatively low cost of cerium reagents and early successes in applications to organic synthesis, organocerium(III) reagents are the dominant carbanion-transfer reagents among the lanthanides. As a result, little exploration of other lanthanide(III) carbanionic reagents has taken place. However, the accessibility of a stable +2 oxidation state for ytterbium leads to the possibility of Grignard-type reagents and chemistry. Indeed, both the methods of preparation and reactions of organoytterbiums reported to date closely mimic those of the corresponding Grignard reagents. In spite of significant study, organoytterbium reagents have really yet to assume a special role in organic synthesis. Nevertheless, some unique reactivity patterns have been observed, and with further systematic study one can expect more of these original reaction manifolds to emerge.

A. Preparation of Organoytterbiums

Organoytterbium(II) halides are most conveniently prepared by oxidative metalation of organic iodides with ytterbium metal (equation 54)[34]. Since an induction period is often noticed in such reactions, activation of the metal with a trace amount of CH_2I_2 can be utilized to facilitate this process[45].

$$RI + Yb \xrightarrow[-20\,^{\circ}C]{thf} RYbI \tag{54}$$

Compounds prepared in this fashion have been determined to consist largely of 'RYbI' stoichiometries, although the possible existence of Schlenk-type equilibria has never been examined. Ytterbium to iodine ratios determined by analysis, the measured magnetic susceptibilities, and the reactivity patterns of these reagents are all consistent with this formulation[34]. From magnetic susceptibilities, the calculated percentage of 'RYbI' generated in solution by this procedure was determined to range from 83 to 93%, depending on the structure of the organic iodide substrate.

Oxidative–reductive transmetalation of ytterbium metal with diorganomercuries has been utilized as an entry to dialkynyl- and polyfluorinated diarylytterbiums (equations 55 and 56)[46]. The dialkynylytterbiums are indefinitely stable in an inert atmosphere at room

$$(Bu^tC{\equiv}C)_2Hg + Yb \xrightarrow[RT,\ 25\,h]{thf} (Bu^tC{\equiv}C)_2Yb + Hg \quad (100\%) \tag{55}$$

$$(C_6F_5)_2Hg + Yb \xrightarrow[RT,\ 4\,h]{thf} (C_6F_5)Yb + Hg \quad (92\%) \tag{56}$$

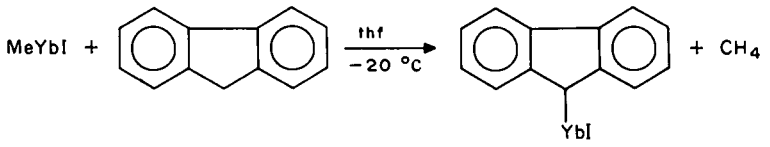
temperature. On the other hand, the polyfluorinated diarylytterbiums exhibit variable stability. The isolated yields are often low owing to thermal decomposition of these organometallics. However, most can be generated in nearly quantitative yields by this procedure and simply characterized *in situ*.

Metal–hydrogen exchange processes have also been exploited to generate dialkynylytterbiums (equation 57)[46b,d]. Clearly, this procedure is of much less synthetic value than

$$(C_6F_5)Yb + 2RC{\equiv}CH \longrightarrow (RC{\equiv}C)_2Yb + 2C_6F_5H \tag{57}$$

the oxidative–reductive transmetalation method described above. Of perhaps greater synthetic utility is the metal–hydrogen exchange reaction of MeYbI with other carbon acids. For example, phenylacetylene and fluorene both react readily to generate reasonable yields of the corresponding organoytterbium iodides (equations 58 and 59)[47]. Triphenylmethane and diphenylmethane do not react under these conditions. Incidentally, methyl Grignard reagents provide far lower yields of metalated products than do organoytterbiums under comparable reaction conditions.

$$MeYbI + PhC{\equiv}CH \xrightarrow[-20\,^{\circ}C]{thf} PhC{\equiv}CYbI + CH_4 \tag{58}$$



(59)

B. Reactions of Organoytterbiums

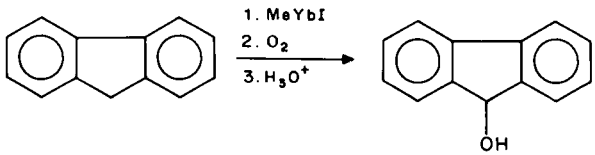
Useful applications of organoytterbium reagents to organic synthesis pale in comparison to those of organocerium reagents described above and to some of the other lanthanide reagents to be discussed. Most reactivity patterns closely follow those of organomagnesium and organolithium reagents. As expected, organoytterbiums are highly sensitive to water. Rapid protonolysis leads to the expected hydrocarbons in most cases[34,46a]. However, hydrolysis of dialkynylytterbiums under a variety of conditions leads not only to the expected alkynes, but also to significant amounts (14–20%) of corresponding alkenes and 1–2% of the alkanes. By utilizing deuterated solvents it has been established that hydrogenation occurs after hydrolysis, rather than by simple cleavage of alkenyl- or alkyl-metallic species contaminating the reaction mixture (equation 60)[46b–d].

Cleavage of bis(pentafluorophenyl)ytterbium with iodine provides nearly quantitative yields of pentafluoroiodobenzene (equation 61) and a trace of material with the composition $C_{12}F_9I$[48]. The latter was ascribed to formation of a benzyne intermediate which added $(C_6F_5)_2Yb$ and then was cleaved by I_2.

Moderate yields of alcohols are obtained when organoytterbium reagents are exposed to oxygen (equation 62)[47]. No other oxidants appear to have been utilized in an attempt to optimize the yields of this process. Carbonation reactions do not fare too much better.

$$2(PhC{\equiv}C)_2Yb \xrightarrow{3D_2SO_4} 3PhC{\equiv}CD + PhCD_2CD_2 + Yb(SO_4)_3 \tag{60}$$

$$(C_6F_5)_2Yb + I_2 \longrightarrow 2C_6F_5I + YbI_2 \tag{61}$$



(62)

40%

Alkynes can be converted to a one carbon homologated carboxylic acid in about 50% overall yield (equation 63)[47]. Carbonation of bis(pentafluorophenyl)ytterbium generates the expected carboxylic acid in 50% yield, together with nearly 20% of 2,3,4,5-tetrafluorobenzoic acid. It is proposed that the latter is generated by an *ortho* oxidative metalation reaction which is triggered by the initially formed ytterbium(II) carboxylate (equation 64)[48].

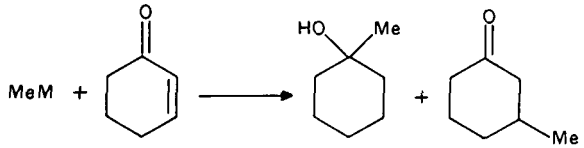
$$PhC{\equiv}CH \xrightarrow[3.H_3O^+]{\substack{1.\ MeYbI \\ 2.\ CO_2}} \underset{50\%}{PhC{\equiv}CCOOH} \tag{63}$$

$$(C_6F_5)_2Yb \xrightarrow[2.\ H_3O^+]{1.\ CO_2} \underset{50\%}{C_6F_5CO_2H} + \underset{16\%}{o\text{-}HC_6F_4CO_2H} \tag{64}$$

Some unusual and potentially important selectivities have been reported in reactions of organoytterbiums with aldehyde and ketone electrophiles. Although ytterbium(III) species have been utilized most effectively in carbonyl addition reactions[13b], most of the chemistry that has been described deals with ytterbium(II) organometallics. The latter react with aldehydes and ketones to provide modest yields of the corresponding alcohols. Significant amounts of pinacol products are generated when diorganoytterbiums are reacted with aromatic ketones, presumably as a result of electron transfer from the ytterbium(II) organometallic (equation 65)[34,49]. Although principally carbanion transfer reagents, it is clear that organoytterbium(II) reagents can also serve as effective reductants.

Organoytterbium(II) halides provide higher 1,2-selectivity in reactions with α,β-unsaturated aldehydes and ketones than their Grignard counterparts, although the yields are sometimes low (equation 66)[45,50]. More surprising is the attenuated reactivity of organoytterbium reagents for ketones, especially when compared with carboxylic esters. Competitive reaction of phenylytterbium iodide with a 1:1 mixture of methyl benzoate and acetophenone results in the formation of 34% benzophenone and only 17% 1,1-diphenylethanol[13b]. Unfortunately, no account was given of the remainder of the material. However, these results imply that organoytterbium reagents are more reactive towards esters than ketones.

$$\underset{\qquad\qquad 42\%}{(PhC{\equiv}C)_2Yb + PhCOPh} \longrightarrow \underset{\qquad\qquad 14\%}{PhC{\equiv}CC(OH)Ph_2 + [Ph_2C(OH)]_2} \tag{65}$$



MeYbI	32%	0%
MeMgX	72%	28%

(66)

The attenuated reactivity towards ketones has been exploited in the development of a selective ketone synthesis from carboxylic acid derivatives (equation 67)[51]. Iron trichloride proved to be an effective catalyst for this reaction, providing higher selectivity than

$$\underset{}{\text{PhYbI} + \text{PhCOCl} \xrightarrow[\text{thf, } -20^\circ\text{C}]{\text{cat.FeCl}_3} \underset{23\%}{\text{PhCOPh}} + \underset{1\%}{\text{Ph}_3\text{COH}}} \quad (67)$$

reactions utilizing copper(I) salts or with the organoytterbium reagents alone. Unfortunately, the yields reported are too low to be of much value in synthesis.

Nitriles do not undergo efficient reactions with organoytterbium reagents[13b]. However, isocyanates are reported to provide good yields of the corresponding amides (equation 68)[34].

$$\underset{}{\text{PhYbI} + \text{PhNCO} \longrightarrow \underset{52\%}{\text{PhNHCOPh}}} \quad (68)$$

The ability of ytterbium(II) species to serve as effective reducing agents has been alluded to previously. Several unusual reductive processes have been observed which serve to display this property. For example, carbon—carbon double bonds conjugated with aromatic rings are readily reduced by PhYbI, providing excellent yields of the corresponding saturated arenes (equation 69)[52]. Even more surprising is a reductive deoxygenation reaction that has been observed when an excess of PhYbI is reacted with chalcone. The major product (60%) observed under these circumstances is 1,1,2-triphenylpropene[45,53]. Evidence for 1,2-addition and subsequent reduction of the alkoxide by PhYbI (generating an allyl anion) has been gathered. For example, quenching the reaction mixture with methyl iodide allows the isolation of alkylated product in 55% overall yield (equation 70).

$$\underset{}{\text{Ph}_2\text{C}{=}\text{CH}_2 + 2\text{PhYbI} \xrightarrow[\text{MeOH}]{\text{thf}} \underset{94\%}{\text{Ph}_2\text{CHMe}}} \quad (69)$$

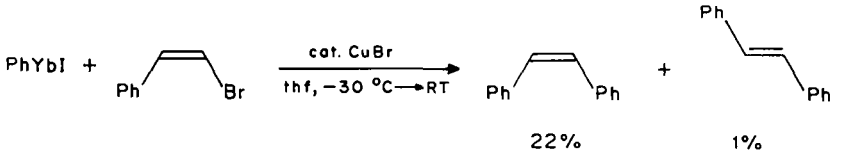
$$\underset{}{\text{PhCH}{=}\text{CHCOPh} + \text{Excess PhYbI} \xrightarrow{\text{RT}} \xrightarrow{\text{MeI}} \underset{55\%}{\text{PhCH(Me)CH}{=}\text{CPh}_2}} \quad (70)$$

Cross-coupling reactions of organoytterbiums with organic halides and related halides have also been explored. For example, both trialkylsilyl and triarylstannyl chlorides react under very mild conditions to provide high yields of the corresponding organometallics (equations 71 and 72)[34,48]. Cross-coupling reactions of phenylytterbium iodides with organic halides (e.g. alkyl, alkenyl, allyl, and benzyl halides) requires transition metal catalysis, and copper salts appear to be the most effective for this process[54]. Even under these conditions, significant problems are encountered. The yields in these coupling reactions tend to be very low, and the desired products are often contaminated by significant amounts of biphenyl. Furthermore, alkenyl halides are coupled with some loss of stereochemistry at the vinylic center. As a consequence, the method has yet to be developed into one of general synthetic utility (equations 73 and 74).

$$\underset{}{\text{MeYbI} + \text{ClSiMe}_2\text{Ph} \longrightarrow \underset{73\%}{\text{PhSiMe}_3}} \quad (71)$$

$$\underset{}{(\text{C}_6\text{F}_5)_2\text{Yb} + \text{Ph}_3\text{SnCl} \xrightarrow[0^\circ\text{C} \rightarrow \text{RT}]{\text{thf}} \underset{64\%}{\text{C}_6\text{F}_5\text{SnPh}_3}} \quad (72)$$

$$PhYbI + CH_2{=}CHBr \xrightarrow[RT,\ 2h]{cat.\ CoCl_2} PhCH{=}CH_2 \quad 90\% \tag{73}$$



(74)

IV. SAMARIUM DIIODIDE-PROMOTED REACTIONS

The development of a simple procedure for the generation of samarium diiodide (SmI_2) by Kagan and coworkers in the late 1970s opened up an incredibly fruitful area of research. Seminal work by Kagan's group on the application of this remarkably versatile reductant was followed by a flood of studies in which the reagent demonstrated notable selectivity in reactions with a variety of organic substrates. Both simple functional group reductions and a host of reductive coupling reactions have since been explored. In these processes, SmI_2 demonstrates reactivity and selectivity patterns which complement well reductants such as zinc, magnesium, and a host of other low-valent metal reductants. In addition to the advantages SmI_2 provides as a thf-soluble reductant, the Sm^{3+} ion generated as a result of electron transfer can serve as a template to control stereochemistry in reductive coupling reactions through chelation. It has therefore become the reagent of choice for numerous synthetic transformations.

A. Preparation and Properties of Samarium Diiodide

Based on redox potentials (Table 3), Sm^{2+} species were expected to be exceptionally powerful reductants. For a variety of reasons, SmI_2 quickly emerged as the most versatile of the readily available salts. It is very conveniently prepared by oxidation of samarium metal with organic dihalides[55] or by iodine (equations 75–77)[56]. Deep blue solutions of

$$Sm + CH_2I_2 \xrightarrow[0°C,\ 1h]{thf} SmI_2 + 0.5CH_2{=}CH_2 \tag{75}$$

$$Sm + ICH_2CH_2I \xrightarrow[0°C,\ 1h]{thf} SmI_2 + CH_2{=}CH_2 \tag{76}$$

$$Sm + I_2 \xrightarrow[65°C,\ 16h]{thf} SmI_2 \tag{77}$$

SmI_2 (0.1 M in thf) are generated in virtually quantitative yields by these processes. This salt can be stored as a solution in thf for long periods, particularly when it is kept over a small amount of samarium metal. Alternatively, the solvent may be removed, providing $SmI_2{\cdot}(thf)_n$ as a powder. For synthetic purposes, SmI_2 is typically generated and utilized *in situ*.

Other ether solvents (e.g. Et_2O, dme) are ineffective for the preparation of SmI_2, and samarium(II) salts such as $SmBr_2$ are only slowly generated by analogous procedures.

Furthermore, none of the other samarium(II) halide salts are nearly as soluble as SmI_2 in thf.

For comparison with other accessible lanthanide(II) salts, it should be pointed out that the preparation of $YbBr_2$ by reaction of ytterbium with 1,2-dibromoethane requires a reaction time of over 2 days. Both YbI_2 and $YbBr_2$ have limiting solubilities of <0.04 M in thf[55b,57]. The redox potential of europium(II) species is too low to be of much value in organic synthesis.

Samarium diiodide has been characterized in solution by absorption spectroscopy, magnetic susceptibility measurements, titrations of lanthanide ions with edta, potentiometric titrations of iodide ion, and acidometric titration and reaction of iodine, which measures the reductive capability of the solutions[55b,c]. All of these tests are consistent with a species possessing the stoichiometry 'SmI_2'. However, little is known of the degree of aggregation or solution structure of this reagent. Crystal structures of $[SmI_2(NCCMe_3)_2]$ and $[SmI_2\{O(CH_2CH_2OMe)_2\}_2]$ have been obtained[58]. The former is an infinite chain of $[SmI_2(NCCMe_3)_2]$ in which all of the iodides are bridging and the geometry about the samarium ion is a distorted octahedron. The diglyme complex is monomeric in the solid state, and the geometry about the octacoordinate samarium ion is best described as a distorted hexagonal bipyramid.

B. Utilization of Samarium Diiodide in Organic Synthesis

From comparison of redox potentials in aqueous media (Table 3), it would appear that SmI_2 is among the strongest one-electron reducing agents soluble in organic solvents. Nevertheless, it has demonstrated highly selective reactivity patterns in a wide range of synthetic transformations.

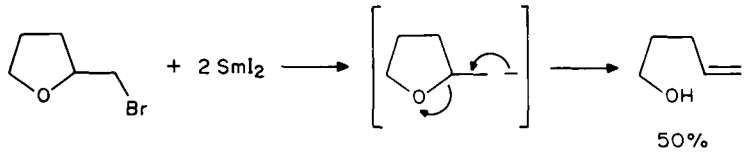
1. Simple functional group reductions

A variety of organic halides are readily reduced to the corresponding hydrocarbons by SmI_2 in the presence of a proton source such as water, methanol, *tert*-butanol, or propan-2-ol[55c,59]. In terms of the halide, ease of reduction follows the expected order (I > Br > Cl). The effectiveness of the reduction is highly solvent dependent. When performed in thf–hmpa solvent, the method can be utilized to reduce primary, secondary, and tertiary alkyl halides, in addition to aryl and alkenyl halides[59]. In thf alone, only primary alkyl iodides and bromides are effectively reduced[55c].

Primary organic tosylates can be reduced to hydrocarbons under the same reaction conditions. Presumably, tosylates are converted to the corresponding iodides by SmI_2 under the reaction conditions, and the iodides are subsequently reduced to the observed products[55c,60]. Reduction of allyl and benzylic halides results in high yields of coupled products.

Mechanistic studies suggest that although stable organosamariums are not generated under the conditions employed, rapidly formed, transient carbanionic species are generated in the reduction of alkyl halides. For example, no carbonyl addition products are detected on addition of ketones to solutions resulting from reduction of organic halides with SmI_2, even though organosamariums are known to undergo such carbonyl additions[60]. In addition, reduction of 1-bromohex-5-ene does not provide detectable amounts of methylcyclopentane, implying that reduction of the intermediate hex-5-enyl radical by SmI_2 is faster than the well known cyclization ($k \approx 10^5\ s^{-1}$). Finally, reaction of tetrahydrofurfuryl bromide with SmI_2 leads to significant amounts of pent-4-en-1-ol, which results from rearrangement and subsequent protonolysis of the tetrahydrofurfuryl anion (equation 78)[60].

As still further evidence for transient anionic species, reduction of 2-bromoadamantane

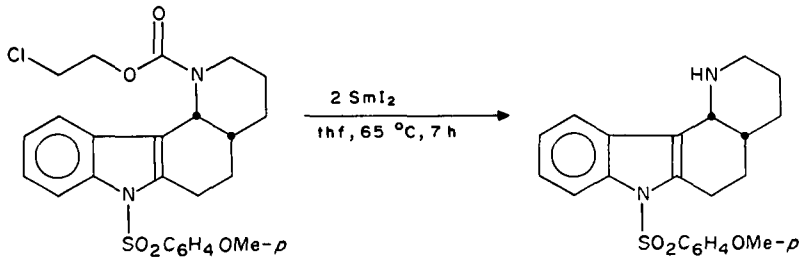


(78)

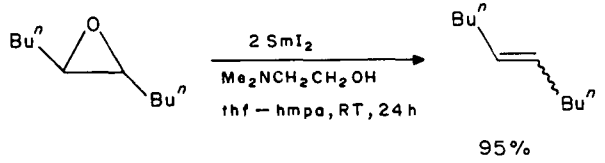
with SmI_2 in thf–hmpa in the presence of D_2O affords adamantane in which 80% deuterium has been incorporated at the 2-position[59]. There is no evidence for such transient carbanionic species in the reduction of aryl halides. When the reduction of 2-bromonaphthalene with SmI_2 is carried out in the presence of D_2O, no deuterium incorporation is observed[59]. This suggests that for aryl (and presumably alkenyl) radicals, hydrogen abstraction from the solvent is more rapid than reduction to the carbanion by SmI_2.

Halide reduction has been utilized to initiate deprotection of a 2-chloroethyl carbamate to the corresponding amine (equation 79)[61]. Several other attempted reduction procedures (Zn–AcOH, $CrCl_2$–HCl, Bu_3SnH–aibn) failed to provide more than a few percent of the desired product.

A number of functional groups can be deoxygenated utilizing SmI_2. Epoxides are readily converted to the corresponding olefin by this reductive process (equation 80)[55c,62].



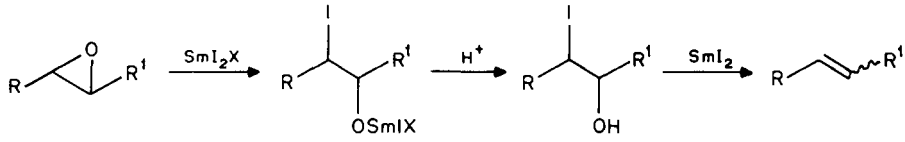
(79)



(80)

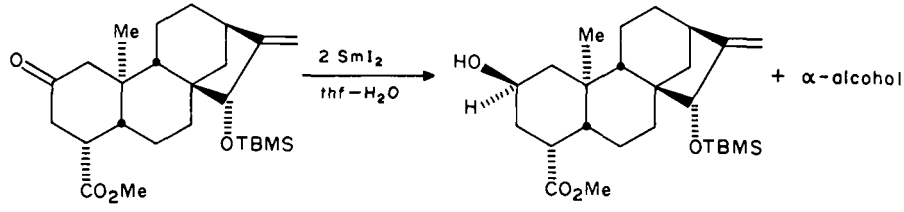
Unfortunately, the reaction is not stereospecific, and a mixture of diastereomeric olefins is isolated. The proposed mechanism for this process involves initial ring opening of the epoxide by a catalytic amount of a Sm^{3+} species[62,63], followed by protonation. Subsequent reduction by SmI_2 and β-elimination provide the observed product (Scheme 1). Sulfoxides are also readily reduced by SmI_2 to sulfides[55c], and amine *N*-oxides are converted to the corresponding amines[64]. Phosphine oxides are inert under similar reaction conditions[55c].

Although carboxylic acids and esters are unreactive towards SmI_2, aldehydes are quantitatively converted to primary alcohols by SmI_2 in the presence of methanol or



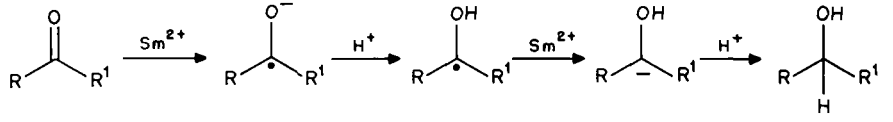
SCHEME 1

water[55c]. Aliphatic ketones are much less reactive, and hence highly selective reduction of aldehydes in the presence of ketones can be accomplished. Samarium diiodide has recently been utilized for the stereoselective reduction of a ketone intermediate in the synthesis of (±)-atractyligenin (equation 81)[65].



(81)

Mechanistic studies performed with deuterated methanol suggest that the reduction of aldehydes and ketones is initiated by electron transfer from SmI_2 to the carbonyl, generating a ketyl. Protonation on oxygen followed by a second electron transfer creates a carbon-centered anion, which is subsequently protonated on carbon to complete the process (Scheme 2)[60].



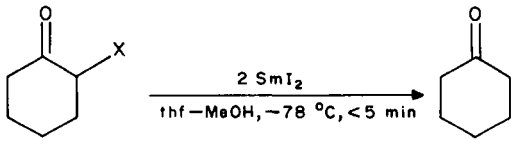
SCHEME 2

α,β-Unsaturated carboxylic acids and esters undergo clean conversion to the saturated derivatives on treatment with SmI_2 in the presence of a proton source. On the other hand, conjugated ketones provide mixtures resulting from 1,2- and 1,4-reduction, and conjugated aldehydes are polymerized by SmI_2[55c].

An impressive range of α-heterosubstituted ketones are rapidly reduced under extremely mild conditions by SmI_2, providing the unsubstituted ketones (equations 82–84)[66]. Reduction of α-halo ketones probably proceeds through generation of a samarium

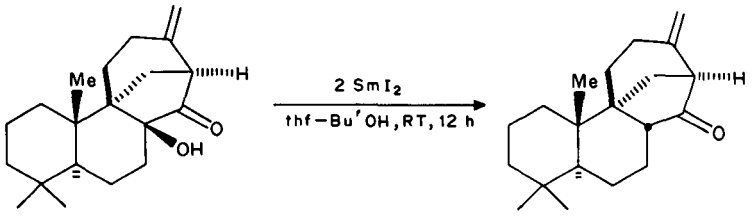
$$C_5H_{11}COCHXC_5H_{11} \xrightarrow[\text{thf–MeOH, } -78\,^\circ\text{C, } <5\,\text{min}]{2SmI_2} C_5H_{11}COC_6H_{13} \qquad (82)$$

X = OAc, $OSiMe_3$, OCOPh, OTs 75–100%



(83)

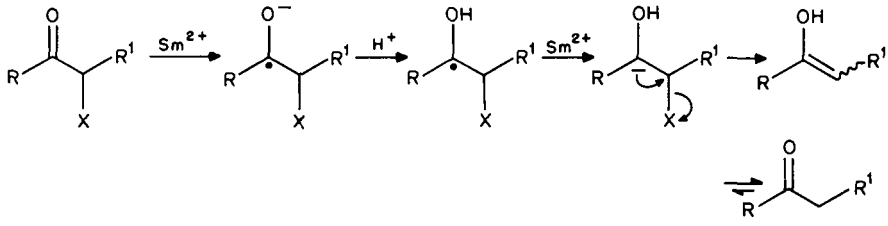
X = Cl, SPh, S(O)Ph, SO_2Ph 64–100%



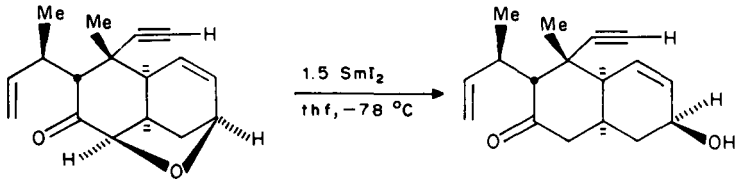
(84)

87%

enolate, with subsequent protonolysis affording the dehalogenated ketone. Other α-hetero-substituted carbonyl substrates must be reduced by a different mechanism. Presumably, reduction of the ketone to a ketyl initiates these reactions. Protonation at oxygen is followed by electron transfer from SmI_2 to generate a carbon-centered anion. β-Elimination of the heteroatom results in generation of an enol. Keto–enol tautomerism to the ketone completes the process (Scheme 3). The reaction is highly selective, and can be performed in the presence of both isolated iodides and isolated ketones[66a]. Pratt and Hopkins utilized the technique in synthetic studies en route to betaenone B (equation 85)[67].



SCHEME 3

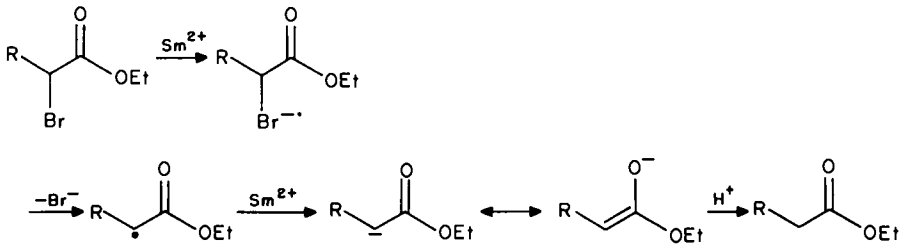


(85)

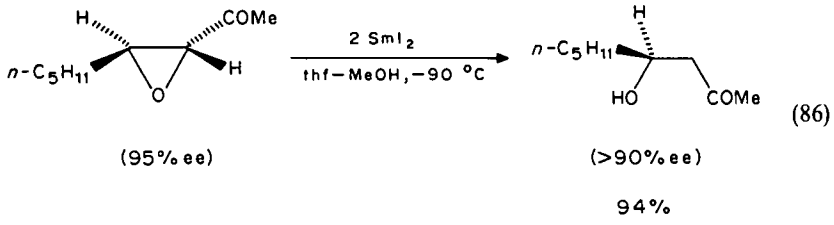
α-Halo esters can be reduced under the same reaction conditions utilized for α-heterosubstituted ketones. However, α-acetoxy esters are inert. Since isolated esters themselves cannot be reduced by SmI_2, these results again imply that α-halo esters react by

direct electron transfer from SmI_2 to the halide, generating an ester enolate. This enolate is immediately protonolyzed under the reaction conditions to provide the unsubstituted ester (Scheme 4)[66a].

Reduction of α,β-epoxy ketones and α,β-epoxy esters has been exploited as a convenient route to chiral, non-racemic β-hydroxy carbonyl compounds[68]. Substrates for such processes are ultimately synthesized from allylic alcohols, utilizing Sharpless asymmetric epoxidation reactions to establish chirality. Reduction of the epoxy ketone substrates proceeds in a straightforward fashion in thf–MeOH at $-90\,^{\circ}C$ (equation 86)[68a]. Little if any retroaldol–aldol equilibration occurs that would serve to



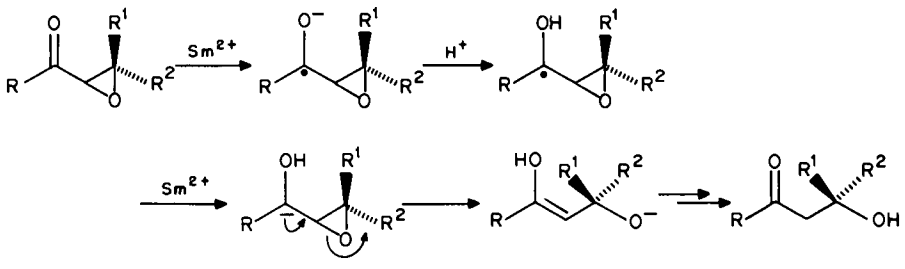
SCHEME 4



(86)

racemize the β-hydroxy ketone product. As a consequence, the procedure provides direct access to a variety of chiral, non-racemic α-unsubstituted β-hydroxy ketones which are difficult to acquire by more traditional procedures. In particular, tertiary alcohol aldols should be accessible in high enantiomeric excess by such processes.

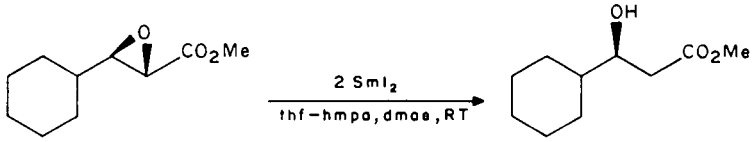
It would seem that the mechanism for the reductive ring opening of epoxy ketones is similar to that proposed for reduction of α-hetero-substituted ketones (Scheme 5)[68a].



SCHEME 5

Reaction of SmI_2 with the ketone generates a ketyl, which is rapidly protonated by methanol. Further reduction by the second equivalent of SmI_2 produces a carbanion, inducing ring opening of the epoxide. Protonolysis and tautomerization of the resulting enol provide the aldol product.

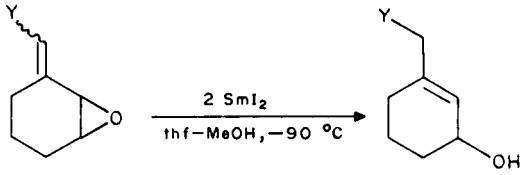
α,β-Epoxy esters require more vigorous conditions for efficient reduction. Reactions on a variety of these substrates have been carried out at room temperature in thf–hmpa utilizing *N*,*N*-dimethylaminoethanol (dmae) as a proton source (equation 87)[68b]. The



(>98%ee) (>98%ee) 94% (87)

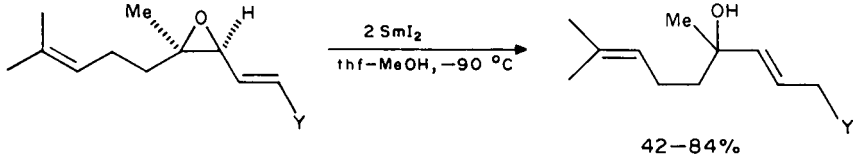
mechanism of these reactions is less clear than that of the epoxy ketones, since electron transfer from SmI_2 to esters is not observed. Direct reduction of the epoxide, generating an ester-stabilized radical, has been proposed[68b]. It has also been suggested that dmae serves not only as an efficient proton source, but also as an effective sequestering agent to remove the Sm^{3+} species generated in the reaction mixture. This chelating agent therefore prevents non-regioselective opening of the epoxide by the Lewis acidic Sm^{3+} ions.

Functionalized vinyloxiranes undergo facile reductive epoxide ring opening with SmI_2 in thf in the presence of a proton source, providing (*E*)-allylic alcohols[68b,69]. The reactions are exceedingly rapid, taking place within minutes at −90 °C. Ketones, esters, nitriles, and other functional groups survive these conditions intact, and the Sharpless asymmetric epoxidation reaction can again be utilized to gain entry to chiral, non-racemic substrates for the reactions (equations 88–90). Higher temperatures (room temperature) are required for electron-rich vinyloxiranes (Y = H, Me, SPh in equation 89), and by-products resulting from simple deoxygenation (i.e. conjugated dienes) are detected in significant amounts (9–32%) in these cases.



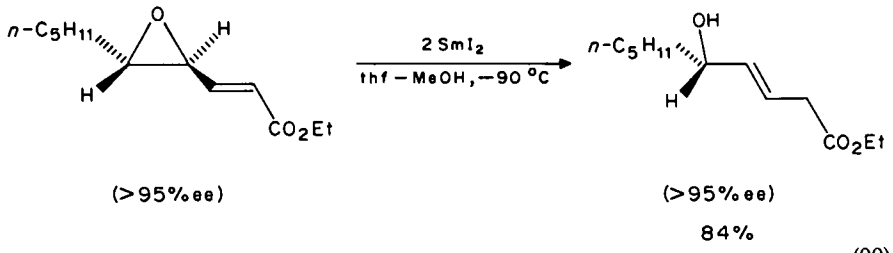
65–70% (88)

Y=CO_2Et, CH=CHCO_2Et, CN, COMe



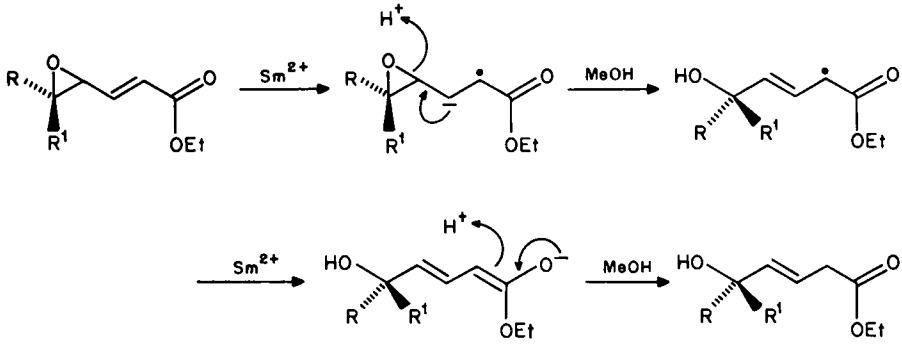
42–84% (89)

Y=H, Me, SPh, COSEt, SO_2Ph, $PO(OEt)_2$



(90)

Significantly, a single regioisomeric and diastereomeric allylic alcohol is generated in nearly every example studied to date. The mechanism of the process presumably involves electron transfer to the readily reducible conjugated system, followed by ring opening of the epoxide and protonation. Subsequent reduction provides a dienoate which is kinetically protonated under the reaction conditions, providing the observed products (Scheme 6). It is clear that nearly neutral conditions are achieved during the reaction, inhibiting equilibration to more stable (conjugated) olefinic isomers. The method therefore provides a very useful entry to highly functionalized, enantiomerically pure organic substrates.

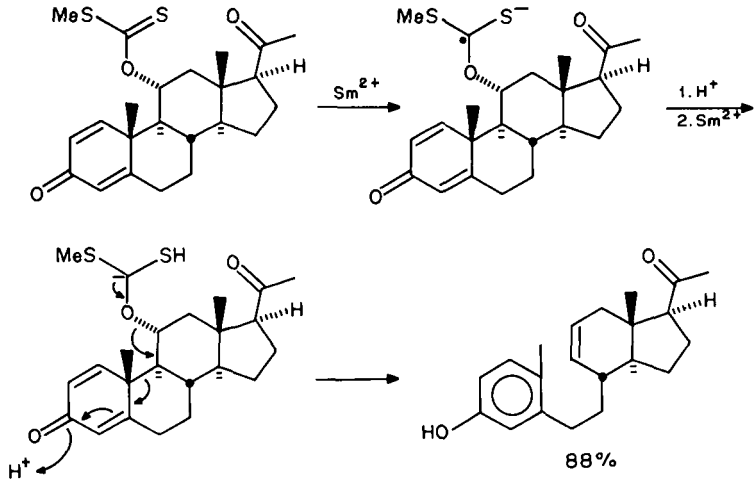


SCHEME 6

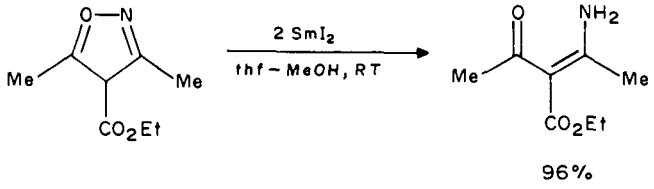
Although nitriles are inert to reduction by SmI_2, other nitrogen-containing functional groups can be reduced. Azo compounds, nitro compounds, and imines can be reduced fairly cleanly to the amines. Oximes provide complex mixtures of reduced products[64,70].

Samarium diiodide has also been utilized to reduce xanthate esters cleanly, effecting a reductive cleavage reaction (Scheme 7)[61]. This particular reaction could not be achieved in satisfactory yields with Bu_3SnH–aibn or with Li–NH_3. The success of SmI_2 in this process was attributed to the ability of Sm^{2+} to reduce the proposed radical intermediate rapidly to an anion. The mechanism of this reaction is not at all clear, however, as an equally viable process can be envisioned by assuming inital electron transfer to the dienone system.

Isoxazoles are also readily reduced by SmI_2 to provide enamino ketones (equation 91)[71]. In competitive reactions, the reduction of aldehydes can be accomplished in the presence of isoxazoles, whereas halides are probably reduced more slowly than these heterocycles.



SCHEME 7



(91)

2. *Barbier-type reactions*

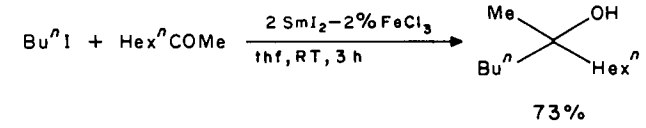
As a homogeneous reductant, SmI_2 provides some advantages over more traditional reagents such as magnesium in Barbier-type syntheses. Both intermolecular and intramolecular versions of the Barbier reaction utilizing SmI_2 have provided novel entries into complex organic molecules.

a. Intermolecular reactions

Samarium diiodide can be utilized to promote intermolecular Barbier-type reactions between ketones and a variety of organic halides[55c]. Allylic and benzylic halides (chlorides, bromides, and iodides) react within a few minutes at room temperature in thf when treated with 2 equivalents of SmI_2. Primary organic iodides and even organic tosylates undergo reaction, but require heating for 8–12 h in refluxing thf. A Finkelstein-type reaction presumably converts tosylates to the corresponding iodides, which subsequently are involved in the coupling reaction. Alkyl bromides are less reactive, and alkyl chlorides are virtually inert.

Much milder reaction conditions can be achieved by utilizing iron(III) salts as a catalyst for the reactions. For example, when 2 mol-% (based on organic halide and ketone) $FeCl_3$ is added to SmI_2, the Barbier reaction between a primary organic iodide and a ketone is complete within 3 h at room temperature (equation 92). The iron(III) is probably reduced

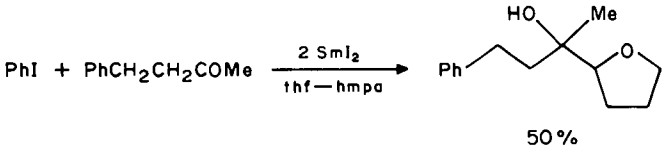
by SmI_2 to a low-valent species which serves as an efficient electron-transfer catalyst, thus lowering the activation energy for the coupling process (see below).



(92)

Another technique which appears viable in facilitating the Barbier-type coupling with SmI_2 is the utilization of thf–hmpa as solvent for the reaction[72]. Even in the absence of a catalyst, both Bu^{n}Br and Bu^{s}Br can be cleanly coupled to octan-2-one within 1 min at room temperature in this solvent system, providing greater than 90% yields of the desired tertiary alcohols.

Alkenyl halides and aromatic halides are unreactive with ketones in the presence of SmI_2 in thf[55c]. Pinacolic coupling reaction products can be detected in 10–20% yield under these conditions. In thf–hmpa, iodobenzene reacts in the presence of a ketone to generate a phenyl radical, which abstracts a hydrogen from thf. Samarium diiodide-induced coupling of the thf radical to the ketone (or ketyl) provides the observed product (equation 93)[59].



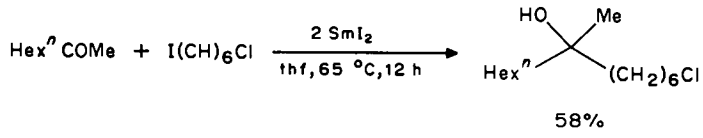
(93)

The weight of available evidence suggests that the mechanism of these Barbier-type reactions involves radical coupling as opposed to carbanionic processes. Direct S_N2-type displacement of the halide by a ketyl or a dianion has been ruled out. Optically active 2-bromooctane reacts with cyclohexanone in the presence of SmI_2 to provide an optically inactive tertiary alcohol[60]. One plausible mechanism for the SmI_2-mediated Barbier reaction involves coupling of ketyl and alkyl radicals in a diradical coupling mechanism[60]. Alternatively, addition of an alkyl radical to a Sm^{3+}-activated ketone carbonyl would also appear viable[73]. Further discussion of the mechanism is presented in the section on intramolecular Barbier reactions (see Section IV.B.2.b).

With regard to the carbonyl substrate, it has been determined that aldehydes cannot be coupled to marginally reactive organic halides. A mixture of products results in these cases as a consequence of a Meerwein–Ponndorf process, initiated by reaction of the secondary samarium alkoxide intermediate with the aldehyde[70,74]. Highly reactive (allylic and benzylic) halides can be utilized and couple fairly efficiently with aldehydes, since they react quickly enough to suppress the undesired consecutive reaction. Unsymmetrical allylic halides provide mixtures of regioisomers in these instances.

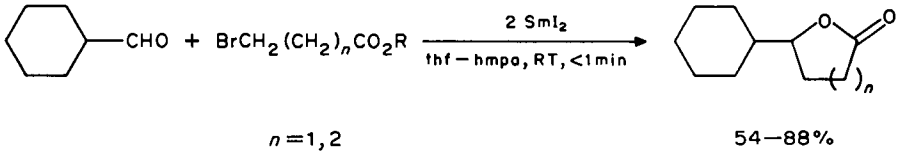
Highly selective synthetic transformations can be readily performed by taking advantage of the chemoselectivity of SmI_2. It has been pointed out that there is a tremendous reactivity differential in the Barbier-type reaction between primary organic iodides or tosylates on the one hand and organic chlorides on the other.As expected, selective alkylation of ketones can be accomplished by utilizing appropriately functionalized dihalides or chlorosulfonates (equation 94)[55c]. Alkenyl halides and, presumably, aryl halides can also be tolerated under these reaction conditions.

Nitriles and esters are also unreactive in SmI_2-promoted Barbier reactions. A very useful procedure for lactone synthesis has been developed which has made use of this fact. Treatment of γ-bromobutyrates or δ-bromovalerates with SmI_2 in thf–hmpa in the



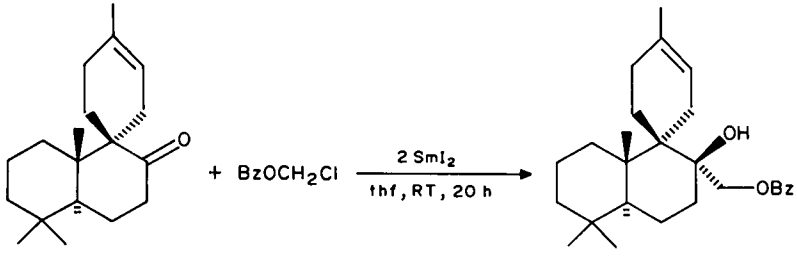
(94)

presence of aldehydes or ketones results in generation of lactones through a Barbier-type process (equation 95)[72]. This complements well the β-metallo ester or 'homoenolate' chemistry of cerium reagents described above (see Section II.B.2) and also the Reformatsky-type chemistry of the lanthanides (see Sections II.B.2 and IV.B.5). Further, it provides perhaps the most convenient route to γ and δ-carbanionic ester equivalents yet devised.



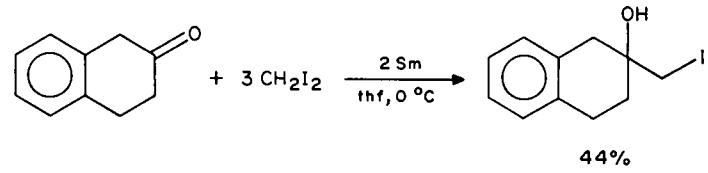
(95)

A very convenient hydroxymethylation process has been developed based on the SmI_2-mediated Barbier-type reaction[75]. Treatment of aldehydes or ketones with benzyl chloromethyl ether in the presence of SmI_2 provides the alkoxymethylated products in good to excellent yields. Subsequent reductive cleavage of the benzyl ether provides hydroxymethylated products. Even ketones with a high propensity for enolization can be alkylated by this process in reasonable yields. The method was utilized by White and Somers as a key step in the synthesis of (±)-desoxystemodinone (equation 96)[66b]. This particular ketone substrate resisted attack by many other nucleophilic reagents (such as methyllithium) owing to competitive enolate formation.

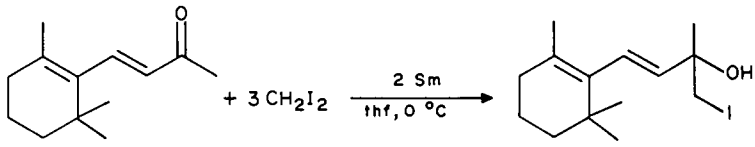


(96)

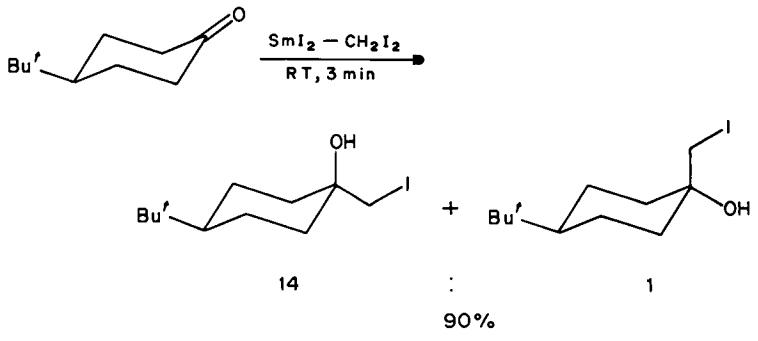
Halomethylation of aldehydes and ketones is difficult to achieve utilizing α-halo organolithium species owing to the extreme thermal instability of these organometallics. Either SmI_2 or samarium metal can be utilized as the reductant in conjunction with diiodomethane to induce an analogous iodomethylation reaction[76]. A wide range of aldehydes and ketones are efficiently alkylated at room temperature under these conditions. Even substrates that are susceptible to enolization react reasonably well, providing moderate yields of the iodohydrin (equation 97)[76a]. Conjugated aldehydes and ketones react to provide only 1,2-addition products (equation 98)[76a]. Excellent diastereoselectivity is achieved in reactions with both cyclic and acyclic ketones (equations 99 and 100)[76b].



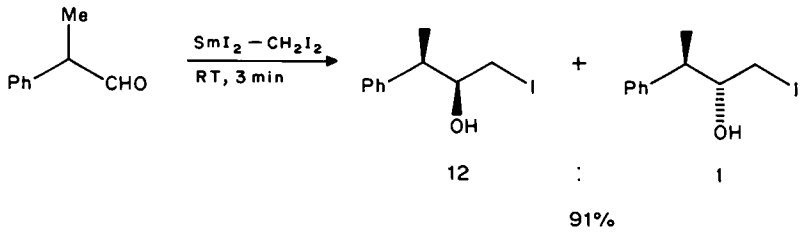
44% (97)



53% (98)



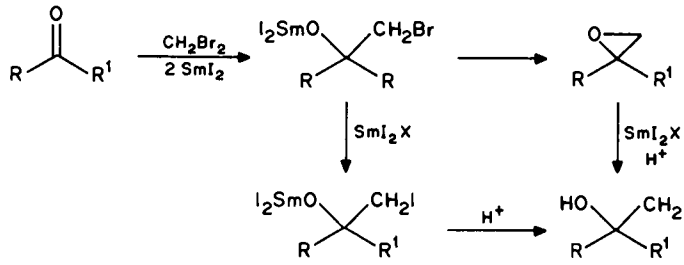
(99)



(100)

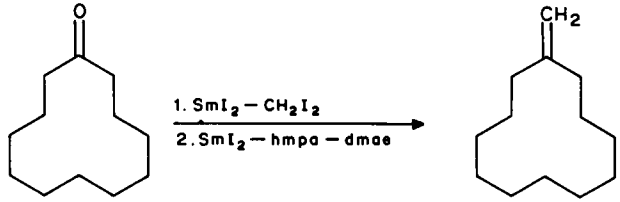
Utilization of dibromomethane also results in the isolation of iodohydrins. Based on this and the fact that SmI_3 will cleave epoxides to generate iodohydrins, it has been suggested that the iodomethyl samarium alkoxide species that is initially generated cyclizes to an epoxide intermediate. The SmI_2X that is produced as a result of this process then serves to open the epoxide, generating the iodohydrin (Scheme 8). Although this appears to be a likely scenario, a more direct route involving a Finkelstein reaction between the bromomethyl samarium alkoxide and various samarium iodide salts[55c,60] cannot be ruled out.

A one-pot carbonyl methylenation reaction has been developed based on this iodomethylenation reaction[62]. Treatment of an iodomethyl samarium alkoxide (generated *in situ* by reaction of aldehydes or ketones with SmI_2–CH_2I_2) with SmI_2–hmpa and



SCHEME 8

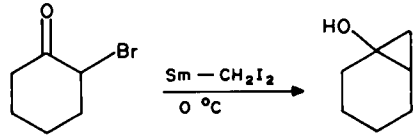
N, *N*-dimethylaminoethanol (dmae) induces a reductive elimination process, resulting in the generation of the corresponding methylenated material (equation 101).



(101)

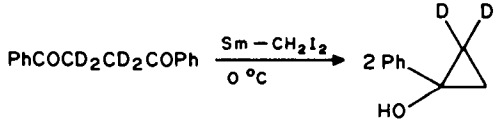
80%

When α-haloketones are treated with diiodomethane and samarium at 0 °C, cyclopropanols can be obtained in reasonable yields. Curiously, under the same conditions 1,2-dibenzoylethane also leads to cyclopropanol products (equations 102 and 103)[76a]. Several mechanisms for conversion of α-halo ketones to the observed cyclopropanols can be envisioned. It has been proposed that the mechanism of this reaction involves reduction of the α-halo ketone by samarium (or SmI_2) to a samarium enolate. Cyclopropanation of this enolate with a samarium-based carbenoid then provides the observed product (see Section IV.B.7)[76c].



(102)

81%



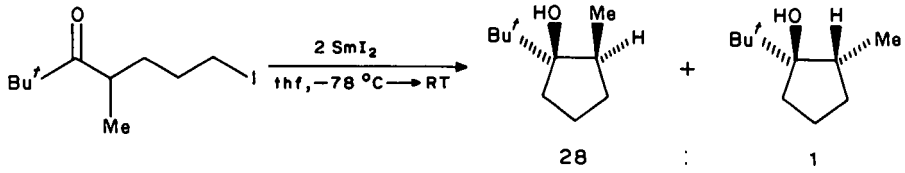
(103)

68%

b. Intramolecular reactions

Although numerous reductants [e.g. magnesium, lithium, sodium, organolithiums, organocuprates, and chromium(II) salts, to name only a few] have been utilized in attempts to promote intramolecular Barbier-type reactions, SmI_2 is by far the most general reductive coupling agent in terms of its utility and its scope of application. It has therefore become the reagent of choice for such processes.

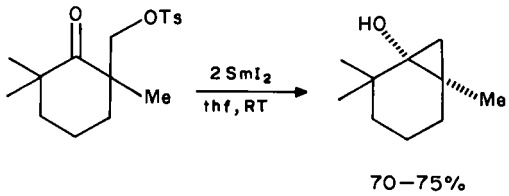
Isolated cyclopentanols can be synthesized with considerable diastereoselectivity in the process when appropriately substituted ω-iodoalkyl ketones are treated with SmI_2 in thf at $-78\,^{\circ}C$ and allowed to warm to room temperature (equation 104)[77].



(104)

The reaction is clearly not subject to steric inhibition about the ketone carbonyl, and provides a useful alternative to intermolecular reactions between organometallic reagents (e.g. RLi or RMgX) and α-substituted cyclopentanones, which in principle would generate the same products. These latter reactions often suffer from competitive enolization and/or reduction processes.

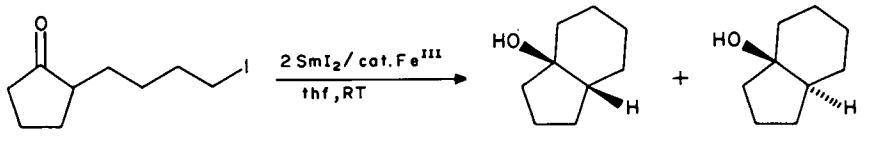
Perhaps more valuable is the application of the SmI_2 reductive coupling technology to the synthesis of bicyclic alcohols. Shiner and Berks have demonstrated that the procedure can be utilized to generate three-membered rings starting from α-tosyloxymethyl cycloalkanones (equation 105)[78]. An advantage of SmI_2 over reductants such as magnesium is that one is not restricted to organic halides in these reactions. As in this example, tosylates appear perfectly well suited to the Barbier process also.



(105)

Although the synthesis of four-membered rings has yet to be thoroughly explored, samarium diiodide can be utilized in the annulation of five- and six-membered rings through an intramolecular Barbier process[79]. The development of this approach to six-membered ring formation in fused bicyclic systems is particularly important, since prior to this discovery there existed no reliable and convenient method to achieve this simple annulation process. The reactions proceed with considerable diastereoselectivity when cyclopentanone substrates are utilized, or when substituents are placed at the α-position of the cycloalkanone (equations 106 and 107).

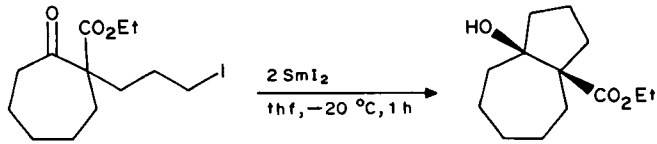
Diastereoselectivity in other systems depends on whether or not an iron(III) catalyst is utilized in the reaction. In addition, in some cases higher diastereoselectivities can be obtained utilizing samarium metal, ytterbium metal, or YbI_2 as reductant. Unfortunately, the sense and magnitude of stereoselectivity than can be achieved by employing these other reductants are unpredictable from substrate to substrate.



18 1

67%

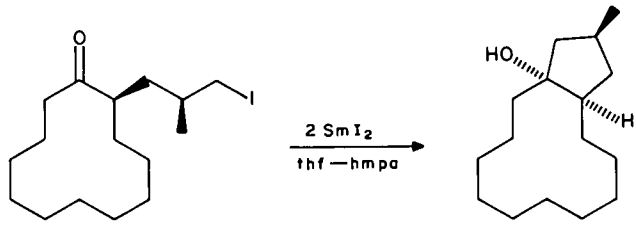
(106)



95%

(107)

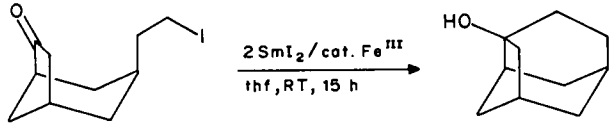
The SmI_2-mediated intramolecular Barbier procedure has been applied to several diverse systems, and in each case has been determined to be superior to other protocols. Suginome and Yamada[80] applied the technique to syntheses of exaltone and (±)-muscone (equation 108). Surprisingly, cyclization in this case apparently generates a single diastereomer. It is claimed that the SmI_2 procedure provides better yields than that of Mg–$HgCl_2$ or *n*-butyllithium.



90%

(108)

Sosnowsky *et al.*[81] used the SmI_2-promoted intramolecular Barbier synthesis in a synthesis of 3-protoadamantanol (equation 109)[81]. Although the yield in this example was not particularly high, it was the only method among several attempted that proved successful[82].

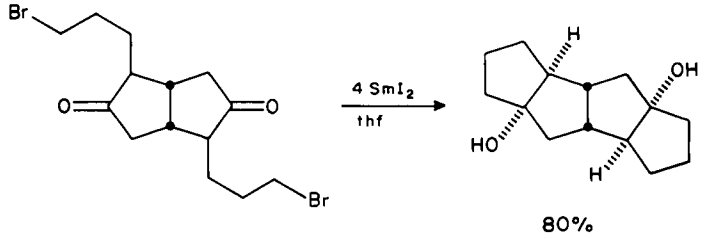


44%

(109)

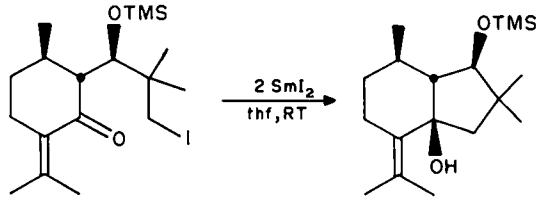
In an elegant approach to polyquinenes, Lannoye and Cook[83] developed a bis-annulation process based on the SmI_2-mediated cyclization process (equation 110). Remarkably, both of the carbon—carbon bond-forming reactions in this process proceed

with approximately 90% yield, providing an incredibly efficient entry to these complex molecules.



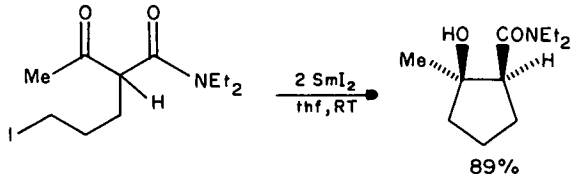
(110)

Exceptionally clean cyclization can be accomplished by utilizing a number of conjugated enones as precursors for the Barbier reaction (equation 111)[84]. High diastereoselectivity is achieved in these reactions, and under the mild conditions required for cyclization the trimethylsilyl ether protecting group remains intact. It is also interesting that a neopentyl halide is effective is the cyclization. This lends further support to the exclusion of an S_N2-type displacement of an organic halide by a ketyl as a possible mechanism for the SmI_2-promoted Barbier reaction.



(111)

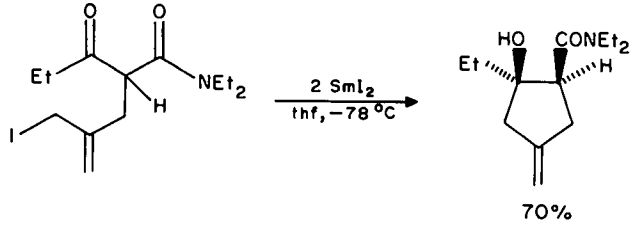
As alluded to previously, much evidence suggests that ketyls are important intermediates formed in reactions between haloketone substrates and SmI_2. This provided the very real possibility that the Sm^{3+} ion generated on electron transfer could be utilized as an effective Lewis acid template to control stereochemistry via chelation in suitably functionalized substrates. Indeed, a number of systems have been designed with this idea in mind. In β-ketoamide systems, the samarium(III) can participate in a rigid, chelated intermediate which serves to control stereochemistry in the cyclization process (equation 112)[85]. As far as one can tell, these particular cyclization reactions are under kinetic control; there is no evidence to suggest that any equilibration takes place under the reaction conditions, and a single diastereomer is generated in each example. Six-membered rings can also be constructed by this process, although the yields are lower. Approximately 30% of reaction mixture by-products derived from simple reduction of the ketone to an alcohol are isolated in these cases.



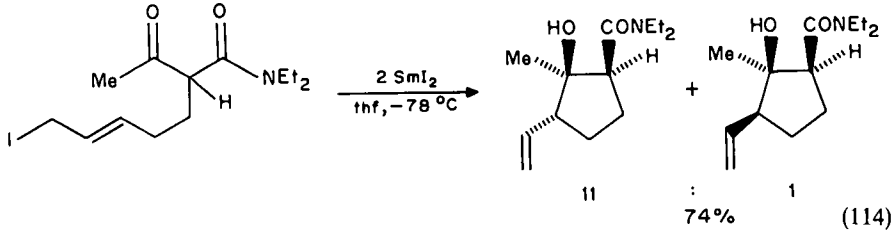
(112)

Allylic halide precursors also provide exceptional yields of cyclic products, and both five- and six-membered rings comprising several different substitution patterns can be

accessed by the same technology (equations 113 and 114)[84]. Some erosion of yield and diastereoselectivity is noted on applying this chemistry to the synthesis of six-membered rings. However, the method still provides unique access to highly functionalized, stereodefined carbocycles.

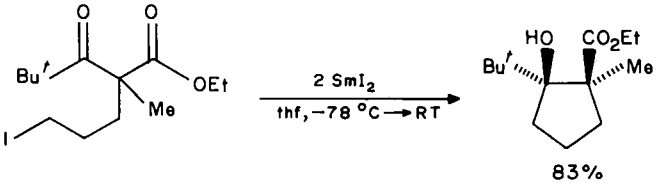


(113)



(114)

A number of analogous β-keto esters have also been explored as substrates for intramolecular Barbier cyclization[85]. In the alkyl halide series, a convenient route to hydroxycyclopentanecarboxylates results. However, six-membered rings are inaccessible utilizing this procedure (equation 115).

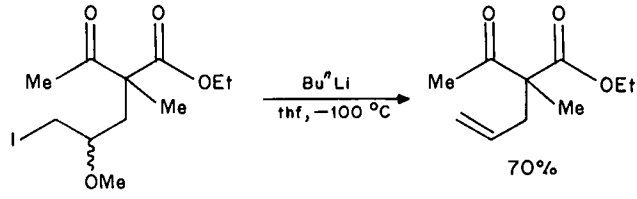


(115)

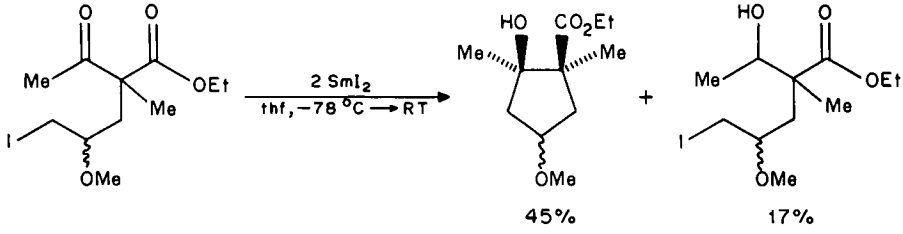
In contrast to β-ketoamide substrates, the β-keto ester series provide products which are clearly under thermodynamic control. That is, the observed diastereoselectivity is the result of a retroaldol–aldol equilibration which serves to equilibrate the initially formed samarium aldolates. In most cases, the diastereoselectivity is actually good, and predictable based on a simple model for the reaction. However, it is highly dependent on substituent and solvent effects. In particular, the use of coordinating solvents or additives (such as tetraglyme, 18-crown-6, or *N*,*N*-dimethylacetoacetamide) that serve to strip the samarium(III) ion away from the chelating center radically diminish the diastereoselectivity observed in these reactions. It should be pointed out that these cyclizations cannot be carried out by treating the substrates with activated magnesium. Unreacted starting material is recovered under the conditions[85].

Further evidence for a radical coupling mechanism (as opposed to a carbanionic carbonyl addition mechanism) in the SmI_2-promoted Barbier reactions has come from studies on appropriately functionalized substrates in the β-keto ester series. It is well known that hetero substituents are rapidly eliminated when they are adjacent to a

carbanionic center. Indeed, treatment of a β-methoxy organic halide (suitably functionalized for cyclization[77,86]) with an organolithium reagent leads only to olefin (equation 116). No cyclized material can be detected. On the other hand, treatment of the same substrate with SmI_2 leads largely to cyclized product and a small amount of reduced alcohols, with none of the olefin detected by gas chromatographic analysis (equation 117)[87].



(116)

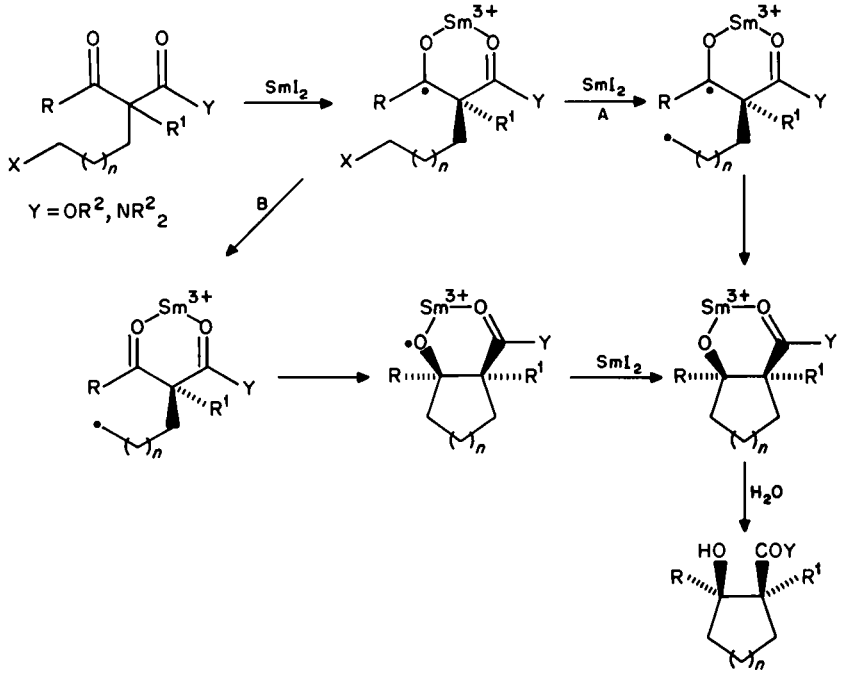


(117)

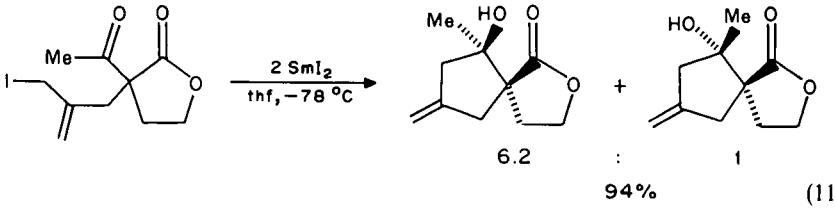
These results, together with the studies described above by Kagan *et al.*[60], provide strong support for a radical cyclization process. Two general mechanisms are suggested (Scheme 9). In both, initial electron transfer from SmI_2 to the ketone carbonyl occurs, generating a ketyl. This chelated intermediate might suffer one of two fates. Dissociative electron transfer from the second equivalent of SmI_2 to the halide could occur (pathway A), providing a diradical species. Closure to the samarium aldolate and hydrolysis would result in the production of the observed product. Alternatively, the initially generated ketyl could undergo a dissociative intramolecular electron transfer to the halide (pathway B). Addition of the alkyl radical to the Sm^{3+}-activated ketone carbonyl[73], subsequent reduction of that intermediate with the second equivalent of SmI_2 and hydrolysis would again complete the process. Experiments have yet to be designed and carried out to distinguish between a process involving cyclization after single electron transfer and a two-electron cyclization processes. However, it is clear that samarium carbanions are not involved in such processes.

Allylic halide substrates in the β-keto ester series cyclize well, and convenient routes to five-, six-, and seven-membered rings have been described (equations 118 and 119)[85]. Unfortunately, the diastereoselectivity in these examples again is highly dependent on the substitution patterns about the dicarbonyl substrate.

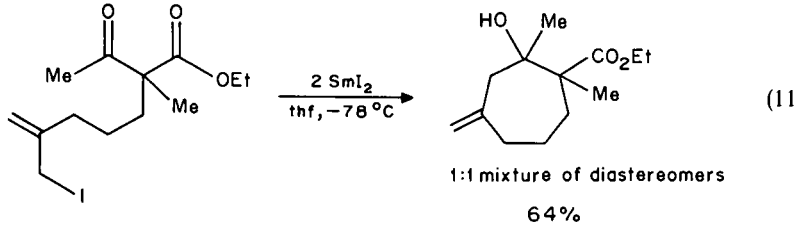
Attempts to cyclize ethyl (*E*)-2-acetyl-2-methyl-6-bromohex-4-enoate have been unsuccessful, ethyl 2-methyl-3-oxobutanoate being isolated as the major product of the reaction (equation 120)[85]. Loss of butadiene, as required for this transformation, is clearly facilitated by the ability of a β-keto ester-stabilized (radical or anion) intermediate to serve as an effective leaving group in the reaction. Thus, cyclization of (*E*)-8-bromo-4-methyloct-6-en-3-one proceeds smoothly to provide the expected carbocycle in 91% isolated yield (equation 121).



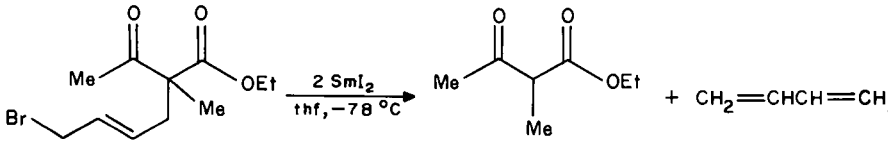
SCHEME 9



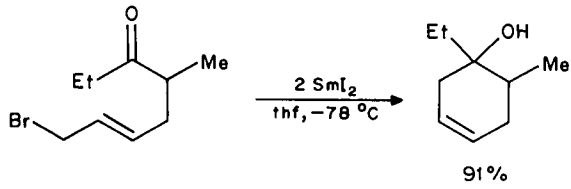
(118)



(119)



(120)



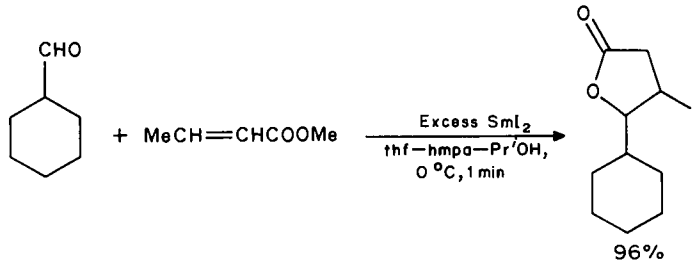
(121)

These examples again have some mechanistic implications in that they appear further to rule out cyclization via S_N2 displacement of the halide by a samarium ketyl. However, one cannot distinguish between a mechanism based on an allylsamarium addition to the carbonyl versus an electron-transfer mechanism as outlined for the alkyl halide substrates above. Both mechanisms allow for isomerization of the double bond (via 1,3-allylic transposition in the case of an allylmetallic[88] or configurational instability in an allylic radical[89] in a diradical coupling mechanism) and also provide reasonable routes for generation of butadiene. Further mechanistic work is clearly required in order to provide a more detailed understanding of all of these intramolecular Barbier-type reactions.

3. Ketyl–olefin coupling reactions

The ability of SmI_2 to generate ketyls cleanly prompted its use for the reductive cross-coupling of ketones with olefins. Both intermolecular and intramolecular processes of this type have been described.

Conjugated esters react with aldehydes and ketones in the presence of SmI_2, affording reasonable yields of butyrolactones (equation 122)[90]. The method complements well electroreductive[91], photoreductive[92], and other metal-induced ketone–olefin cyclizations[93] that have been developed. Mixtures of diastereomers are generated in all of the examples studied. The presence of hmpa dramatically enhances the reactivity (and yields), permitting reactions to run to completion in 1 min as opposed to 3–6 h without this additive[90b]. Conjugated nitriles do not fare as well as their ester counterparts in these reactions. Yields of 17–20% are reported for the nitrile substrates[90a]. In terms of the ketyl precursor, both aliphatic and aromatic ketones and aldehydes can be utilized[90a], and even formaldehyde is effective to some extent[90b].

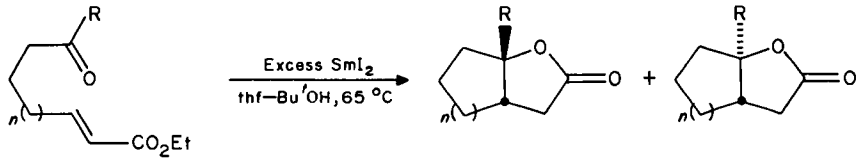


(122)

Although a mechanism involving ketyl addition to the electron-deficient olefin seems likely, it has been pointed out that one cannot ignore a mechanism in which reduction of the unsaturated ester by SmI_2 leads to generation of a samarium β-metallo ester[90a]. Direct addition of such an intermediate to a ketone or aldehyde and subsequent protonation would lead to the observed products.

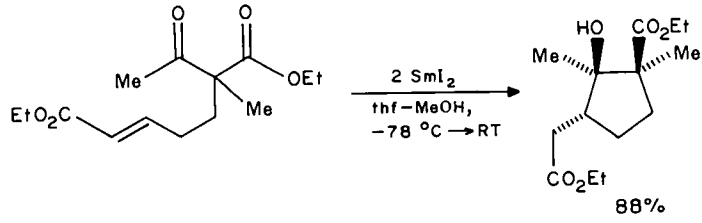
Bicyclic butyrolactones can be generated when intramolecular versions of the reaction are carried out (equation 123)[94]. The yields are improved by addition of hmpa, and reactions can be carried out under milder conditions. Addition of a catalytic amount

of $FeCl_3$ has little effect on the yields. In most cases, diastereoselectivities range from 2.5 to 4:1.

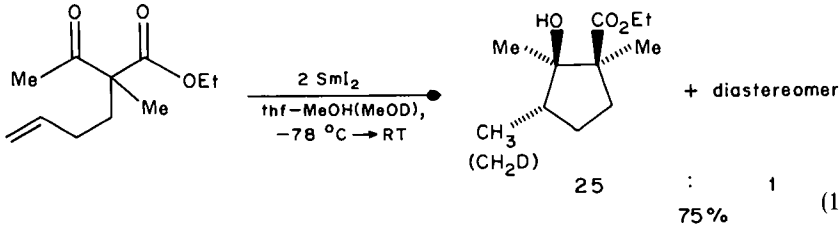


$n = 1, 2, 3$
R = H, Me (123)

A much more highly diastereoselective process results when olefinic β-keto ester and β-ketoamide substrates can be utilized in the ketone–olefin reductive coupling process. Both electron-deficient and unactivated olefins can be utilized in the reaction (equations 124 and 125)[95]. In such examples, one can take advantage of chelation to control the relative stereochemistry about the developing hydroxyl and carboxylate stereocenters. Favorable secondary orbital interactions between the developing methylene radical center and the alkyl group of the ketyl[91c,93a,96] and /or electrostatic interactions in the transition state[91a,92,96] account for stereochemical control at the third stereocenter.



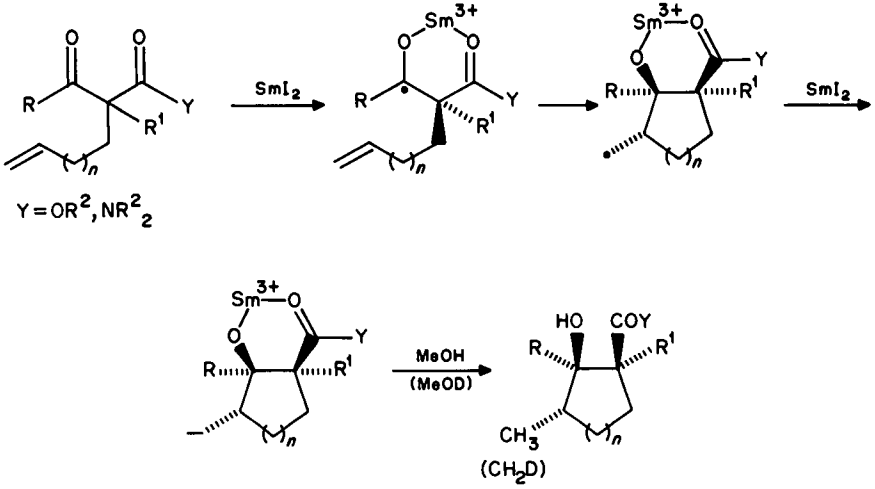
(124)



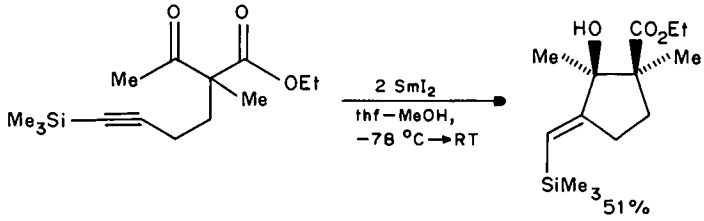
(125)

Since 2 equivalents of SmI_2 are required for the reaction, the reductive coupling process must be a two-electron process overall (Scheme 10)[95]. Cyclization appears to occur after transfer of a single electron, with Sm^{3+} controlling the stereochemistry at this stage by chelation with the Lewis basic ester carbonyl. Subsequent reduction to a transient carbanion, followed by immediate protonation, accounts for the observed products. Only if a transient anion is generated can one account for > 90% deuterium incorporation at the methyl group when the reaction is performed in MeOD (equation 125)[87].

Ketyl–alkyne coupling can also be achieved, although the yields are lower (equation 126). This might have been expected on the basis that radical additions to alkynes are more difficult than those to olefins[97].

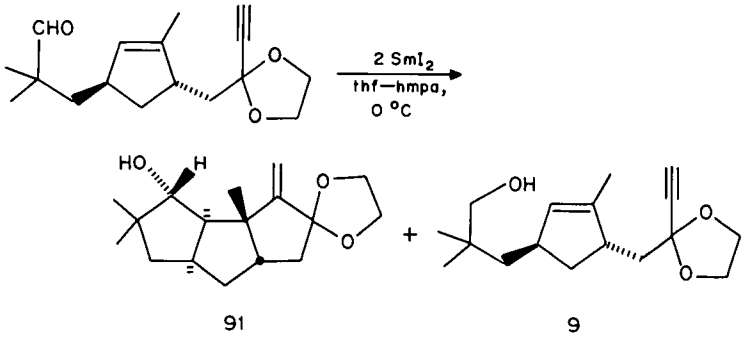


SCHEME 10



(126)

An elegant tandem radical cyclization process promoted by SmI_2 has been developed as a key step in the synthesis of (±)-hypnophilin and formal total synthesis of (±)-coriolin (equation 127)[98]. Cyclization in this case again occurs after transfer of a single electron, and in fact the entire process requires less than 2 equivalents of SmI_2. When cyclizations were quenched with D_2O, no deuterium was incorporated at the newly formed vinyl carbon. This implies that the alkenyl radical produced after tandem cyclization abstracts a hydrogen from the solvent faster than it is reduced to the anion by SmI_2. This and the work by Molander and Kenny[95] described above are completely in line with observations of

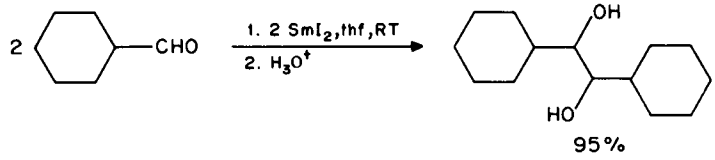


(127)

Inanaga *et al.*[59] in work on the reduction of organic halides with SmI_2. Thus, alkyl halides are reduced to hydrocarbons by means of a transient anion (which can be trapped by D_2O) with SmI_2, whereas aryl (and presumably alkenyl) halides show no deuterium incorporation on reduction. Further studies in this area are bound to lead to exciting new entries to highly complex carbocyclic ring systems.

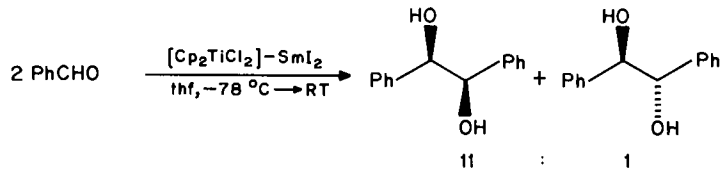
4. Pinacolic coupling reactions

As might be expected with a reagent that is capable of generating ketyls, pinacolic coupling reactions can also be carried out with considerable efficiency using SmI_2. Treatment of aldehydes or ketones with SmI_2 in the presence of a proton source such as methanol results in selective reduction to the corresponding alcohols, and the formation of pinacols is negligible. However, in the absence of a proton source, both aldehydes and ketones can be cleanly coupled in the presence of SmI_2 to generate pinacols (equation 128)[99]. The yields are excellent in nearly every case, and the method therefore competes effectively with other established procedures for this process. Unfortunately, roughly equimolar ratios of *threo* and *erythro* isomers are generated in these reactions. Aromatic aldehydes and aromatic ketones couple within a few seconds at room temperature in thf. Aliphatic aldehydes require a few hours under these conditions, and a day is needed for complete reaction of aliphatic ketones. Amines, nitriles, and nitro groups are tolerated under these conditions. Surprisingly, carboxylic acids can also be incorporated into substrates with little decrease in the yields of pinacolic products. It is not clear why competitive reduction to the alcohols is not observed in this instance, since a proton source is provided by the acid.



(128)

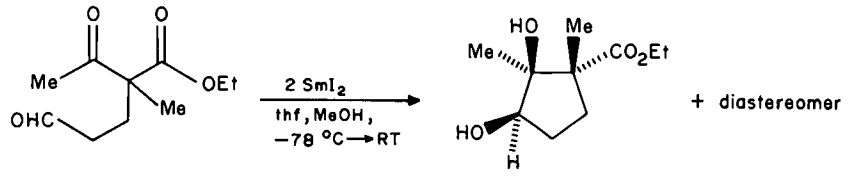
Samarium diiodide has also been utilized as a reductant to promote pinacolic coupling reactions mediated by low-valent titanium species (equation 129)[100]. Utilizing this protocol, fairly high diastereoselectivity can be achieved, although yields for this particular process were not reported.



(129)

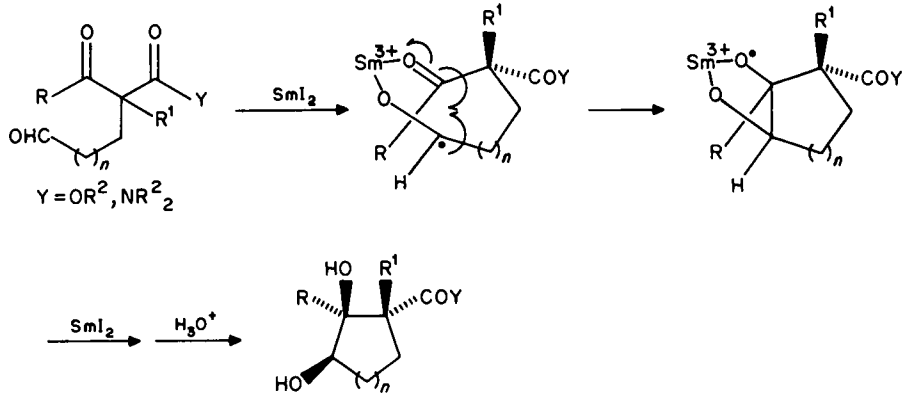
Excellent yields and diastereoselectivity over three contiguous stereocenters are achieved in intramolecular pinacolic coupling reactions promoted by SmI_2 (equation 130)[101]. Six-membered rings can also be generated by this process, but substantially lower yields and diastereoselectivities are observed. Yields obtained for β-ketoamide substrates are also lower than those observed in the β-keto ester series.

Curiously, the relative stereochemistry between the carboxylate and the adjacent hydroxy group in the SmI_2-mediated intramolecular pinacolic coupling reaction is opposite to that observed in the intramolecular Barbier reactions and ketone–olefin



(130)

reductive coupling reactions discussed previously (compare equation 130 with equations 115 and 125, for example). From a synthetic point of view, this result is highly advantageous because it provides entry to the manifold of diastereomeric products. The results also have mechanistic implications; electron transfer to the most readily reduced functional group (aldehyde) apparently initiates the process, with chelation control of stereochemistry now centered about the developing diol stereocenters. Perhaps the most plausible mechanism involves cyclization after one-electron reduction[91c,95,102]. In this case, initial electron transfer to the aldehyde would generate the ketyl. Cyclization would occur by coordination of Sm^{3+} to the ketone carbonyl, followed by (or concomitant with) carbon—carbon bond formation (Scheme 11). Dipolar repulsion between the Sm^{3+} chelate and the carboxylate (or carboxamide) would account for the relative stereochemistry between the diol stereocenters and the carboxylate (carboxamide). Subsequent intermolecular reduction of the chelate complex by SmI_2 and hydrolysis produce the observed products.

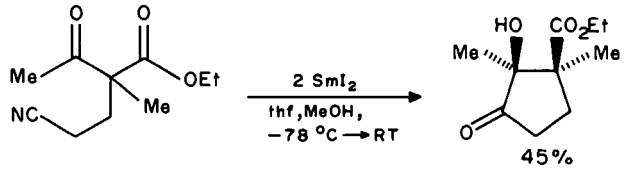


SCHEME 11

Several pertinent examples of apparent ketyl addition to Lewis acid-complexed carbonyl substrates have been documented[102,103], and intramolecular addition of alkyl radicals to unactivated ketones and aldehydes is now even well established[73]. At present, one cannot definitively rule out a two-electron (diketyl) coupling. However, unless a single Sm^{3+} cation complexes both ketyls, one might not expect pure *cis*-diols to be formed by such a two-electron process[102].

Related to the intramolecular pinacolic coupling reactions in some respects is a ketone–nitrile reductive coupling process. This process also permits the construction of highly

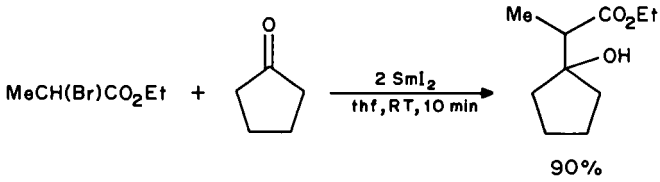
functionalized carbocycles[87], although the yields are somewhat reduced owing to the reluctance of nitriles to undergo radical addition reactions (equation 131).



(131)

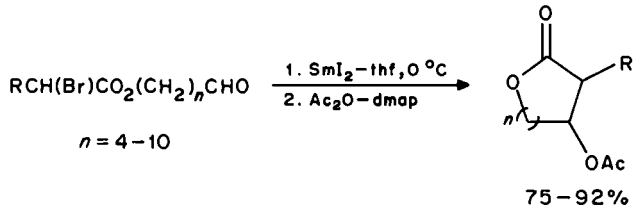
5. *Reformatsky-type reactions*

Reduction of α-halo esters by SmI_2 has been discussed previously[66a], and it has been suggested that samarium ester enolates are likely intermediates in this reaction (see Scheme 4). Indeed, a Reformatsky-type coupling reaction can be carried out between α-halo esters and ketone electrophiles when mediated by SmI_2 (equation 132)[55c,60]. Although a systematic survey has not been conducted, it would appear that this reaction provides a useful alternative to the normal zinc-promoted Reformatsky reaction. The latter often performs well only when an activated form of zinc is utilized, and thus the homogeneous conditions afforded by SmI_2 may provide some advantages.



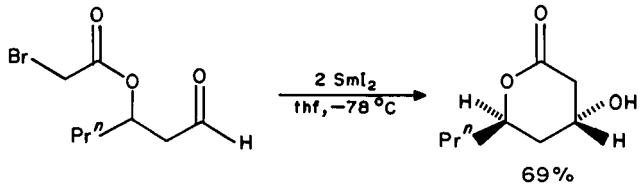
(132)

The procedure has been adapted to permit construction of medium- and large-ring lactones through an intramolecular process (equation 133)[104]. Eight- to fourteen-membered ring lactones can be synthesized in this fashion in 75–92% yields, and the process appears to be much better than procedures involving use of Zn–Ag–Et_2AlCl[105]. The diastereoselectivity in the SmI_2-mediated cyclizations was less than 2.5:1.



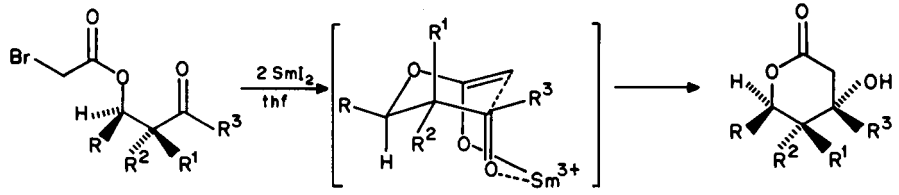
(133)

Reductive cyclizations of β-bromoacetoxy aldehydes and ketones promoted by SmI_2 afford β-hydroxy valerolactones with unprecedented degrees of 1,3-asymmetric induction in the process (equation 134)[106]. Stereodefined β-hydroxy valerolactones generated in this fashion are structurally analogous to compactin lactone, and are expected to be potent inhibitors of HMG-CoA reductase (the key enzyme involved in biosynthesis of cholesterol). Numerous attempts at utilizing zinc-mediated intramolecular Reformatsky reactions to access these lactones have failed. The successful development of the SmI_2-based methodology therefore provides perhaps the most convenient entry to this important class of molecules[106].



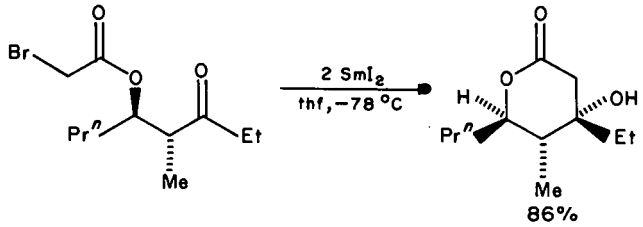
(134)

Yields in the SmI_2-promoted intramolecular Reformatsky reaction are typically higher for ketone than for aldehyde substrates, but in both diastereoselectivity is virtually complete. It has been suggested that reaction of SmI_2 with the β-bromoacetoxy carbonyl substrate initially generates an Sm^{3+} ester enolate, with cyclization taking place through a rigid cyclic transition structure enforced by chelation (Scheme 12)[106].

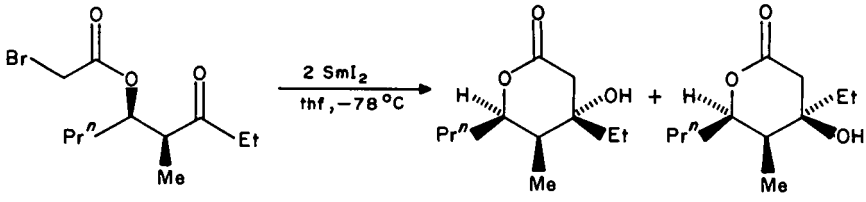


SCHEME 12

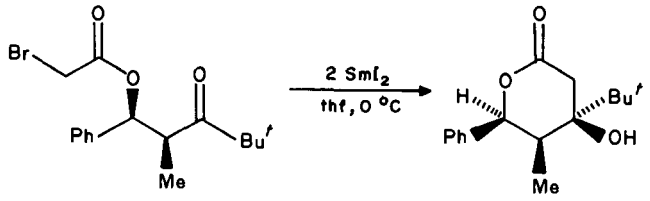
In contrast to other reported methods of 1, 3-asymmetric induction, the SmI_2-mediated intramolecular Reformatsky procedure permits strict control of stereochemistry even in diastereomeric pairs of substrates bearing α substituents (equations 135 and 136)[106]. Although the diastereoselectivity is decreased for the *syn* diastereomeric substrate where the α-substituent would be axially disposed in the proposed transition structure leading to the product, 1, 3-asymmetric induction is still predominant, and overwhelms other effects to an impressive extent. A single exception to this general pattern of diastereoselection has been reported (equation 137)[106]. Steric factors which preclude access to the chair transition structure may be responsible for the change in the sense of diastereoselectivity in this example.



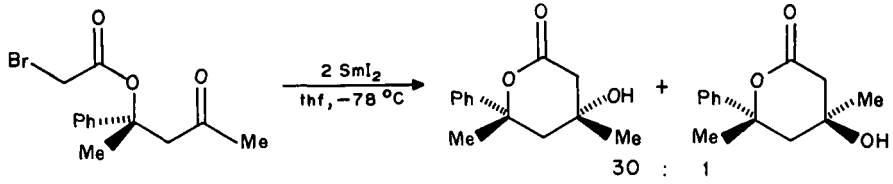
(135)



(136)



(137)



(138)

Perhaps even more impressive is the fact that 1, 3-asymmetric induction can be relayed from a tertiary acetoxy stereocenter (equation 138)[107]. The unprecedented degree of stereochemical control exhibited by this process appears to be general for aldehydes and ketones, although the scope of the reaction with regard to substituent effects at the β-position remains to be fully explored.

6. *Samarium acyl anions*

Lithium acyl anions, long sought as unique intermediates, have only recently been synthesized and utilized in synthetic organic chemistry[108]. These reactive organometallics are generated by reaction of organolithiums with carbon monoxide at extremely low temperatures. Samarium acyl anions, on the other hand, can apparently be prepared under reductive conditions by reaction of SmI_2 with acyl halides[1c,109]. In the absence of any other electrophiles, the acyl halides provide moderate yields of α-diketones under these conditions (equation 139). The main by-product generated in these reactions is the α-ketol.

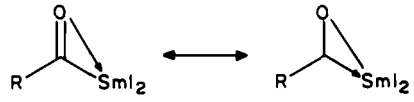
$$Cl(CH_2)_4COCl \xrightarrow[\text{thf, RT, 8min}]{2SmI_2} Cl(CH_2)_4COCO(CH_2)_4Cl \quad (139)$$

54%

Mechanistic studies strongly suggest the intermediacy of a samarium acyl anion. For example, the phenyl acetyl radical ($PhCH_2CO^{\cdot}$) is known to decarbonylate rapidly ($k = 5.2 \times 10^7\,s^{-1}$), providing a benzyl radical which dimerizes to bibenzyl[110]. However, addition of phenylacetyl chloride to a solution of SmI_2 in thf leads to a 75% yield of the expected diketone, and neither toluene nor bibenzyl is detected. Apparently, reduction of the acyl radical to the corresponding anion proceeds at a rate which is much greater than $5.2 \times 10^7\,s^{-1}$.

The acylsamarium species has not been isolated or characterized spectroscopically. Its structure (1) has tentatively been assigned as analogous to that of [$Cp_2LuCOBu^t$], which has been prepared from [Cp_2LuBu^t] and CO[1c].

The samarium acyl anions can be trapped by electrophiles other than acid halides. For example, addition of a mixture of a carboxylic acid chloride and an aldehyde or ketone to a solution of SmI_2 in thf results in the synthesis of α-hydroxy ketones (equations 140 and



(1)

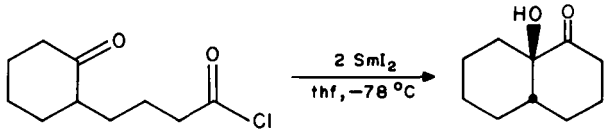
141)[111]. Intramolecular versions of the reaction have also been performed, although the scope of the reaction is limited owing to the difficulty in obtaining suitable substrates for the reaction (equation 142)[112].

$$\text{Oct}^n\text{COCl} + \text{EtCHO} \xrightarrow[2.\ H_3O^+]{1.\ 2SmI_2} \text{Oct}^n\text{COCH(OH)Et} \quad (140)$$

63%

$$\text{Ph}_2\text{NCOCl} + \text{Hept}^n\text{CHO} \xrightarrow[2.\ H_3O^+]{1.\ 2SmI_2} \text{Ph}_2\text{NCOCH(OH)Hept}^n \quad (141)$$

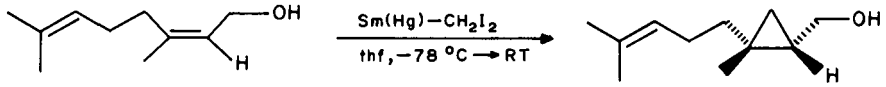
67%



82% (142)

7. *Samarium-promoted Simmons–Smith-type reactions*

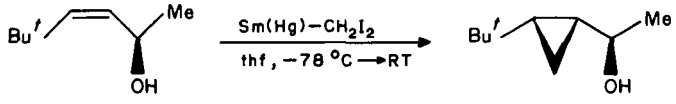
One of the best methods for preparing SmI_2 is to treat samarium metal with diiodomethane (equation 75). Presumably, oxidative metalation occurs to provide '$ISmCH_2I$'. α-Elimination ensues, generating SmI_2 and methylene. This suggested that the presumed carbenoid intermediate might be trapped by olefins, providing an alternative to the traditional Simmons–Smith procedure for the preparation of cyclopropanes. Indeed, the procedure works very well, providing a useful alternative to the zinc-promoted process[113]. Reaction of nerol with $Sm(Hg)–CH_2I_2$ provides a single diastereomeric product (equation 143). In contrast to the zinc-mediated reaction, no by-products can be detected which result from cyclopropanation of the isolated olefin. In fact, subjection of monocyclopropanated nerol to the reaction conditions leads to complete recovery of the starting material. This result and failed attempts to cyclopropanate other isolated olefins and even homoallylic alcohol substrates demonstrate that the $Sm(Hg)–CH_2I_2$ protocol is highly specific for allylic alcohols[113].



99% (143)

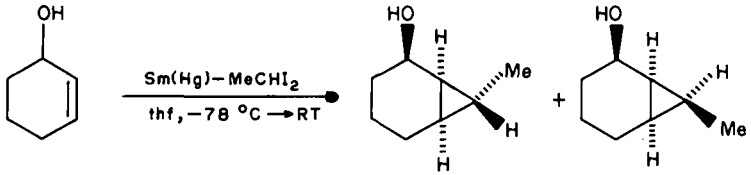
In addition to enhanced chemoselectivity, higher diastereoselectivity can often be achieved in the samarium-promoted reactions than in classical Simmons–Smith reactions (equation 144). Perhaps a major reason for this is that Sm(Hg)-promoted reactions appear to initiate at −60 °C, whereas most zinc-mediated reactions are carried out in boiling

diethyl ether. Alkylidenation reactions can also be performed utilizing Sm(Hg), allowing one to avoid the use of pyrophoric diethylzinc for such processes. In addition, the samarium-promoted reaction permits higher diastereoselectivities to be achieved in this transformation (equation 145).



99%

(144)

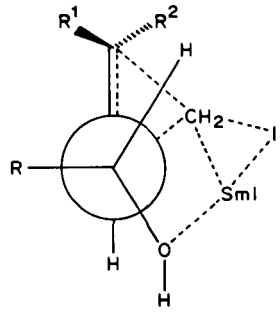


5 : 1

100%

(145)

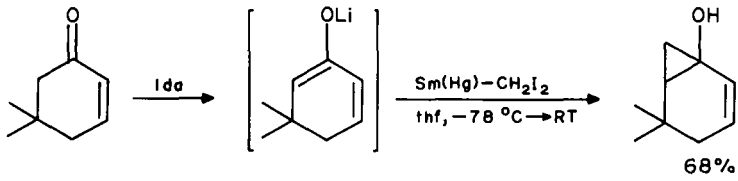
It is clear from the studies that have been performed that a very prominent hydroxy-directing effect is operative in these reactions. Based on this fact and the observed stereochemistry of the products, an empirical model (**2**) has been developed for the reaction[113]. The model is based on a combination of Houk and coworkers' staggered model for electrophilic addition to olefins[114] and their model for addition of carbenoids to olefins[115].



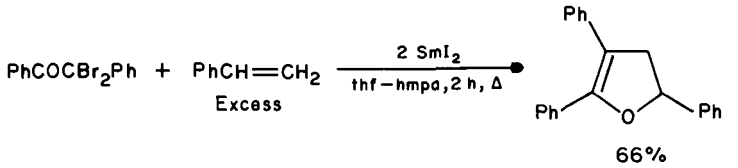
(2)

Cyclopropanation reactions can also be achieved by utilizing SmI_2 in place of Sm(Hg) as a reductant for the process[116]. The SmI_2–CH_2I_2 combination exhibits much the same selectivity as the Sm(Hg)–CH_2I_2 protocol, leading to speculation that the same active reagent is generated in each case. Further studies have revealed that Sm(Hg)–CH_2ICl may provide an even better combination of reagents in terms of reactivity and selectivity for these cyclopropanation reactions[117].

The first successful cyclopropanation of enolates was carried out utilizing SmI_2–CH_2I_2 (equation 146)[76c]. The reaction appears to be general for a variety of lithium enolates. This particular study was initiated to support the postulate that cyclopropanation of α-halo ketones by Sm–CH_2I_2 proceeds via initial generation of a samarium enolate



(146)



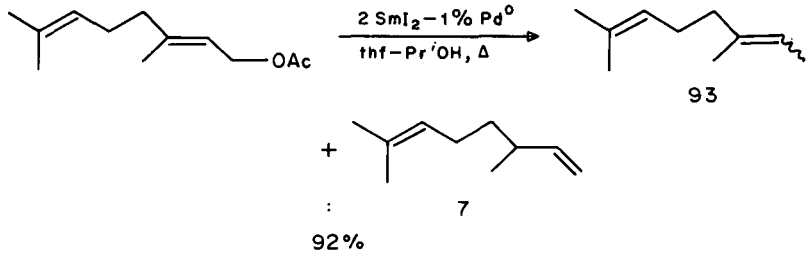
(147)

(see equation 102). Subsequent cyclopropanation of the enolate, resulting in the production of cyclopropanols, appears to be feasible based on this mechanistic study.

Ketocarbenoids can be generated from α,α-dibromodeoxybenzoin by reaction with SmI_2. The reactive intermediates produced in this fashion undergo a formal 1,3-dipolar cycloaddition with activated alkenes, resulting in formation of dihydrofurans (equation 147)[118]. The same procedure utilizing zinc as the reductant requires 2 days in benzene heated at reflux to proceed to completion, and very low yields are obtained. Most aryl-substituted alkenes and isoprene provide good conversions to the desired products. However, aliphatic alkenes such cyclohexene and hex-1-ene provide little, if any, dihydrofurans.

8. Oxidative–reductive transmetalation reactions

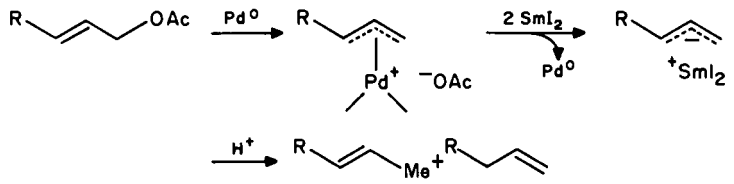
Allylic acetates can be reduced to the corresponding alkenes by employing SmI_2 in the presence of a catalytic amount of palladium(0) complexes (equation 148)[119]. The



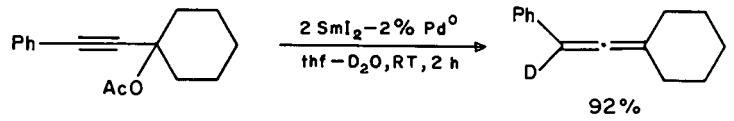
(148)

regiochemistry of the double bonds is greatly dependent on the substitution patterns in these systems. No reaction occurs in the absence of the palladium(0) catalyst, and an η^3-allylpalladium species is undoubtedly a key intermediate. Once generated, the η^3-allylpalladium probably undergoes oxidative–reductive transmetalation with SmI_2 to generate an allylsamarium species. The latter is protonated, providing the observed products (Scheme 13). Significantly, palladium(II) salts can also be utilized in the reaction, indicating that SmI_2 produces a palladium(0) species *in situ* which is capable of entering the catalytic cycle.

Propargyl acetates undergo the same type of conversion, which provides a mild and convenient entry to allenes[120]. Tertiary propargylic acetates lead exclusively to allenes, and utilization of D_2O as a proton source provides a monodeuterated product (equation 149).



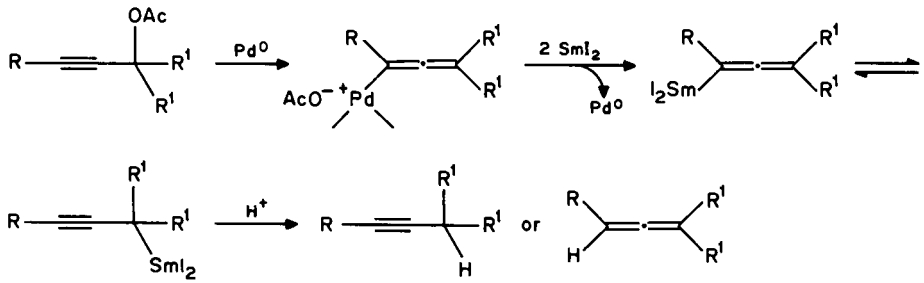
SCHEME 13



(149)

92%

The proposed mechanism is similar to that suggested for the allylic acetates above. In this instance, an allenic–propargylic samarium anion is presumably generated and protonated after the oxidative–reductive transmetalation from the originally formed organopalladium species (Scheme 14).



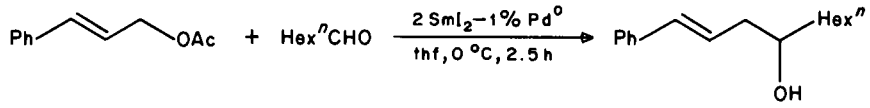
SCHEME 14

The ratio of allene to alkyne product derived from secondary propargylic acetates by this process is highly dependent on the steric bulk of the protonating agent. Highly hindered alcohols dramatically increase the proportion of allenes that are generated in these reactions (equation 150). Primary propargylic acetates provide mixtures of allene and alkyne in which the alkyne predominates, even when sterically encumbered alcohols are employed as proton sources.

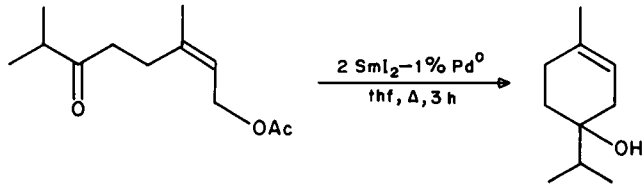
$$Ph(CH_2)_2CH(OAc)C{\equiv}C(CH_2)_3Me \xrightarrow[\text{thf, 40°C, 2h, proton source}]{2SmI_2\text{–}5\%Pd^0} Ph(CH_2)_2CH{=}C{=}CH(CH_2)_3Me + Ph(CH_2)_3C{\equiv}C(CH_2)_3Me \quad (150)$$

Proton source	Allene	:	Alkyne
H_2O	1	:	1.5
Pr^iOH	7	:	1
2,4-dimethylpentan-3-ol	20	:	1

Samarium anions generated as intermediates can also be trapped by other electrophiles. Successful carbonyl addition to aldehydes and ketones can be accomplished, providing a facile route to homoallylic alcohols (equation 151)[121]. Since allylic acetates (and η^3-



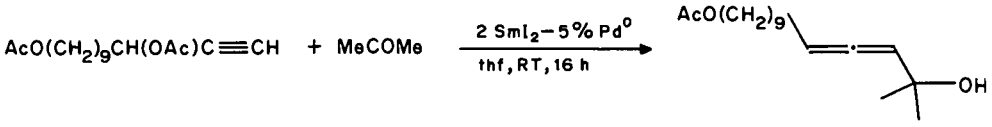
63% (151)



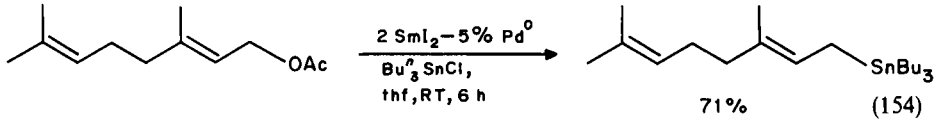
62% (152)

allylpalladiums) are normally considered to be electrophilic species, the SmI_2 creates a polarity inversion in these substrates. In most cases, carbon–carbon bond formation occurs at the least substituted terminus of the allylic unit, in accord with the allylcerium chemistry described above. A wide range of aldehydes and ketones can be utilized in the reaction, and one cyclization process has been reported (equation 152). Aromatic and α,β-unsaturated substrates cannot be used owing to competitive pinacolic coupling reactions.

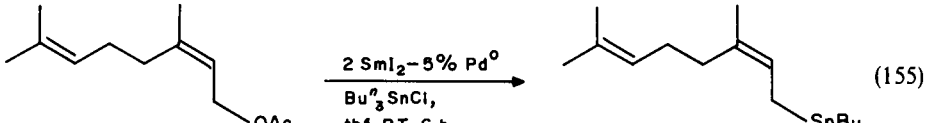
Progargylic acetates undergo an analogous reaction with ketones[122]. Aldehydes can be utilized only with highly reactive propargylic acetates owing to competitive pinacolic coupling. Primary propargylic acetates produce mixtures of allenic and homopropargylic alcohols, whereas most secondary and all tertiary propargylic carboxylates provide exclusively the allenic alcohols (equation 153). Although other transition metal salts [e.g. palladium(II), nickel(II), and cobalt(II)] can be utilized as catalysts, lower yields are obtained.



46% (153)

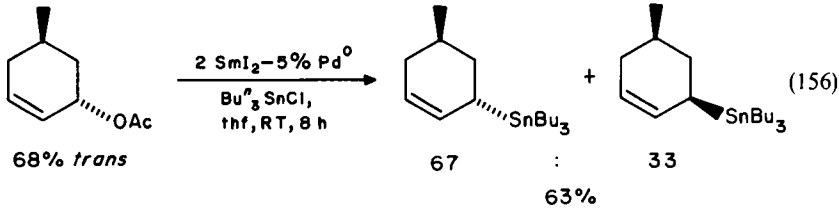


71% (154)

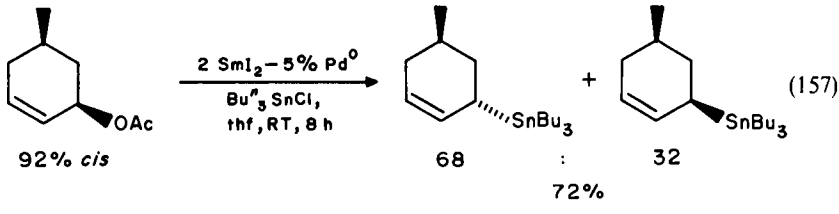


85% (155)

A novel method for the synthesis of allylstannanes has stemmed from the oxidative–reductive transmetalation studies[123]. Reaction of allylic acetates with SmI_2–palladium(0) in the presence of trialkyltin chlorides produces allylstannanes under mild conditions. The R_3SnCl electrophile reacts at the least substituted terminus of the allylic unit and, further, the original stereochemistry of trisubstituted allylic acetates is retained in the final product (equations 154 and 155). Unfortunately, the oxidative–reductive transmetalation appears to eradicate the stereochemical integrity established by the catalyst in generating η^3-allylpalladium species. Stereodefined *cis*- and *trans*-5-methylcyclohexenyl acetates thus converge to the same mixture of stereoisomeric allylstannanes, indicative of a common anionic intermediate (equations 156 and 157). Isolated esters and organic halides can be tolerated in allylic acetate substrates, permitting the construction of functionalized allylstannanes.



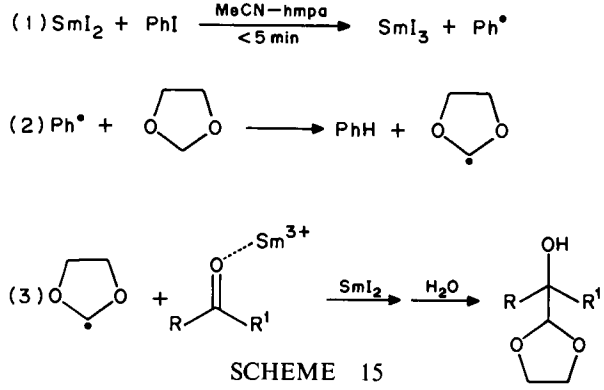
(156)



(157)

9. *Miscellaneous related studies*

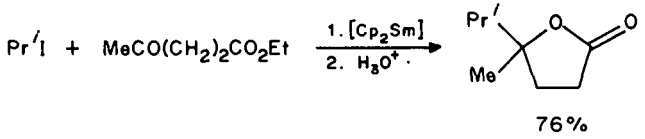
A new method for the masked formylation of aldehydes and ketones has been developed which relies on the ability of SmI_2 to generate phenyl radicals from iodobenzene. As pointed out previously, aryl halides do not undergo Barbier-type coupling reactions with ketones in the presence of SmI_2. Instead, thf adducts of the carbonyl compounds are



SCHEME 15

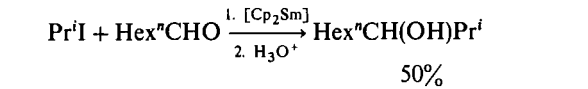
obtained (equation 93)[59]. When 1,3-dioxolane is utilized in place of thf, the initially formed phenyl radical can abstract a hydrogen from the dioxolane. The resulting dioxolanyl radical can couple to the carbonyl generating the observed products (Scheme 15)[124]. Both aldehydes and ketones can be utilized in the reaction, with yields ranging from 73 to 77% for five different substrates.

Although SmI_2 has been utilized to the near exclusion of other Sm^{2+} species as a reductant for organic synthesis, preliminary results have appeared on a promising new samarium(II) reductant. Dicyclopentadienylsamarium, $[Cp_2Sm]$, readily prepared from SmI_2 by reaction with dicyclopentadienylsodium, has been developed as an alternative to SmI_2, and shows improved reactivity in some reactions[125]. For example, experimental conditions in intermolecular Barbier reactions are much milder with $[Cp_2Sm]$ (room temperature) than with SmI_2 (thf heated at reflux). Secondary alkyl iodides, reluctant to react with SmI_2, can be efficiently coupled with $[Cp_2Sm]$ (equation 158).



(158)

Dicyclopentadienylsamarium also allows efficient Barbier coupling of organic iodides with aldehydes. Only highly reactive organic halides (e.g. allyl bromide or benzyl bromide) can be efficiently coupled to aldehydes with SmI_2. The enhanced reactivity of $[Cp_2Sm]$ permits even secondary alkyl iodides to undergo Barbier reactions with aldehydes, providing the desired alcohols in reasonable yields (equation 159). Further studies are likely to uncover other useful reactivity patterns for this reductant which complement SmI_2.



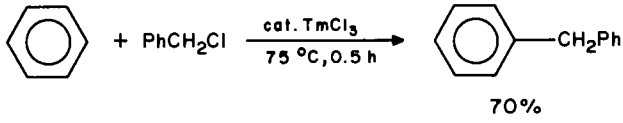
(159)

V. LANTHANIDE SALTS AS LEWIS ACID CATALYSTS FOR CARBON—CARBON BOND-FORMING REACTIONS

As pointed out previously, lanthanide(III) ions are considered to be 'hard' Lewis acids according to the HSAB concept enunciated by Pearson[10]. This property has been used to great advantage in various aspects of organic chemistry. For example, lanthanide complexes are salts of choice as shift reagents for NMR studies[11]. In addition, they serve as mild yet effective Lewis acids for acetal formation, for the selective reduction of conjugated ketones into allylic alcohols, for a variety of rearrangement reactions, and for a number of other transformations[1]. Several efficient methods for carbon—carbon bond-forming reactions can also be promoted by lanthanide Lewis acids, and these are outlined below.

A. Friedel–Crafts Alkylation Reactions

Although early reports suggested that lanthanide trichlorides were weak catalysts for the Friedel–Crafts alkylation process[126], later studies have demonstrated that nearly all of the lanthanide trichlorides are in fact fairly effective in promoting this very important process[127]. The late lanthanide salts ($DyCl_3$, $TmCl_3$, and $LuCl_3$) demonstrate particularly



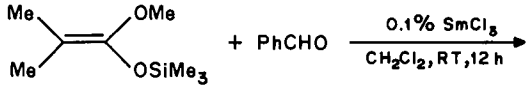
(160)

high activity in the process, whereas $LaCl_3$ possesses little catalytic reactivity (equation 160).

In these processes, the arene is used as the solvent. Only small amounts of dibenzylbenzenes are generated under these reaction conditions. A number of different alkyl halides can apparently be utilized, and the lanthanide catalysts can be reused after the usual aqueous work-up of the reaction mixture. This is a great advantage over more traditional catalysts, such as $AlCl_3$, which cannot be recovered in active form after the desired reaction is complete.

B. Directed Aldol Reactions

A preliminary report has appeared on the use of lanthanide Lewis acids to promote aldol condensations of trimethylsilyl ketene acetals with aldehydes[128]. Although a number of these salts have proved effective, the most active catalyst for these particular reactions appears to be $SmCl_3$. The latter is much more effective than $CeCl_3$, $LaCl_3$, or tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionatoeuropium(III), [Eu(fod)$_3$], (equation 161). It is presumed that the lanthanides, like Ti^{4+}, form stable aldolate chelates, preventing retroaldol reactions leading to mixtures of products. It will be of interest to determine the scope of these lanthanide-promoted aldol reactions, including the sense and degree of relative asymmetric induction that can be achieved in appropriate examples.



$$PhCH(OSiMe_3)C(Me)_2CO_2Me + PhCH(OH)C(Me)_2CO_2Me \quad (161)$$

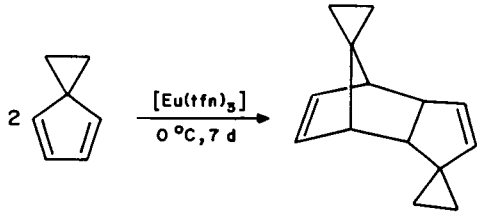
66% 28%

C. Diels–Alder Reactions

Numerous Lewis acids have been utilized as catalysts to facilitate Diels–Alder reactions. In addition to a large rate acceleration, enhanced regioselectivity and stereoselectivity (*endo*:*exo* ratios) is also observed in these Lewis acid-catalysed cycloaddition reactions[129]. Various lanthanide reagents have found applications as highly selective catalysts for these transformations, and again provide access to unique reaction manifolds that appear difficult, if not impossible, to achieve utilizing other more common Lewis acid reagents.

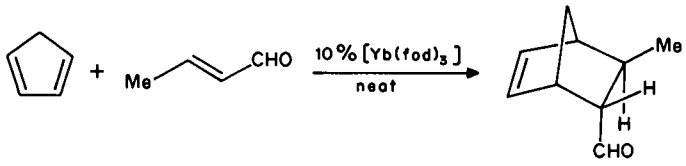
1. Homo Diels–Alder reactions

During the course of an investigation of new chiral shift reagents for n.m.r., it was discovered that Eu^{3+} salts could catalyse the dimerization of spiro[2.4]hepta-4,6-diene by a Diels–Alder cycloaddition process (equation 162)[130]. The shift reagent utilized in this particular study was tris[1,1,1,2,2,3,3,7,7,8,8,9,9,9]tetradecafluorononane-4,6-dionatoeuropium(III), [Eu(tfn)$_3$]. No dimerization was evident in mixtures where the lanthanide catalyst was not present.



(162)

The mild experimental conditions permitted by using lanthanide catalysts in these reactions allow the extension of the methodology to reactions in which acid labile components are to be combined. For example, the Diels–Alder reaction between acrolein and other sensitive dienophiles with a variety of dienes has been examined[131]. Most dienes (even furan) react with acrolein at room temperature in 1–2 days. High yields of the desired product can be obtained, with *endo* selectivity exhibited in most of the examples studied. Crotonaldehyde can also be utilized, again providing adducts in which the *endo* isomer predominates by a factor of 10:1 (equation 163).

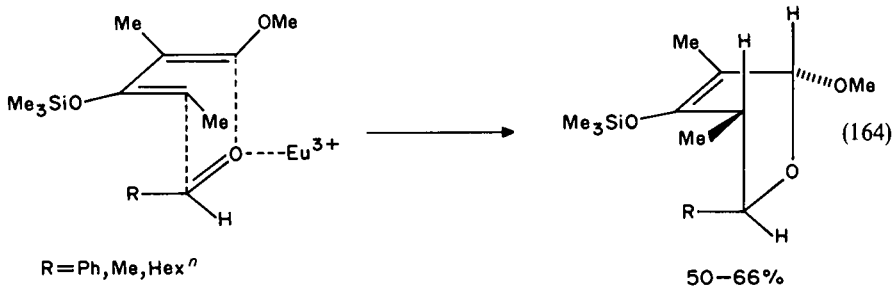


(163)

2. *Hetero Diels–Alder reactions*

Perhaps the most dramatic examples of lanthanide Lewis acid catalysis have resulted from pioneering work by Danishefsky and coworkers in hetero Diels–Alder reactions. These elegant studies have led to unprecedented entries to highly substituted, stereodefined dihydropyran derivatives.

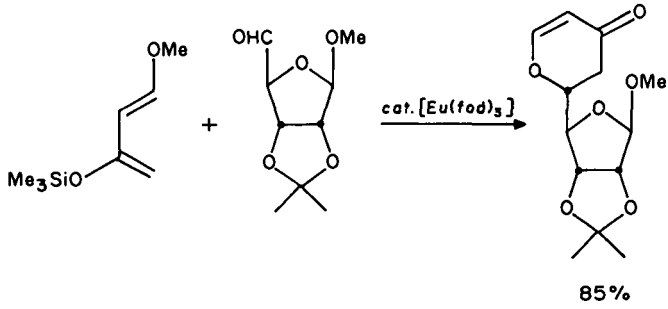
In the reaction scheme devised by Danishefsky and coworkers, oxophilic lanthanide salts complex with aldehyde substrates, generating potent heterodienophiles for the desired cyclocondensation. The Lewis acid complex also serves to effectively control stereochemistry of the process (equation 164)[132]. Since there are no obvious secondary orbital interactions which would place the simple alkyl (R) group of the aldehyde *endo* in the transition structure, it has been suggested that steric effects associated with the Lewis acid complex control the overall stereochemistry of the process. Hence it is logical to assume that the lanthanide cation binds *anti* to the alkyl group of the aldehyde. If the effective size of the cation–solvent array is more substantial than that of the alkyl (R) group of the aldehyde, then one could explain the observed *endo* selectivity as a consequence of



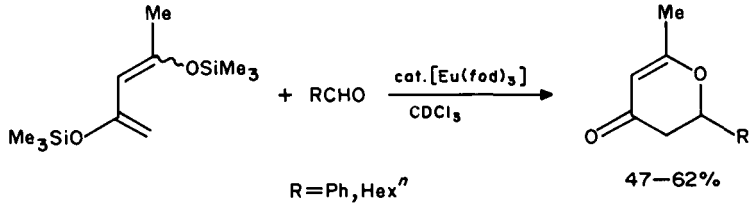
(164)

exo directivity of the catalyst–solvent ensemble. It is interesting that this '*endo* selectivity' is very much a function of the substitution pattern about the diene, and the stereoselectivity decreases considerably for some simpler dienes[133].

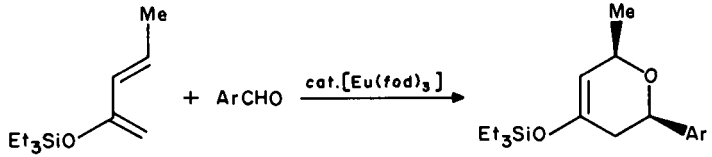
Various dienes with several different substitution patterns successfully undergo the lanthanide-catalysed cyclocondensation reaction with aldehydes. For example, 1,3-dioxygenated dienes react very efficiently with aldehydes under Lewis acid catalysis to provide the desired adducts in excellent yield (equation 165)[134]. 1-Alkyl-1,3-dioxygenated dienes afford a simple, one-step route to 6-substituted-2,3-dihydropyrones (equation 166)[135]. 1-Alkyl-3-oxygenated dienes also perform extremely well in the cycloaddition reaction, providing essentially quantitative yields of the desired adducts (equation 167). Again in this instance, the Lewis acid complex apparently serves to control stereochemistry through *exo*-directing steric effects.



(165)

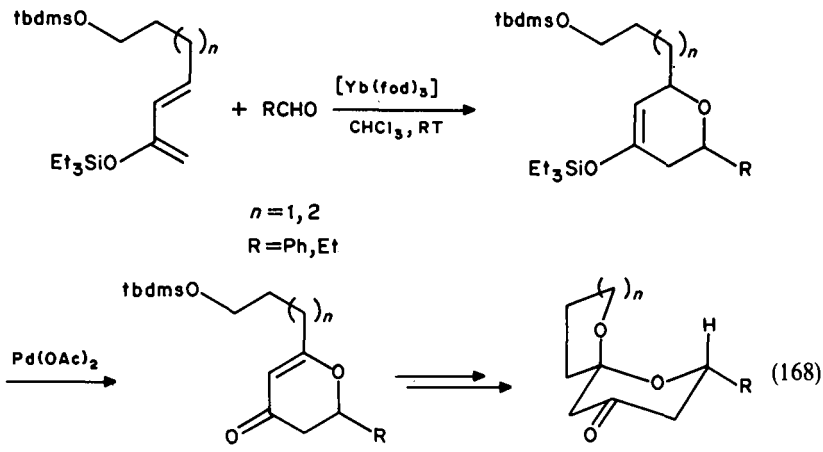


(166)



(167)

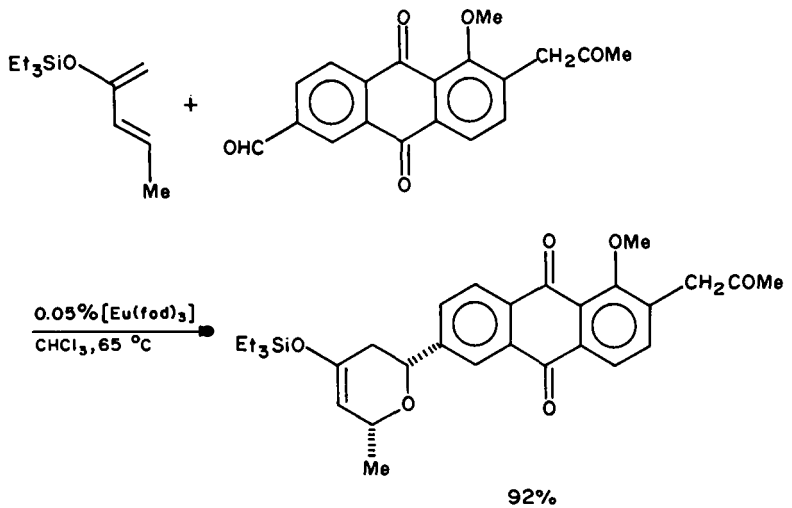
A strategy for the generation of spiroketals has emerged from the cyclocondensation of aldehydes with appropriately functionalized 1-alkyl-3-oxygenated dienes[136]. The catalyst of choice for this hetero Diels–Alder process is $[Yb(fod)_3]$. Less than 5% of this Yb^{3+} catalyst is required for the process, whereas a full equivalent of $ZnCl_2$ is necessary for complete reaction (equation 168). The $[Yb(fod)_3]$ catalyst is also more effective than the corresponding $[Eu(fod)_3]$ species, perhaps owing to the former's enhanced Lewis acidity.



(168)

Subsequent oxidation of the crude cycloadducts with $Pd(OAc)_2$ followed by cyclization provides hemiketals. A variety of substitution patterns can be obtained, depending on the nature of the final cyclization strategy.

The demonstrated *endo* selectivity provided by Lewis acid-catalysed hetero Diels–Alder reactions has been exploited in a key step in the total synthesis of vineomycin B_2 aglycon[137]. Construction of the *C*-glycoside fragment in the molecule was accomplished by a $[Eu(fod)_3]$-catalysed cyclocondensation between an aromatic aldehyde and appropriate diene (equation 169). One advantage in utilizing a lanthanide catalyst for this

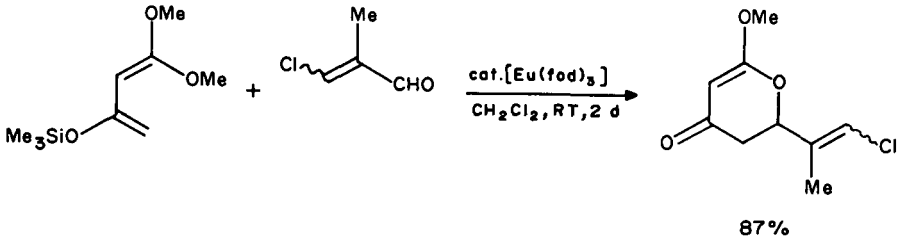


(169)

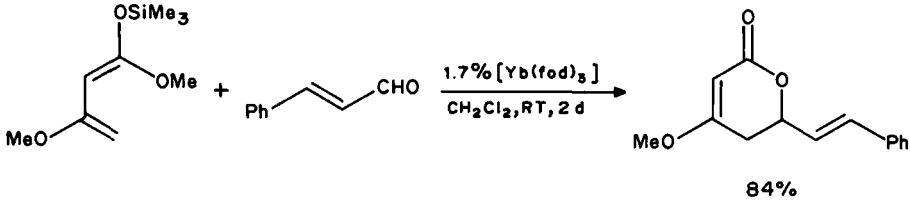
process is the ability to tolerate the sensitive silyl enol ether functionality under the mild reaction conditions required.

Several groups have exploited the hetero Diels–Alder chemistry to provide efficient routes to dihydropyrones[135,138]. Thus, 1,1,3-trialkoxydienes treated with appropriate aldehydes in the presence of a lanthanide(III) catalyst provide excellent yields of the

desired 2-alkoxy-5, 6-dihydro-γ-pyrones (equation 170). The example shown is particularly remarkable since the aldehyde substrate contains two potential dienophiles, i.e. the carbonyl double bond in addition to a very dienophilic carbon—carbon double bond. In the absence of the lanthanide catalyst, a 1.35:1 mixture of the desired product and the product resulting from cycloaddition to the carbon—carbon bond is generated in 29% yield. The lanthanide catalyst serves not only to improve yields and provide a single regioisomeric product in these processes, but also directs cyclocondensation to the activated carbonyl subunit of conjugated enal systems. A highly efficient synthesis of (±)-kawain has been completed based on this dramatic selectivity (equation 171)[138b]. Again in this instance, the stronger Lewis acid catalyst, Yb^{3+}, provides higher yields than either Eu^{3+} or stoichiometric $ZnCl_2$.

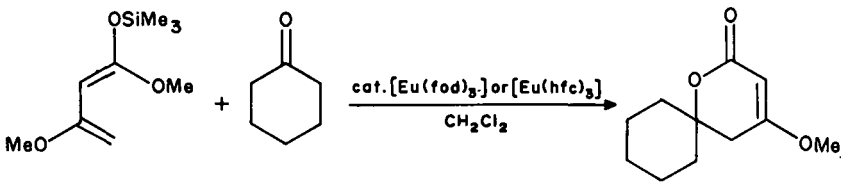


(170)



(171)

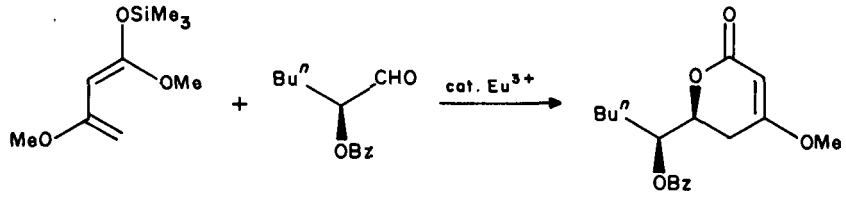
Noting that simple alkyl and aryl ketones had received little attention as dienophiles for the hetero Diels–Alder reaction, Midland and Graham[138c] examined the use of 1,3-dimethoxy-1-(silyloxy)butadiene (Brassard's diene) with several unactivated ketones (equation 172). In fact, regiospecific condensation was achieved utilizing a variety Lewis acid promoters, including [Eu(fod)$_3$] and tris{3-[(heptafluoropropyl)-hydroxymethylene[-*d*-camphorato}europium(III), [Eu(hfc)$_3$].



(172)

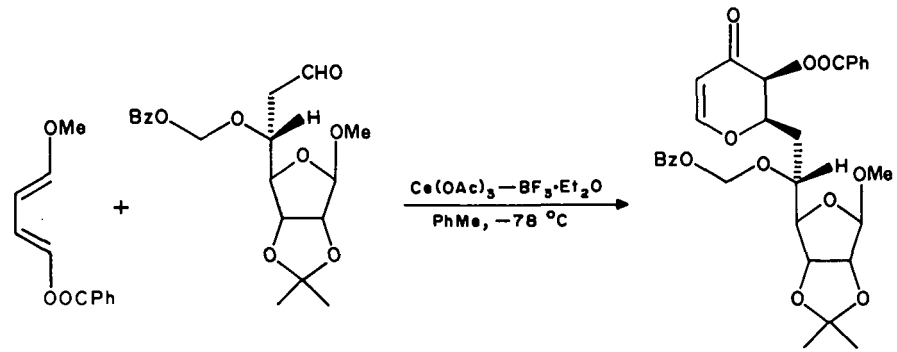
The cyclocondensations of Brassard's diene with aldehydes possessing an adjacent stereocenter provided the opportunity for achieving 1,2-asymmetric induction in the

process. Although aldehydes bearing α-substituents incapable of chelation as well as β-alkoxyaldehydes show marginal selectivity with Brassard's diene, α-alkoxyaldehydes provide > 60:1 diastereoselectivity through a chelation-controlled process utilizing the Eu^{3+} catalysts (equation 173)[138c]. Zinc chloride, boron trifluoride etherate, and magnesium bromide all yielded disappointing diastereoselectivity. These results were very surprising since previous studies had shown that magnesium bromide and titanium tetrachloride (but not lanthanides) demonstrated excellent stereochemical control through chelation in related processes[132,139]. The difference was ascribed to the 1,1-dialkoxy substitution pattern of Brassard's diene versus the single alkoxy group at the 1-position of Danishefsky's diene. Substituents at the 1-position of these systems appear to play a key role in achieving relative asymmetric induction in cyclocondensation processes.



(173)

A single example in which lanthanide catalysts have been utilized to control the conformation of a β-alkoxy-substituted aldehyde in a hetero Diels–Alder process has been reported[134]. In this instance, a Ce^{3+} complex was utilized in conjunction with boron trifluoride etherate to promote cyclocondensation and control stereochemistry in the process through chelation (equation 174). The reaction was performed as a key step in the fully synthetic route to tunicaminyluracil.

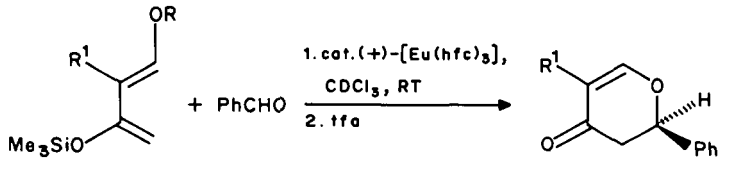


45%

(174)

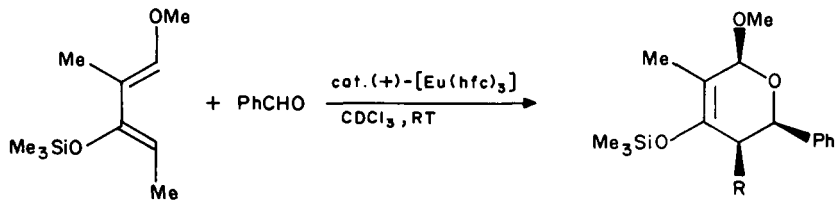
Some success has been achieved in utilizing chiral, non-racemic lanthanide catalysts for absolute asymmetric induction in cyclocondensation processes. A systematic survey of the effect of substitution patterns about the diene has revealed that, in general, substituents at the termini of the diene system play a large role in determining the extent of chiral

induction, whereas substituents at the 2- or 3-positions appear to be of little consequence (equations 175 and 176)[138c,140]. The most dramatic increase in enantioselectivity in these processes is produced by modifying the reaction conditions. Whereas essentially no change in the enantiomeric excess was noted on increasing the proportion of chiral catalyst, conducting the reaction in the absence of solvent at reduced temperatures considerably improved chiral induction (equation 177). The source of asymmetric induction in these systems is unknown, and no model has been proposed that has predictive value. Other diene–heterodienophile systems have been reported which exhibit modest[141] or no asymmetric induction utilizing the same chiral lanthanide catalyst[138c].



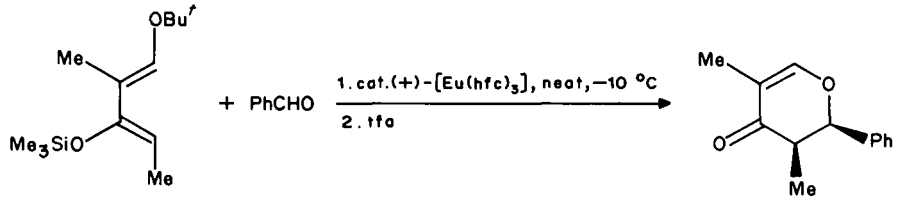
R	R^1	%ee
Me	H	18
Bu^t	H	38
Bu^t	OAc	33

(175)



R	%ee
H	15
Me	36

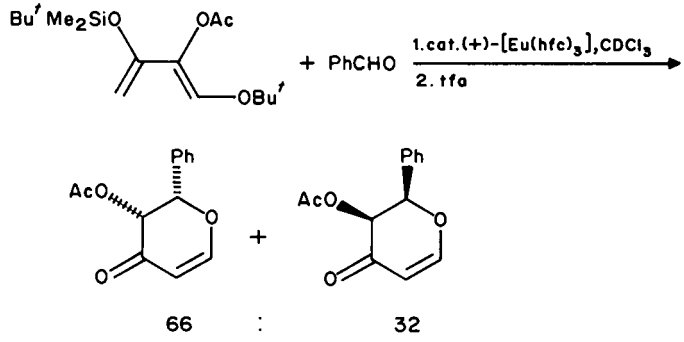
(176)



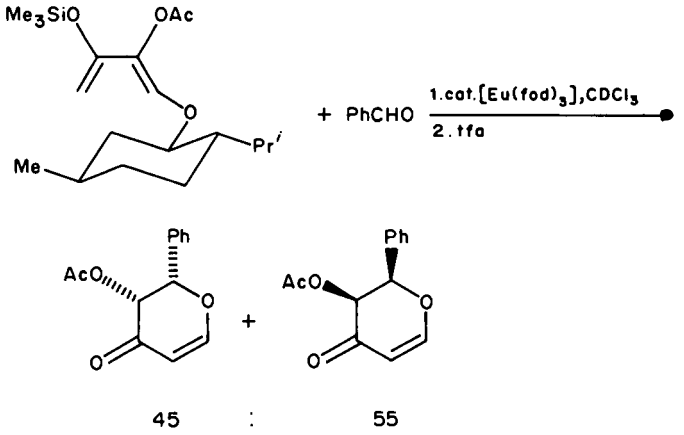
55%ee

(177)

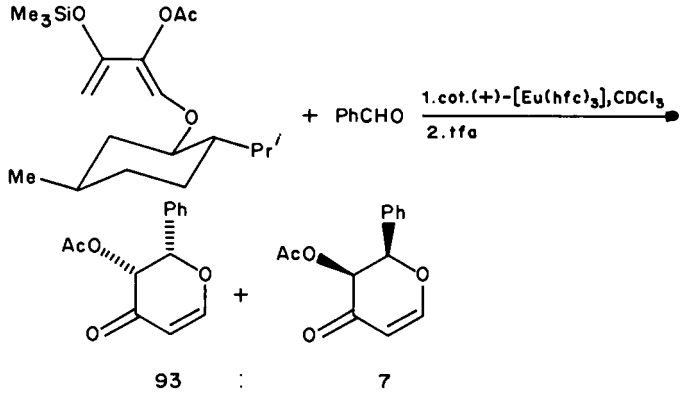
A totally new concept in asymmetric induction has been introduced as a result of hetero Diels–Alder reaction studies employing chiral catalysts in conjunction with dienes containing chiral auxiliaries[142]. Termed 'specific interactivity' of chiral catalysts and chiral auxiliaries, the method results in diastereofacial excesses of 95% in select cases. Equations 178–180 serve to illustrate the concept.



(178)



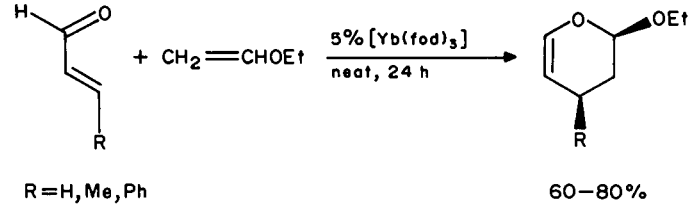
(179)



(180)

Utilizing a chiral lanthanide catalyst as in equation 178, modest enantioselectivity for the L-isomeric product can be achieved in the cyclocondensation reaction. Equation 179 demonstrates that a chiral (menthyl) auxiliary attached to the diene permits some selectivity for the D-isomeric pyranose derivative. The 'mismatched' pair{i.e. L-selective (+)-[Eu(hfc)$_3$] and D-selective diene, equation 180} produces a strikingly high diastereomeric ratio of the desired product. The diastereomeric excesses clearly do not reflect a simple numerical factoring of individual biases of these reagents (simple double stereodifferentiation), but are a consequence of 'specific interactivity' inherent in the process itself. The process shows great promise in the hetero Diels–Alder chemistry described herein, and could prove important in many other transformations as well.

It has been mentioned many times that lanthanide catalysts permit reactions of dienes and dienophiles which contain sensitive functional groups. A particularly good illustration of this is the inverse electron demand Diels–Alder reaction reported by Danishefsky and Bednarski[143]. In this version of the hetero Diels–Alder reaction, heterodienes and enol ethers combine to generate dihydropyrans (equation 181). These reactions are apparently stereospecific, providing only products resulting from '*endo*' addition. The reaction is sensitive to steric and/or electronic effects, as more highly substituted enol ethers provide lower yields of the desired cyclocondensation products.



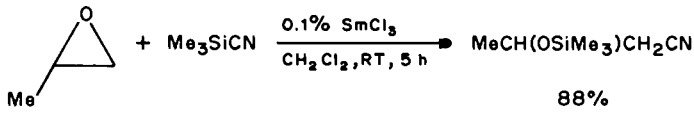
(181)

D. Addition and Substitution Reactions of Trimethylsilyl Cyanide

Other processes have been reported in which Lewis acidic lanthanide complexes facilitate carbon—carbon bond formation. For example, the addition of trimethylsilyl cyanide to aldehydes and ketones is effectively promoted by several lanthanide salts (equation 182)[128]. Preliminary studies have revealed that epoxides undergo efficient ring opening when treated with trimethylsilyl cyanide in the presence of lanthanide Lewis acid catalysts (equation 183)[128]. Although some feeling for regioselectivity to be expected can be gained from this example, no data are available on the stereoselectivity of the process when unsymmetrical epoxides are subjected to these reagents.

$$\mathrm{PhCHO} + \mathrm{Me_3SiCN} \xrightarrow[\mathrm{CH_2Cl_2,\ RT,\ 5h}]{0.05\%\ \mathrm{SmCl_3}} \mathrm{PhCH(CN)OSiMe_3} \quad (182)$$

>98%

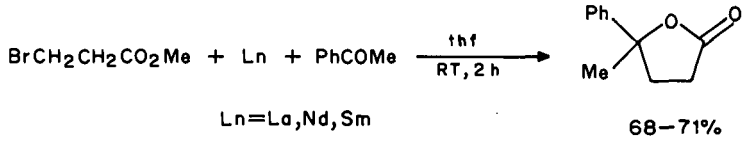


(183)

VI. MISCELLANEOUS PROCESSES

Preliminary reports have appeared concerning several promising areas of organolanthanide chemistry applied to organic synthesis. Although not as thoroughly developed as the procedures discussed so far, these diverse contributions point to future arenas where concentration of effort will provide exciting new breakthroughs in the application of lanthanide reagents to the selective synthesis of organic molecules.

As already discussed, a large effort has been devoted to exploring the use of organocerium reagents in organic synthesis, and these organometallics have rightfully assumed a very pivotal place in the arsenal of synthetic weapons at one's disposal. Cerium reagents may not be unique among the lanthanides in their reactivity, however. Indeed, a number of other organolanthanide reagents may be equally effective. One example is provided by nucleophilic reactions of β-metallo esters. Cerium metal has been settled upon as the most convenient metal reductant to use for these reactions. However, other lanthanides have been demonstrated to be equally effective (equation 184)[37].



(184)

Another example is provided by organolanthanides derived from simple transmetalation reactions. Organoceriums derived from organolithiums or Grignard reagents have been determined to be extremely useful in their ability to undergo carbonyl addition to highly enolizable aldehydes and ketones. Again, preliminary studies indicate that other organolanthanide reagents may also provide enhanced yields in such carbonyl addition reactions (equation 185)[13b].

$$PhCH_2COCH_2Ph + Bu^nLi\text{–}LnCl_3 \longrightarrow PhCH_2C(OH)(Bu^n)CH_2Ph \quad (185)$$

Ln = La, Nd, Pr, Sm, Yb 60–98%

At present, perhaps the only advantage in using cerium for these transformations is the low cost of this metal and its derivatives. It remains to perform studies which delineate more completely the reactivity differences between the various organolanthanide nucleophiles. This has been done to a limited extent by Kauffmann *et al.*[144] in studies designed to determine chemoselectivity in carbonyl addition reactions to aldehydes and ketones utilizing several organolanthanides. The results demonstrate that rather dramatic reactivity differences exist among the various reagents, with the 'early' organolanthanides providing much higher degrees of selectivity than the 'late' lanthanide counterparts (equation 186). Systematic investigations on a wider range of substrates to determine yields, chemoselectivity, and stereoselectivity patterns of the individual organolanthanide reagents will provide further insight into the unique reactivity of each of these nucleophiles.

$$Hex^nCHO\text{–}EtCOEt + MeM \xrightarrow{thf} Hex^nCH(OH)Me + Et_2C(OH)Me \quad (186)$$

$MeLaCl_2$	83%	11.5	:	1
$MeCeI_2$	40%	6.7	:	1
$MeSmCl_2$	49%	2.1	:	1
$MeNdI_2$	66%	2.0	:	1

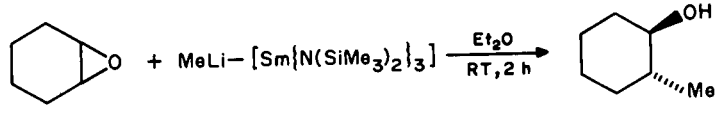
Different reactivity manifolds and reagent compositions also need to be assessed. For example, it has been reported that novel alkyl- and aryl-lanthanum triflates react with tertiary amides to provide the corresponding alkyl or aryl ketones in excellent yields (equation 187)[145]. In many instances this procedure is superior to that of more traditional methods utilizing organolithium reagents alone. Yields are generally higher with organolanthanum reagents, there is no metal–halogen exchange evident in reactions involving halogenated amides, and there is little if any enolization in amides prone to this side-reaction. Highly hindered amides do not react, but the procedure is otherwise quite general. Competition experiments have established that ketones react much more rapidly with organolanthanum reagents than do the corresponding amides. The success of the process is thus ascribed to the slow breakdown of an initially formed tetrahedral intermediate to the corresponding ketone. Further studies may well reveal other advantages to utilization of these unique organolanthanide reagents.

$$\underset{\text{R = Me, Bu}^n\text{, Ph}}{\text{RLi} + [\text{La(OTf)}_3] \xrightarrow[-78\,^\circ\text{C}]{\text{thf or Et}_2\text{O}} [\text{RLa(OTf)}_2] \xrightarrow[-78\rightarrow 0\,^\circ\text{C}]{\text{R}^1\text{CONR}^2_2} \underset{80\text{–}98\%}{\text{RCOR}^1}} \qquad (187)$$

Novel complexes of the lanthanides exhibit good regioselectivity in reactions with conjugated aldehydes and ketones. Tris[(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)-lithium]hexamethylpraseodymate(III) and the corresponding samarium-based reagent both react to provide allylic alcohols resulting from nearly exclusive 1,2-addition to the unsaturated electrophilic substrates (equation 188)[146]. Chemoselectivity for unsaturated aldehydes relative to that of unsaturated ketones is less impressive. Competition experiments show the former more reactive by a factor of only 1.5–2:1.

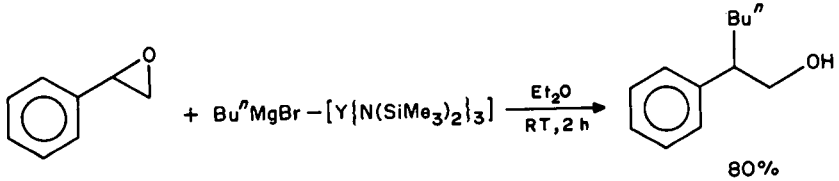
$$\begin{gathered}\text{PhCH=CHCOMe} + [\text{Li(tmed)}]_3(\text{PrMe}_3)_6 \longrightarrow \\ \text{PhCH=CHC(OH)Me}_2 + \text{PhCH(Me)CH}_2\text{COMe} \\ > 9 : < 1 \\ > 80\%\end{gathered} \qquad (188)$$

Lanthanide 'ate' complexes have also found utility in nucleophilic ring-opening reactions of epoxides[147]. Excellent yields of *trans*-2-methylcyclohexanol are obtained on addition of cyclohexene oxide to a reagent derived from methyllithium and $[\text{Sm}\{\text{N(SiMe}_3)_2\}_3]$ or $[\text{Y}\{\text{N(SiMe}_3)_2\}_3]$ (equation 189). 1,2-Epoxybutane reacts as expected with these reagents to provide pentan-3-ol in 74% yield. Interestingly, styrene



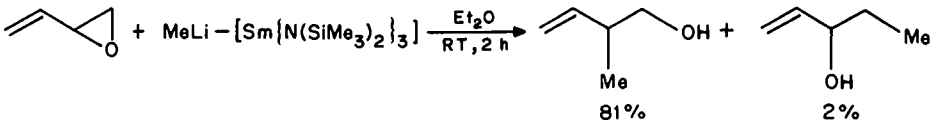
100%

(189)



80%

(190)



(191)

oxide and butadiene monoepoxide are alkylated with regioselectivities that complement those obtained with organocopper reagents (equations 190 and 191).

Butadiene monoepoxide represents an especially challenging substrate, because in principle three sites for nucleophilic attack exist in this molecule. It is clear that the organolanthanide 'ate' complexes are 'hard nucleophiles' that react with these substrates under charge control, seeking the most positive center of the electrophilic substrate[148].

VII. CONCLUSIONS

Much has been accomplished in the relatively brief period of time that organic chemists have turned their attention to the lanthanides as a source of selective reagents for organic synthesis. To date, most of the effort has been expended in determining how these reagents might complement more traditional nucleophiles or Lewis acids in accomplishing known transformations. In this regard, initial investigations have been extremely successful. Indeed, lanthanide reagents have replaced their more common main group or transition metal counterparts in many instances, becoming the reagents of choice for numerous conversions. However, the future of organolanthanide chemistry applied to organic synthesis lies in areas where the lanthanide reagents can bring truly unique and as yet unknown reactivity patterns to bear on synthetic problems. Few concerted efforts along these lines have so far been reported, and yet the possibilities are endless. It can be safely predicted, therefore, that the most exciting applications of lanthanide reagents to organic synthesis are yet to be uncovered.

VIII. REFERENCES

1. (a) N. R. Natale, *Org. Prep. Proced. Int.*, **15**, 387 (1983); (b) H. B. Kagan and J. L. Namy, in *Handbook on the Physics and Chemistry of the Rare Earths* (Eds K. A. Gschneidner and L. Eyring), Elsevier, Amsterdam, 1984, p. 525; (c) H. B. Kagan, in *Fundamental and Technological Aspects of Organo-f-Element Chemistry* (Eds T. J. Marks and I. L. Fragalà), Reidel, Dordrecht, 1985, p. 49; (d) H. B. Kagan and J. L. Namy, *Tetrahedron*, **42**, 6573 (1986); (e) J. R. Long, in *Handbook on the Physics and Chemistry of Rare Earths* (Eds K. A. Gschneidner and L. Eyring), Elsevier, Amsterdam, 1986, p. 335.
2. (a) H. Schumann and W. Genthe in *Handbook on the Physics and Chemistry of Rare Earths* (Eds K. A. Gschneidner and L. Eyring), Elsevier, Amsterdam, 1984, p. 445; (b) W. J. Evans, *Adv. Organomet. Chem.*, **24**, 131 (1985); (c) W. J. Evans, *Polyhedron*, **6**, 803 (1987).
3. J. E. Huheey, *Inorganic Chemistry*, Harper and Row, New York, 1983.
4. *Rare Earths Reminder*, Rhône-Poulenc, Paris, 1986.
5. F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley–Interscience, New York, 1980.
6. (a) T. J. Haley, *J. Pharm. Sci.*, **54**, 663 (1965); (b) D. W. Bruce, B. E. Hietbrink, and K. P. DuBois, *Toxicol. Appl. Pharmacol.*, **5**, 750 (1963).
7. L. R. Morss, *Chem. Rev.*, **76**, 827 (1976).
8. T. L. Ho, *Synthesis*, 347 (1973).
9. K. M. Mackay and R. A. Mackay, *Introduction to Modern Inorganic Chemistry*, Intertext Books, London, 1969.
10. R. G. Pearson (Ed.), *Hard and Soft Acids and Bases*, Dowden, Hutchinson & Ross, Stroudsburg, PA, 1973.
11. (a) R. E. Sievers (Ed.), *Nuclear Magnetic Resonance Shift Reagents*, Academic Press, New York,

1973; (b) B. C. Mayo, *Chem. Soc. Rev.*, **2**, 49 (1973); (c) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973); (d) F. Inagaki and T. Miyazawa, *Prog. Nucl. Magn. Reson. Spectrosc.*, **14**, 67 (1980); (e) R. R. Fraser, in *Asymmetric Synthesis* (Ed. J. D. Morrison), Vol. 1, Academic Press, New York, 1983, p. 173.
12. E. Murad and D. L. Hildebrand, *J. Chem. Phys.*, **73**, 4005 (1980).
13. (a) T. Imamoto, T. Kusumoto, and M. Yokoyama, *J. Chem. Soc., Chem. Commun.*, 1042 (1982); (b) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).
14. T. Imamoto, N. Takiyama and K. Nakamura, *Tetrahedron Lett.*, **26**, 4763 (1985).
15. T. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, **25**, 4233 (1984).
16. K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1935).
17. M. Suzuki, Y. Kimura, and S. Terashima, *Chem. Lett.*, 1543 (1984).
18. T. Tamura, M. Sasho, H. Ohe, S. Akai, and Y. Kita, *Tetrahedron Lett.*, **26**, 1549 (1985).
19. C. R. Johnson and B. D. Tait, *J. Org. Chem.*, **52**, 281 (1987).
20. T. Imamoto and Y. Sugiura, *J. Organomet. Chem.*, **285**, C21 (1985).
21. T. Cohen, W. D. Abraham, and M. Myers, *J. Am. Chem. Soc.*, **109**, 7923 (1987).
22. B.-S. Guo, W. Doubleday, and T. Cohen, *J. Am. Chem. Soc.*, **109**, 4710 (1987).
23. (a) L. A. Paquette and K. S. Learn, *J. Am. Chem. Soc.*, **108**, 7873 (1986); (b) L. A. Paquette, K. S. Learn, J. L. Romine, and H.-S. Lin, *J. Am. Chem. Soc.*, **110**, 879 (1988).
24. M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, **26**, 2693 (1985).
25. K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *Tetrahedron Lett.*, **26**, 861 (1985).
26. T. Imamoto, T. Kusumoto, and M. Yokoyama, *Tetrahedron Lett.*, **24**, 5233 (1983).
27. K. Nagasawa, H. Kanbara, K. Matsushita, and K. Ito, *Tetrahedron Lett.*, **26**, 6477 (1985).
28. N. R. Natale, S. G. Yocklovich, and B. M. Mallet, *Heterocycles*, **24**, 2175 (1986).
29. (a) A. D. Petrov, V. A. Ponomarenko, and A. D. Snegove, *Dokl. Akad. Nauk SSSR*, **112**, 79 (1957); (b) I. Fleming, and A. Pearce, *J. Chem. Soc., Perkin Trans. 1*, 251 (1981); (c) M. Ochiai, E. Fujita, M. Arimoto and H. Yamaguchi, *J. Chem. Soc., Chem. Commun.*, 1108 (1982); (d) T. Yamazaki and N. Ishikawa, *Chem. Lett.*, 521 (1984).
30. B. A. Narayanan and W. H. Bunnelle, *Tetrahedron Lett.*, **28**, 6261 (1987).
31. M. B. Anderson and P. L. Fuchs, *Synth. Commun.*, **17**, 621 (1987).
32. S. E. Denmark, T. Weber, and D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987).
33. E. J. Corey and M. M. Mehrotra, *Tetrahedron Lett.*, **29**, 57 (1988).
34. D. F. Evans, G. V. Fazakerley, and R. F. Phillips, *J. Chem. Soc. A*, 1931 (1971).
35. T. Imamoto, Y. Hatanaka, Y. Tawarayama, and M. Yokoyama, *Tetrahedron Lett.*, **22**, 4987 (1981).
36. S. Fukuzawa, T. Fujinami, and S. Sakai, *J. Organomet. Chem.*, **299**, 179 (1986).
37. S. Fukuzawa, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, 475 (1986).
38. T. Imamoto, T. Kusumoto, Y. Hatanaka, and M. Yokoyama, *Tetrahedron Lett.*, **23**, 1353 (1982).
39. T.-L. Ho, *Synth. Commun.*, **9**, 241 (1979).
40. S. Fukuzawa, T. Tsuruta, T. Fujinami, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, 1473 (1987).
41. T. Harada and T. Mukaiyama, *Chem. Lett.*, 467 (1982).
42. E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.*, **93**, 524 (1971).
43. M. E. Kurz and P. Ngoviwatchai, *J. Org. Chem.*, **46**, 4672 (1981).
44. E. Baciocchi, G. Civitarese, and R. Ruzziconi, *Tetrahedron Lett.*, **28**, 5357 (1987).
45. A. B. Sigalov, E. S. Petrov, L. F. Rybakova, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR*, Ser. Khim., 2615 (1983).
46. (a) G. B. Deacon, W. D. Raverty, and D. G. Vince, *J. Organomet. Chem.*, **135**, 103 (1977); (b) G. B. Deacon and A. J. Koplick, *J. Organomet. Chem.*, **146**, C43 (1978); (c) G. B. Deacon, A. J. Koplick, W. D. Raverty and D. G. Vince, *J. Organomet. Chem.*, **182**, 121 (1979); (d) G. B. Deacon, A. J. Koplick and T. D. Tuong, *Aust. J. Chem.*, **35**, 941 (1982).
47. K. Yokoo, Y. Kijima, Y. Fujiwara, and H. Taniguchi, *Chem. Lett.*, 1321 (1984).
48. G. B. Deacon, P. I. Mackinnon, and T. D. Tuong, *Aust. J. Chem.*, **36**, 43 (1983).
49. (a) G. B. Deacon, and T. D. Tuong, *J. Organomet. Chem.*, **205**, C4 (1981); (b) T. Fukagawa, Y. Fujiwara, K. Yokoo, and H. Taniguchi, *Chem. Lett.*, 1771 (1981).
50. K. Yokoo, Y. Yamanaka, T. Fukagawa, H. Taniguchi, and Y. Fujiwara, *Chem. Lett.*, 1301 (1983).
51. T. Fukagawa, Y. Fujiwara, and H. Taniguchi, *Chem. Lett.*, 601 (1982).
52. Z. Hou, H. Taniguchi, and Y. Fujiwara, *Chem. Lett.*, 305 (1987).
53. Z. Hou, N. Mine, Y. Fujiwara, and H. Taniguchi, *J. Chem. Soc., Chem. Commun.*, 1700 (1985).

54. (a) A. G. Sigalov, L. F. Rybakova, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1692 (1983); (b) K. Yokoo, T. Fukagawa, Y. Yamanaka, H. Taniguchi, and Y. Fujiwara, *J. Org. Chem.*, **49**, 3237 (1984).
55. (a) J. L. Namy, P. Girard and, H. B. Kagan, *Nouv. J. Chim.*, **1**, 5 (1977); (b) J. L. Namy, P. Girard, and H. B. Kagan, *Nouv. J. Chim.*, **5**, 479 (1981); (c) P. Girard, J. L. Namy, and H. B. Kagan, *J. Am. Chem. Soc.*, **102**, 2693 (1980).
56. T. Imamoto and M. Ono, *Chem. Lett.*, 501 (1987).
57. P. Watson. *J. Chem. Soc., Chem. Commun.*, 652 (1980).
58. V. Chebolu, R. R. Whittle, and A. Sen, *Inorg. Chem.*, **24**, 3082 (1985).
59. J. Inanaga, M. Ishikawa, and M. Yamaguchi, *Chem. Lett.*, 1485 (1987).
60. H. B. Kagan, J. L. Namy, and P. Girard, *Tetrahedron*, **37**, Suppl. 1, 175 (1981).
61. T. P. Ananthanarayan, T. Gallagher, and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 709 (1982).
62. M. Matsukawa, T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Chem. Lett.*, 2101 (1987).
63. J. Prandi, J. L. Namy, G. Menoret, and H. B. Kagan, *J. Organomet. Chem.*, **285**, 449 (1985).
64. Y. Zhang and R. Lin, *Synth. Commun.*, **17**, 329 (1987).
65. A. K. Singh, R. K. Bakshi, and E. J. Corey, *J. Am. Chem. Soc.*, **109**, 6187 (1987).
66. (a) G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986); (b) J. D. White and T. C. Somers, *J. Am. Chem. Soc.*, **109**, 4424 (1987).
67. D. V. Pratt and P. B. Hopkins, *Tetrahedron Lett.*, **28**, 3065 (1987).
68. (a) G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 2596 (1986); (b) K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 4437 (1987).
69. G. A. Molander, B. E. La Belle, and G. Hahn, *J. Org. Chem.*, **51**, 5259 (1986).
70. J. Souppe, L. Danon, J. L. Namy and H. B. Kagan, *J. Organomet. Chem.*, **250**, 227 (1983).
71. N. R. Natale, *Tetrahedron Lett.*, **23**, 5009 (1982).
72. K. Otsubo, K. Kawamura, J. Inanaga and M. Yamaguchi, *Chem. Lett.*, 1487 (1987).
73. P. Dowd and S.-C. Choi, *J. Am. Chem. Soc.*, **109**, 6548 (1987), and references cited therein.
74. (a) J. Souppe, J. L. Namy, and H. B. Kagan, *Tetrahedron Lett.*, **23**, 3497 (1982); (b) J. L. Namy, J. Souppe, J. Collin, and H. B. Kagan, *J. Org. Chem.*, **49**, 2045 (1984).
75. T. Imamoto, T. Takeyama, and M. Yokoyama, *Tetrahedron Lett.*, **25**, 3225 (1984).
76. (a) T. Imamoto, T. Takeyama, and H. Koto, *Tetrahedron Lett.*, **27**, 3243 (1986); (b) T. Tabuchi, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 3891 (1986); (c) T. Imamoto, and N. Takiyama, *Tetrahedron Lett.*, **28**, 1307 (1987).
77. G. A. Molander and J. B. Etter, *Synth. Commun.*, **17**, 901 (1987).
78. C. S. Shiner and A. H. Berks, personal communication.
79. G. A. Molander and J. B. Etter, *J. Org. Chem.*, **51**, 1778 (1986).
80. H. Suginome and S. Yamada, *Tetrahedron Lett.*, **28**, 3963 (1987).
81. J. J. Sosnowski, E. B. Danaher, and R. K. Murray, Jr, *J. Org. Chem.*, **50**, 2759 (1985).
82. R. K. Murray, Jr, personal communication.
83. G. Lannoye and J. M. Cook, *Tetrahedron Lett.*, **29**, 171 (1988).
84. B. A. Barner and M. A. Rahman, Third Chemical Congress of North America, Toronto, Canada, June 5–10, 1988, Abstract ORGN 419.
85. G. A. Molander, J. B. Etter, and P. W. Zinke, *J. Am. Chem. Soc.*, **109**, 453 (1987).
86. M. P. Cooke, Jr, and I. N. Houpis, *Tetrahedron Lett.*, **26**, 4987 (1985).
87. C. Kenny, unpublished work.
88. L. A. Fedorov, *Russ. Chem. Rev.*, **39**, 655 (1970).
89. H.-G. Korth, P. Lommes, and R. Sustmann, *J. Am. Chem. Soc.*, **106**, 663 (1984).
90. (a) S. Fukuzawa, A. Nakanishi, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, 624 (1986); (b) K. Otsubo, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 5763 (1986).
91. (a) T. Shono, I. Nishiguchi, H. Ohmizu, and M. Mitani, *J. Am. Chem. Soc.*, **100**, 545 (1978); (b) D. P. Fox, R. D. Little, and M. M. Baizer, *J. Org. Chem.*, **50**, 2202 (1985); (c) E. Kariv-Miller and T. J. Mahachi, *J. Org. Chem.*, **51**, 1041 (1986).
92. D. Belotti, J. Cossy, J. P. Pete, and C. Portella, *J. Org. Chem.*, **51**, 4196 (1986).
93. (a) S. K. Pradhan, S. R. Kadam, J. N. Kolhe, T. V. Radhakrishnan, S. V. Sohani, and V. B. Thaker, *J. Org. Chem.*, **46**, 2622 (1981); (b) E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, **24**, 2821 (1983); (c) T. Ikeda, S. Yue and C. R. Hutchinson, *J. Org. Chem.*, **50**, 5193 (1985).
94. S. Fukuzawa, M. Iida, A. Nakanishi, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, 920 (2987).
95. G. A. Molander and C. Kenny, *Tetrahedron Lett.*, **28**, 4367 (1987).

96. A. J. Beckwith, *Tetrahedron*, **37**, 3073 (1981).
97. B. Giese, *Radicals in Organic Synthesis: Formation of Carbon—Carbon Bonds*, Pergamon Press, Oxford, 1986.
98. T. L. Fevig, R. L. Elliott, and D. P. Curran, *J. Am. Chem. Soc.*, **110**, 5064 (1988).
99. J. L. Namy, J. Souppe, and H. B. Kagan, *Tetrahedron Lett.*, **24**, 765 (1983).
100. Y. Handa and J. Inanaga, *Tetrahedron Lett.*, **28**, 5717 (1987).
101. G. A. Molander and C. Kenny, *J. Org. Chem.*, **53**, 2132 (1988).
102. E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, **24**, 2821 (1983).
103. (a) A. Clerici and O. Porta, *Tetrahedron*, **39**, 1239 (1983); (b) A. Clerici and O. Porta, *J. Org. Chem.*, **48**, 1690 (1983); (c) A. Clerici and O. Porta, *J. Org. Chem.*, **52**, 5099 (1987).
104. T. Tabuchi, K. Kawamura, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 3889 (1986).
105. K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).
106. G. A. Molander and J. B. Etter, *J. Am. Chem. Soc.*, **109**, 6556 (1987).
107. P.-J. Thorel, unpublished work.
108. (a) D. Seyferth and R. M. Weinstein, *J. Am. Chem. Soc.*, **104**, 5534 (1982); (b) D. Seyferth, R. M. Weinstein, and W.-L. Wang, *J. Org. Chem.*, **48**, 1144 (1983); (c) R. M. Weinstein, W.-L. Wang, and D. Seyferth, *J. Org. Chem.*, **48**, 3367 (1983); (d) D. Seyferth, W.-L. Wang, and R. C. Hui, *Tetrahedron Lett.*, **25**, 1651 (1984).
109. P. Girard, R. Couffignal, and H. B. Kagan, *Tetrahedron Lett.*, **22**, 3959 (1981).
110. D. Griller and K. U. Ingold, *Acc. Chem. Res.*, **13**, 317 (1980).
111. J. Souppe, J.-L. Namy, and H. B. Kagan, *Tetrahedron Lett.*, **25**, 2869 (1984).
112. P. W. Zinke, *PhD Thesis*, University of Colorado, Boulder, CO, 1987.
113. G. A. Molander and J. B. Etter, *J. Org. Chem.*, **52**, 3942 (1987).
114. (a) M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.*, **104**, 7162 (1982); (b) K. N. Houk, N. G. Rondan, Y.-D. Wu, J. T. Metz, and M. N. Paddon-Row, *Tetrahedron*, **40**, 2257 (1984).
115. J. Mareda, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.*, **105**, 6997 (1983).
116. J. T. Link, unpublished work.
117. L. S. Harring, unpublished work.
118. S. Fukuzawa, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, 919 (1987).
119. T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 601 (1986).
120. T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 5237 (1986).
121. T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 1195 (1986).
122. T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Chem. Lett.*, 2275 (1987).
123. T. Tabuchi, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 215 (1987).
124. M. Matsukawa, J. Inanaga, and M. Yamaguchi, *Tetrahedron Lett.*, **28**, 5877 (1987).
125. J. L. Namy, J. Collin, J. Zhang, and H. B. Kagan, *J. Organomet. Chem.*, **328**, 81 (1987).
126. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **92**, 7448 (1972).
127. N. Mine, Y. Fujiwara, and H. Taniguchi, *Chem. Lett.*, 357 (1986).
128. A. E. Vougioukas and H. B. Kagan, *Tetrahedron Lett.*, **28**, 5513 (1987).
129. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
130. T. C. Morrill, R. A. Clark, D. Bilobran, and D. S. Youngs, *Tetrahedron Lett.*, 397 (1975).
131. S. Danishefsky and M. Bednarski, *Tetrahedron Lett.*, **26**, 2507 (1985).
132. S. J. Danishefsky, W. H. Pearson, and D. F. Harvey, *J. Am. Chem. Soc.*, **106**, 2456 (1984).
133. M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **105**, 3716 (1983).
134. S. Danishefsky and M. Barbachyn, *J. Am. Chem. Soc.*, **107**, 7761 (1985).
135. S. J. Danishefsky, D. F. Harvey, G. Quallich, and B. J. Uang, *J. Org. Chem.*, **49**, 393 (1984).
136. S. J. Danishefsky and W. H. Pearson, *J. Org. Chem.*, **48**, 3866 (1983).
137. S. J. Danishefsky, B. J. Uang, and G. Quallich, *J. Am. Chem. Soc.*, **106**, 2453 (1984).
138. (a) S. Castellino and J. J. Sims, *Tetrahedron Lett.*, **25**, 2307 (1984); (b) S. Castellino and J. J. Sims, *Tetrahedron Lett.*, **25**, 4059 (1984); (c) M. M. Midland and R. S. Graham, *J. Am. Chem. Soc.*, **106**, 4294 (1984).
139. S. J. Danishefsky, W. H. Pearson, and D. F. Harvey, *J. Am. Chem. Soc.*, **106**, 2455 (1984).
140. M. Bednarski, C. Maring, and S. Danishefsky, *Tetrahedron Lett.*, **24**, 3451 (1983).
141. M. Quimpère and K. Jankowski, *J. Chem. Soc., Chem. Commun.*, 676 (1987).
142. (a) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **105**, 6968 (1983); (b) M. Bednarski and S. Danishefsky, *J. Am. Chem. Soc.*, **108**, 7060 (1986).

143. S. Danishefsky and M. Bednarski, *Tetrahedron Lett.*, **25**, 721 (1984).
144. T. Kauffmann, C. Pahde, A. Tannert and D. Wingbermühle, *Tetrahedron Lett.*, **26**, 4063 (1985).
145. S. Collins and Y. Hong, *Tetrahedron Lett.*, **28**, 4391 (1987).
146. H. Schumann, J. Müller, N. Bruncks, H. Lauke, and J. Pickardt, *Organometallics*, **3**, 69 (1984).
147. I. Mukerji, A. Wayda, G. Dabbagh, and S. H. Bertz, *Angew. Chem., Int. Ed. Engl.*, **25**, 760 (1986).
148. C. Jaime, R. M. Ortuño, and J. Font *J. Org. Chem.*, **53**, 139 (1988).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 9

The use of organoantimony and organobismuth compounds in organic synthesis

LEON D. FREEDMAN and GEORGE O. DOAK

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, USA

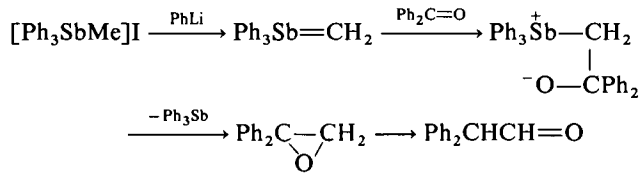
I. INTRODUCTION

Although organoantimony and organobismuth compounds have been known for well over a century, they have found comparatively little use in organic synthesis. A number of recent developments, however, have suggested that these substances may prove to have considerable utility in this area. Thus, it has been shown that organoantimony compounds can be used for the conversion of aldehydes and ketones to olefins, for the oxidation and reduction of various functional groups, for the transfer of aryl groups to acyl halides and olefins, for the acylation of amines, and for a number of other synthetically interesting applications. Trivalent organobismuth compounds have been used only to a very limited extent in organic synthesis. Pentavalent organobismuth reagents, however, have been employed (especially by Barton and coworkers) for the synthesis of organic compounds that could not easily be obtained in any other manner. These reagents are especially useful as oxidizing agents and for the transfer of aryl groups to carbon, oxygen, nitrogen, and sulfur. They have proved to be particularly valuable where the substrates are sensitive natural products. It seems likely that organoantimony and organobismuth compounds may soon be recognized as important reagents in synthetic organic chemistry.

II. ORGANOANTIMONY COMPOUNDS

A. Use of Antimony Ylides in the Wittig and Related Reactions

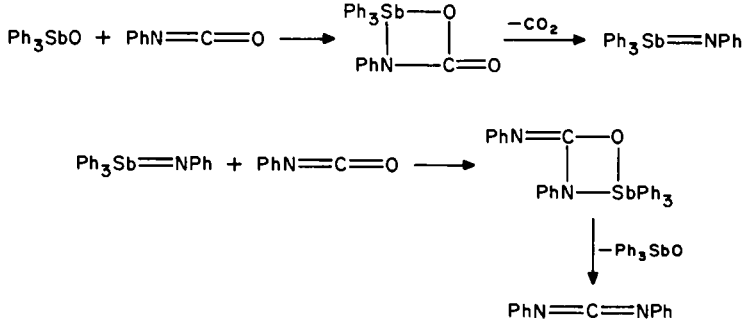
Although the first condensation between a carbonyl compound and a phosphorus ylide was reported in 1919[1], it was not until the 1950s that it was shown[2] that this type of reaction can be made the basis of a useful and versatile method for the conversion of an aldehyde or ketone to an olefin. In 1960 Henry and Wittig[3] investigated the reaction of benzophenone with ylides of arsenic or antimony; their attempts to obtain a bismuth ylide or even an alkyltriaryl derivative of bismuth were unsuccessful, however. The antimony ylide was prepared in ethereal solution by the reaction of methyltriphenyl antimony iodide with phenyllithium and was then treated with the ketone. After the reaction mixture had been hydrolysed with 6 M hydrochloric acid, the products were isolated with the aid of column chromatography. Only a trace of the expected 1,1-diphenylethene was detected. High yields of diphenylethanal and triphenylstibine, however, were obtained. The sequence of reactions shown in Scheme 1 was suggested.



SCHEME 1

Two years later Monagle[4] reported that triphenylstibine oxide (and also a number of other oxides or sulfides of organic derivatives of nitrogen, phosphorus, arsenic, and sulfur)

catalyse the conversion of organic isocyanates to carbodiimides. He suggested that a triphenylstibine imide is a key intermediate in this process and that this intermediate undergoes a carbonyl condensation reaction analogous to the Wittig reaction (Scheme 2). In contrast to these results, trialkylstibine oxides catalyse the trimerization of alkyl and aryl isocyanates to isocyanurates[5].



SCHEME 2

Later work definitely showed that antimony imides can react with carbonyl compounds. Thus, two imides derived from triphenylstibine react readily with benzaldehyde (equation 1)[6]. Imides in which Ar is 4-ClC_6H_4, 4-BrC_6H_4, or 4-$O_2NC_6H_4$ are, however, unaffected by the aldehydes. Two imides derived from trialkystibines react with 4-methoxybenzaldehyde but not with benzaldehyde or 4-nitrobenzaldehyde (equation 2)[7].

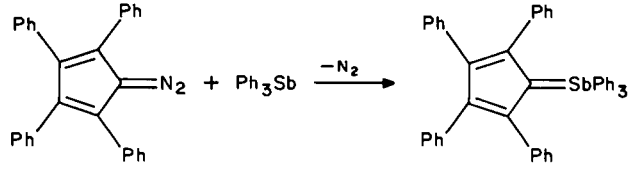
$$Ph_3Sb{=}NSO_2Ar + PhCH{=}O \xrightarrow[20\,^\circ C]{ClCH_2CH_2Cl} Ph_3SbO + ArSO_2N{=}CHPh \qquad (1)$$

Ar = Ph, 4-Tol

$$R_3Sb{=}NSO_2Ph + 4\text{-}MeOC_6H_4CH{=}O \longrightarrow R_3SbO + PhSO_2N{=}CHC_6H_4OMe\text{-}4$$

R = Et, Pr (2)

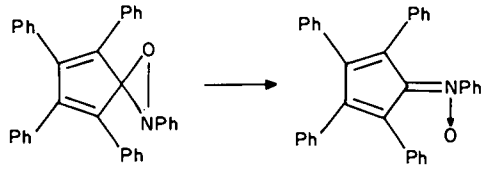
The isolation of an antimony ylide in the solid state and its conversion to an olefin was first accomplished by Lloyd and Singer[8] in 1967. The ylide is obtained by heating a mixture of triphenylstibine and diazotetraphenylcyclopentadiene under nitrogen at 140 °C (equation 3). No reaction appears to occur when the ylide is refluxed with



(3)

benzaldehyde in chloroform for 4 h. The ylide does react with 4-nitrobenzaldehyde, however, to give the expected fulvene in high yield. Later papers[9] reported that fulvenes are obtained from both aldehydes on being refluxed with the ylide in carbon tetrachloride for 18 h. A rapid reaction between the ylide and nitrosobenzene in refluxing benzene is also observed. After only 10 min, an 80% yield of a nitrone is obtained; the formation of this substance presumably involves the intermediacy of an oxaziridine (equation 4)[9b].

Attempts to prepare a dichlorofulvene by the interaction of the ylide and di-



(4)

chlorocarbene (generated from chloroform and potassium *tert*-butoxide) were unsuccessful and led to the formation of 1,2,3,4-tetraphenylcyclopentadiene[9b]. A recent paper[10] described the preparation of six new antimony ylides that have electron-withdrawing groups bonded to the anionic carbon. These compounds are obtained under mild conditions by reactions between triphenylstibine and a diazo compound in the presence of bis(hexafluoroacetylacetonate)copper(II) as a homogeneous catalyst. They are colorless (or nearly so) and seem to be indefinitely stable in a dry atmosphere. Like their arsonium analogues, these antimony ylides do not appear to take part in Wittig reactions, even with reactive aldehydes such as 2,4-dinitrobenzaldehyde.

Tributylstibine has been used to mediate the olefination of eight aldehydes and three ketones with esters of bromoacetic acid (equation 5)[11]. This convenient one-pot process is carried out without the use of any added base, and the products are exclusively in the *E* form. No solvent is required, and solvents such as hexane, benzene, thf, or acetonitrile do not significantly affect the yields. Bromoacetophenone, bromomalonic acid, and chloroacetonitrile can also be used for the olefination of aldehydes and ketones, but details of these reactions have not yet been published. Although the role of the tributylstibine in the olefination of carbonyl compounds has not been elucidated, the mechanism presumably involves the intermediacy of antimony ylides.

$$\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}O + BrCH_2CO_2R^3 \xrightarrow{Bu_3Sb} \begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}CHCO_2R^3 \qquad (5)$$

R^1 = alkyl, aryl, vinylic; R^2 = H, alkyl; R^3 = Me, Et

A thermally unstable antimony ylide has been obtained by employing a phosphorus ylide to dehydrohalogenate a quaternary antimony compound (equation 6)[12]. The reaction of this ylide with carbonyl compounds has apparently not been studied.

$$Et_3P{=}CHMe + (Me_3SiCH_2)_4SbCl \longrightarrow (Me_3SiCH_2)_3Sb{=}CHSiMe_3 + Et_4PCl \qquad (6)$$

B. Ph_2Sb, $Ph_2Sb(O)$, and $Ph_2Sb(NTos)$ as Leaving Groups

As discussed in Section II.A, antimony ylides are able in some cases to convert carbonyl compounds to olefins. Several papers from Kauffmann's laboratory have noted that certain α-lithio derivatives of alkyldiphenylstibines can be employed for the same purpose. This procedure involves the interaction of the lithium compound and an aldehyde or ketone, addition of water to the reaction mixture, and subsequent thermal or acid-catalysed decomposition of the resulting β-hydroxyalkyldiphenylstibine. Thus, it was reported[13] that diphenylstibinomethyllithium [prepared by the interaction of methylenebis(diphenystibine) and phenyllithium in thf at −70 °C[14]] reacts with benzaldehyde, benzophenone, or cyclohexanone to give modest yields of the expected alcohols **1**, **2**, and **3**, respectively. When the alcohols are heated (**1** and **2** in the dry state at 180 °C and **3** in toluene at 110 °C) or treated at room temperature with 2 equivalents of perchloric acid in methanol, the olefins **4**, **5**, and **6** are obtained in yields ranging from 21 to 68%[15]. Another method of obtaining the olefins is by passing thf solutions of the alcohols through

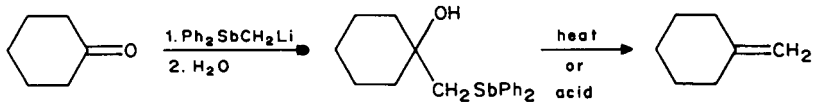
a short silica gel column[16,17].

$$PhCH{=}O \xrightarrow[2.\,H_2O]{1.\,Ph_2SbCH_2Li} Ph_2SbCH_2CH(OH)Ph \xrightarrow[\text{or acid}]{\text{heat}} PhCH{=}CH_2 \quad (7)$$

(1) (4)

$$Ph_2C{=}O \xrightarrow[2.\,H_2O]{1.\,Ph_2SbCH_2Li} Ph_2SbCH_2C(OH)Ph_2 \xrightarrow[\text{or acid}]{\text{heat}} Ph_2C{=}CH_2 \quad (8)$$

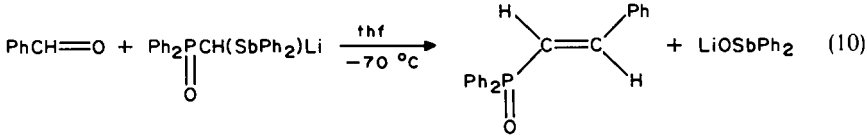
(2) (5)



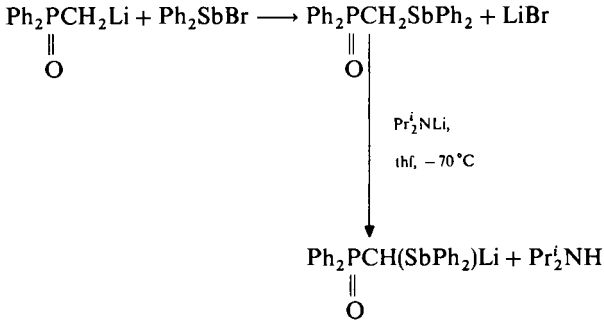
(9)

(3) (6)

Another paper[18] described the conversion of benzaldehyde to a diphenylphosphoryl-substituted olefin in 25% yield (equation 10). The α-lithio derivative required for this synthesis is obtained by the sequence of reactions shown in Scheme 3.

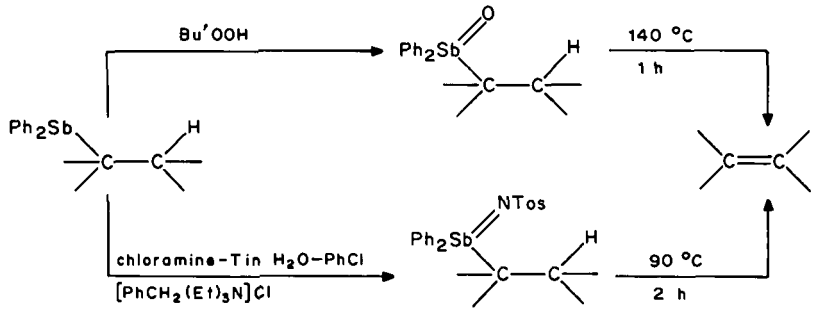


(10)



SCHEME 3

In a review in 1982, Kauffmann[17] noted that olefins can be formed by the elimination of the $Ph_2Sb(O)$ or $Ph_2Sb(NTos)$ group together with a β-H atom from alkyldiphenylstibine oxides or imides. The structures of the alkyl groups were not given, but they were said to be primary. The stibine oxides are obtained by the oxidation of the corresponding tertiary stibine with *tert*-butyl hydroperoxide; the imides are obtained by the phase-transfer reaction of the stibines with chloramine-T. Thermal decomposition of the stibine oxides leads to 21–23% yields of the olefins; better yields (53–60%) are obtained from the imides. The reactions are shown in Scheme 4. It is surprising that in analogous reactions with 2-



SCHEME 4

diphenylstibinopentane (which contains a secondary alkyl group), only minimal amounts of olefin could be detected.

Kauffmann *et al.*[17,19] also described the conversion of alkyldiphenylstibines to alkyl halides. Thus, the interaction of hexyldiphenylstibine and bromine at 220 °C for 24 h gives a 65% yield of hexyl bromide. The corresponding iodide can be prepared by the so-called 'onium cleavage' reaction. This involves treatment of the tertiary stibine with triethyloxonium tetrafluoroborate and cleavage of the resulting quaternary antimony compound with sodium iodide at 20 °C. The alkyldiphenylstibines required for these syntheses can be obtained by converting the diphenylstibinomethyllithium to an organocopper compound and allowing the latter substance to react with an alkyl halide (equations 11 and 12)[13,19].

$$Ph_2SbCH_2Li + CuCl \longrightarrow Ph_2SbCH_2Cu + LiCl \quad (11)$$

$$Ph_2SbCH_2Cu + RI \longrightarrow Ph_2SbCH_2R + CuI \quad (12)$$
$$R = Pr, Bu, Pen, Hex, Oct$$

C. Trivalent Organoantimony Compounds as Reducing Agents

1. *Primary and secondary stibines*

It has been known for over 20 years that primary and secondary stibines can reduce a number of inorganic substrates[20–25]. The potential usefulness of these substances as reducing agents in organic chemistry has not, however, been extensively explored. Recently, it was reported that aldehydes and ketones can be selectively reduced to the corresponding alcohols by the interaction of the carbonyl compound and diphenylstibine in the presence of a Lewis acid (e.g. $AlCl_3$ or $TiCl_4$) and subsequent hydrolysis of the reaction mixture with dilute sulfuric acid or sodium hydroxide[26]. In the absence of a Lewis acid, the stibine does not react with aldehydes or ketones. Even in the presence of a Lewis acid, the stibine does not attack esters, acid chlorides, alkyl halides, or olefins. Open-chain α,β-unsaturated aldehydes or ketones undergo reduction only at the carbonyl group. α,β-Unsaturated cyclic ketones, however, may give 1,2- or 1,4- reduction products. When a mixture of an aldehyde and a ketone is allowed to react with a limited amount of diphenylstibine, the aldehyde is reduced preferentially.

Primary and secondary stibines can reduce organic compounds other than aldehydes and ketones, but such reactions appear to be of little preparative interest. For example, the interaction of phenylstibine and styrene in refluxing benzene results in reduction of the vinyl group (equation 13)[27].

$$n\text{PhSbH}_2 + n\text{PhCH}{=}\text{CH}_2 \longrightarrow (\text{PhSb})_n + n\text{PhEt} \quad (13)$$

Alkylstibines reduce carbon tetrachloride to chloroform (equation 14)[28]. Similarly, diphenylstibine reduces benzotrichloride to benzylidene chloride (equation 15)[22]. Diphenylstibine can also reduce azo compounds to hydrazo derivatives (equation 16)[29] Concurrently, the starting materials undergo an addition reaction (equation 17).

$$RSbH_2 + 2CCl_4 \longrightarrow RSbCl_2 + 2CHCl_3 \quad (14)$$

R = Me, Et, Bu

$$Ph_2SbH + PhCCl_3 \longrightarrow Ph_2SbCl + PhCHCl_2 \quad (15)$$

$$2Ph_2SbH + RN{=}NCO_2Et \longrightarrow Ph_2SbSbPh_2 + RNHNHCO_2Et \quad (16)$$

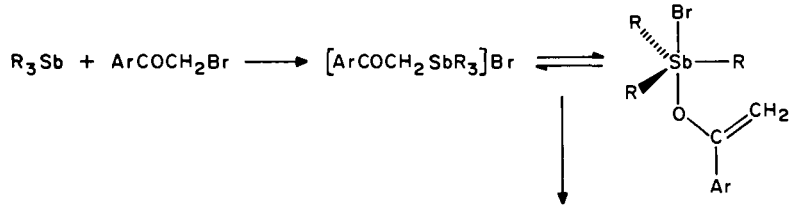
R = Ph, CO_2Et

$$Ph_2SbH + RN{=}NCO_2Et \longrightarrow Ph_2SbN(R)NHCO_2Et \quad (17)$$

2. *Tertiary stibines*

The first synthesis of a trialkylstibine (Et_3Sb) was accomplished in 1850[30], and it has been recognized since then that substances of this type are powerful reducing agents[31a]. Triarylstibines are also reducing agents but are less reactive in this respect. Neither type of tertiary stibine, however, has often been used for the reduction of organic compounds.

The use of tributyl- or triphenyl-stibine for the replacement of halogen with hydrogen in phenacyl and benzylic bromides has been recently reported[32]. For example, the reduction of phenacyl bromide with tributylstibine proceeds smoothly at room temperature to afford acetophenone in 67% yield; the addition of a protic solvent such as methanol to the reaction mixture increases the yield to about 80%. The mechanism shown in Scheme 5 has been suggested for the interaction of a phenacyl bromide and a tertiary stibine.



R=Bu, Ph; Ar=Ph, 4-BrC_6H_4

SCHEME 5

The reaction of the added protic solvent with the ylide formed in the last step presumably leads to the observed increase in the yield of the acetophenone. When phenacyl chloride is allowed to react with tributylstibine, the yield of acetophenone is only 10%, even on addition of methanol to the reaction mixture. The reaction of the secondary bromide PhCOCH(Br)Me with triphenylstibine gives the expected $PhCOCH_2Me$. The tertiary bromide $PhCOC(Br)Me_2$, however, does not react with triphenylstibine. The phenacylidene dibromide 4-$BrC_6H_4COCHBr_2$, on reaction with triphenylstibine, gives a 10% yield of the bromoketone 4-$BrC_6H_4COCH_2Br$ and a 22% yield of *p*-bromoacetophenone. The interaction of a benzylic bromide with tributylstibine leads to the formation of a quaternary antimony bromide of the type $[ArCH_2SbBu_3]Br$; refluxing these substances with ethanolic potassium hydroxide gives the ArMe compounds. In the

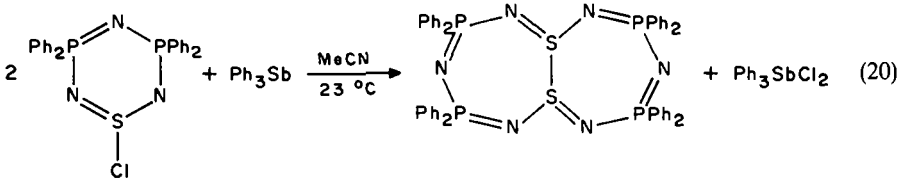
presence of tributyl- or triphenyl-stibine, certain vicinal dibromides undergo 1,2-elimination (equations 18 and 19).

$$PhCHBrCHBrPh \xrightarrow{Bu_3Sb} trans\text{-}PhCH{=}CHPh \quad (18)$$

$$PhCHBrCHBrCO_2Et \xrightarrow{R_3Sb} trans\text{-}PhCH{=}CHCO_2Et \quad (19)$$

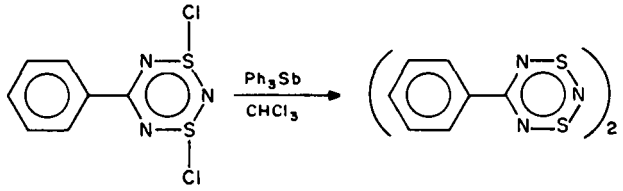
R = Bu, Ph

In two cases, triphenylstibine has been used to effect dechlorination and the formation of sulfur—sulfur linkages. Thus, the preparation of a twelve-membered inorganic heterocycle with a transannular sulfur—sulfur bond has been accomplished by employing the stibine as a reducing agent (equation 20)[33]. The interaction of the stibine and a



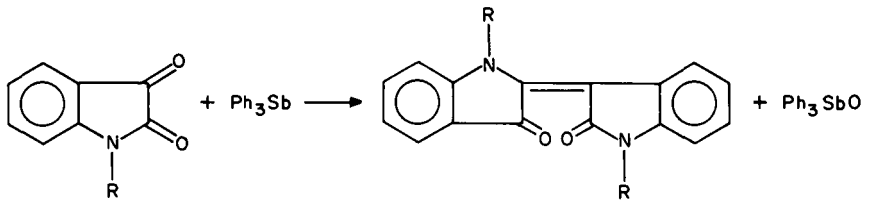
(20)

dichlorodithiatriazine has been found to yield an interesting dimeric product (equation 21)[34]. Triphenylantimony dichloride is presumably also formed, but it apparently has not been isolated from the reaction mixture.



(21)

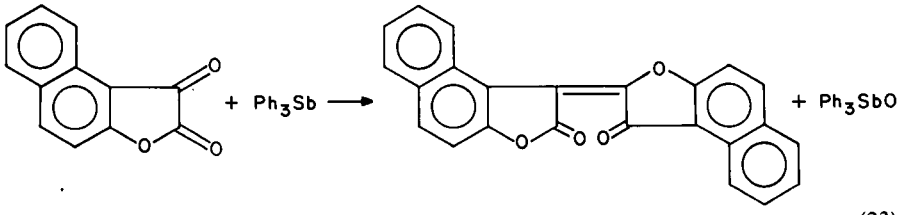
Triphenylstibine has been found to lead to partial deoxygenation of certain α-dicarbonyl compounds and the formation of substances known to be useful as dyestuffs[35]. Thus, when the stibine reacts with isatin or *N*-methylisatin in dry toluene for 25 h, indirubin or dimethylindirubin precipitates from the reaction mixture (equation 22).



(22)

The reduction of naphtho[2,1-*b*]furan-1,2-dione proceeds in a similar manner (equation 23). Acenaphthenequinone, however, is stable towards triphenylstibine in boiling toluene or xylene even after 40 h.

A study of the reaction of triphenylstibine with a number of *para*-quinones has shown that reduction accompanied by phenylation often occurs[36]. This work will be discussed in



(23)

Section II.E. Triphenylstibine reduces benzenediazonium chloride to biphenyl (equation 24)[37]. Aryl thiosulfinates are converted to disulfides by triphenylstibine (equation 25).[38]

$$Ph_3Sb + 2PhN_2Cl \longrightarrow Ph_3SbCl_2 + PhPh + N_2 \quad (24)$$

$$Ph_3Sb + ArSS(O)Ar \longrightarrow Ph_3SbO + ArSSAr \quad (25)$$

Ar = Ph, 4-Tol

The reaction of equimolar amounts of triphenylstibine, benzenesulfonamide, and diethyl azodicarboxylate in thf at 0 °C has been found to yield triphenylstibine oxide and diethyl hydrazinedicarboxylate[39]. It seems possible that the reaction initially forms a triphenylstibine imide that is then hydrolysed by the inadvertent introduction of water, as shown in Scheme 6.

$$Ph_3Sb + PhSO_2NH_2 + EtO_2CN{=}NCO_2Et \longrightarrow$$
$$EtO_2CNHNHCO_2Et + [Ph_3Sb{=}NSO_2Ph]$$
$$\downarrow H_2O$$
$$Ph_3SbO + PhSO_2NH_2$$

SCHEME 6

The reduction of organic hydroperoxides by tertiary stibines has been observed (equation 26)[40–43], but this type of reaction seems to have little synthetic value.

$$R^1_3Sb + R^2OOH \longrightarrow R^1_3SbO + R^2OH \quad (26)$$

R^1 = Me, Et, Ph; R^2 = Bu^t, $PhMe_2C$

D. Pentavalent Organoantimony Compounds as Oxidizing Agents

The oxidizing properties of pentavalent organoantimony compounds have long been recognized[31b], but these substances have seldom been used as oxidizing agents in organic synthesis. Several recent papers, however, have reported cases in which organoantimony(V) compounds served as efficient oxidizing agents.

The base-promoted interaction of triphenylantimony dibromide and α-hydroxy ketones or α-hydroxy esters has been found to give excellent yields of the corresponding dicarbonyl compounds (equation 27)[44].

$$R^1{-}\underset{\underset{OH}{|}}{CH}{-}\underset{\underset{O}{\|}}{C}{-}R^2 + Ph_3SbBr_2 + 2R^3_3N \xrightarrow[\text{or } CDCl_3]{CH_2Cl_2} R^1{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}R^2$$
$$+ Ph_3Sb + 2R^3_3NHBr \quad (27)$$

$R^1 = R^2$ = Ph, 2-Fu, 2-thi; R^1 = Ph, R^2 = 2-Fu, Me, OEt; R^1 = Me, R^2 = OEt; $R^3_3N = Et_3N$, dbu

An 89% yield of diketone can be obtained by the oxidation of 4,4′-dimethylbenzoin with trimethylantimony dichloride under similar conditions. Since triphenylstibine is easily converted to triphenylantimony dibromide by bromine or a bromine donor, the oxidation of an α-hydroxycarbonyl compound can be accomplished with a catalytic amount of the stibine or antimony dibromide plus one equivalent of ethyl 2,3-dibromo-3-phenylpropanoate. Thus, the interaction of this bromine donor and 4,4′-dimethylbenzoin in the presence of 2 equivalents of 2,6-lutidine and catalytic amounts of triphenylstibine or triphenylantimony dibromide gives excellent yields of the diketone. A possible disadvantage of the oxidation procedures discussed in this paragraph is that they appear to require long reaction times (up to 2 days).

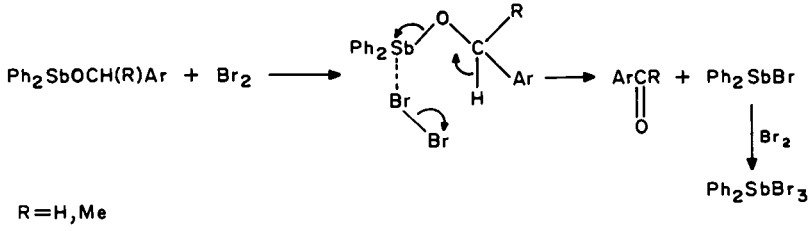
Other workers[45] have reported that triphenylantimony diacetate can also oxidize benzoin to benzil in high yield under mild conditions (equation 28). They found, however, that organoantimony(V) compounds [Ph_3SbBr_2, $Ph_3Sb(OAc)_2$, Ph_2SbBr_3, or Ph_3SbS] do not oxidize benzyl alcohol even in the presence of a variety of bases. A method of oxidizing benzyl alcohols to aldehydes was then devised that involves converting the alcohol to a benzyloxydiphenylstibine and then adding bromine (equations 29 and 30). The yields varied from 40 to 86%. 1-Phenylethanol can also be oxidized by this procedure, but the yield of acetophenone is only 28%. Cyclohexanol and 2-phenylethanol are not converted to carbonyl compounds under these conditions. The mechanism shown in Scheme 7 has been suggested for the reaction between the benzyloxydiphenylstibines and bromine.

$$Ph{-}\underset{\underset{OH}{|}}{CH}{-}\overset{\overset{O}{\|}}{C}{-}Ph + Ph_3Sb(OAc)_2 \longrightarrow Ph{-}\overset{\overset{O}{\|}}{C}{-}\overset{\overset{O}{\|}}{C}{-}Ph + Ph_3Sb + 2HOAc \quad (28)$$

$$YC_6H_4CH_2OH + Ph_2SbBr + Et_2NH \xrightarrow{PhH} YC_6H_4CH_2OSbPh_2 + Et_2NH_2Br \quad (29)$$

$$YC_6H_4CH_2OSbPh_2 + 2Br_2 \xrightarrow{5\text{–}10\,^{\circ}C} YC_6H_4CH{=}O + Ph_2SbBr_3 + HBr \quad (30)$$

Y = H, 4-F, 4-Cl, 4-Br, 2-Me, 3-Me, 4-Me, 4-MeO, 4-O_2N



SCHEME 7

The oxidation of thiols to disulfides by organoantimony(V) compounds has been noted in a number of papers. Thus, Kupchik and Calabretta[46] reported that thiuram disulfides can be obtained by means of the reaction shown in equation 31. Later, Matsumura *et al.*[47] found that a similar reaction occurs between trimethylantimony dibromide and sodium dialkyldithiocarbamates. The oxidation of thiols by trimethylantimony diethoxide was

also described (equation 32).

$$Ph_3SbCl_2 + 2NaSCNR_2 \longrightarrow Ph_3Sb + R_2NCSSCNR_2 + 2NaCl \quad (31)$$

R = Me, Et, Ph

$$Me_3Sb(OEt)_2 + 2RSH \xrightarrow[PhH]{RT} Me_3Sb + RSSR + 2EtOH \quad (32)$$

R = Et, Pr, Bu, Ph, $HOCH_2CH_2$

When thioacetic or thiobenzoic acid is used in this type of reaction, organoantimony(V) intermediates can be isolated (equation 33). The acetyl compound decomposes at room temperature, whereas the benzoyl compound requires refluxing in benzene (equation 34). The oxidation of thiols by trimethylstibine oxide was also mentioned[47], but no experimental details were given. A subsequent paper reported that trimethylstibine sulfide reacts rapidly with alkyl halides to give quantitative yields of disulfides (equation 35)[48]. The reaction of stibine sulfides with ditin compounds results in cleavage of the Sn—Sn bond and insertion of sulfur (equation 36)[49].

$$Me_3Sb(OEt)_2 + 2RCSH \longrightarrow Me_3Sb(SCR)_2 + 2EtOH \quad (33)$$

R = Me, Ph

$$Me_3Sb(SCR)_2 \longrightarrow Me_3Sb + RCSSCR \quad (34)$$

$$2Me_3SbS + 2RX \xrightarrow[reflux]{CHCl_3} Me_3Sb + Me_3SbX_2 + RSSR \quad (35)$$

RX = MeI, EtI, $PhCH_2I$, $PhCH_2Br$

$$R^1_3SbS + R^2_3SnSnR^2_3 \xrightarrow[reflux]{CHCl_3} R^1_3Sb + R^2_3SnSSnR^2_3 \quad (36)$$

R^1 = Me, R^2 = Ph, $PhCH_2$; R^1 = Ph, R^2 = Ph

Schmidbaur and Mitschke[50] also investigated the interaction of organoantimony(V) compounds and thiols. They found that the carefully controlled reaction of pentamethylantimony with thiols at temperatures ranging from −30 to 20 °C gives methane and quaternary antimony compounds in yields of 77–95% (equation 37). These substances are stable only if kept below room temperature. One warming they decompose to thioethers and trimethylstibine (equation 38).

$$Me_5Sb + RSH \longrightarrow Me_4SbSR + MeH \quad (37)$$

R = Me,Et, Ph, $PhCH_2$

$$Me_4SbSR \xrightarrow{RT} Me_3Sb + RSMe \quad (38)$$

The interaction of pentamethylantimony and 2 mol of a thiol at 40–60 °C yields disulfides (equation 39). The base-promoted reaction of trimethylantimony dichloride with thiols at −30 to −25 °C gives antimony(V) dithiolates in yields of 74–79% (equation 40). These substances decompose at room temperature to disulfides and

trimethylstibine (equation 41).

$$Me_5Sb + 2RSH \longrightarrow Me_3Sb + RSSR + 2MeH \tag{39}$$

$$Me_3SbCl_2 + 2RSH + 2Et_3N \xrightarrow{Me_2C=O} Me_3Sb(SR)_2 + 2Et_3NHCl \tag{40}$$

$$Me_3Sb(SR)_3 \longrightarrow Me_3Sb + RSSR \tag{41}$$

Attempts in another laboratory to prepare triphenylantimony dithiolates resulted in quantitative yields of tertiary stibine and disulfide (equation 42)[51].

$$Ph_3SbCl_2 + 2RSH + 2NH_3 \xrightarrow{PhH} Ph_3Sb + RSSR + 2NH_4Cl \tag{42}$$

Wardell and Grant[52] studied the thermal decomposition of a number of tetraphenylantimony thiophenoxides. In several cases a reasonable yield (50–97%) of thioether is obtained (equation 43). Other compounds formed in these decompositions include benzene, biphenyl, and diaryl disulfides of the type $YC_6H_4SSC_6H_4Y$.

$$Ph_4SbSC_6H_4Y \xrightarrow{\Delta} Ph_3Sb + PhSC_6H_4Y \tag{43}$$

Y = H, 4-Me, 4-Br, 2-OMe, 4-OMe

Triphenylstibine oxide has been found to oxidize thiols at room temperature within 5 min[53]. Under aerobic conditions, moreover, triphenylstibine *or* triphenylstibine oxide catalyses the oxidation of thiols. The catalysis presumably involves a cyclic mechanism in which the stibine is oxidized to the stibine oxide, which then reacts with the thiol and is thereby reconverted to the stibine.

E. Transfer of Organic Groups from Antimony to Carbon

Grignard reagents and other reactive organometallic compounds owe their great importance in organic synthesis largely to their ability to transfer alkyl and aryl groups to carbon atoms of carbonyl, epoxide, and other groups. In contrast, the carbon—antimony bond in most organoantimony compounds is rather unreactive, but triarylstibines have nevertheless found a few applications as arylating agents.

Malinovsky and Olifirenko[54] showed that triphenylstibine can be used for transferring a phenyl group from antimony to carbon. Thus, the interaction of the stibine and an acyl chloride in the presence of aluminium chloride gives modest yields (15–63%) of a ketone (equation 44). Phenyldichlorostibine and an antimony-containing tar are also obtained in these reactions. Under the same conditions, triphenylstibine reacts with alkyl bromides or benzyl chloride according to equation 45[55]. The yields of arenes range from 19 to 58%. The interaction of triphenylstibine and bromobenzene gives only a small amount of biphenyl. No triphenylmethane is obtained when the stibine is allowed to react with chloroform.

$$Ph_3Sb + 3RC(=O)Cl \xrightarrow[CS_2]{AlCl_3} 3PhC(=O)R + SbCl_3 \tag{44}$$

R = Me, Et, Pr^i, Bu^i, Ph

$$Ph_3Sb + 3RX \xrightarrow[CS_2]{AlCl_3} 3PhR + SbX_3 \tag{45}$$

R = Et, Pr^i, Bu^n, Bu^i, Pen^i; X = Br

R = $PhCH_2$; X = Cl

In a later paper[56], it was shown that diphenylchlorostibine and phenyldiiodostibine can also be used for obtaining moderate yields of ketones and arenes (equations 46–49).

$$Ph_2SbCl + 2RC(=O)Cl \xrightarrow[CS_2]{AlCl_3} 2PhC(=O)R + SbCl_3 \quad (46)$$

$R = Me, Et, Pr^i, Bu^i$

$$Ph_2SbCl + 2RBr \xrightarrow[CS_2]{AlCl_3} 2PhR + SbBr_2Cl \quad (47)$$

$R = Bu^n, Bu^i, Pen^i$

$$PhSbI_2 + RC(=O)Cl \xrightarrow[CS_2]{AlCl_3} PhC(=O)R + SbClI_2 \quad (48)$$

$R = Et, Pr^i, Bu^i$

$$PhSbI_2 + RBr \xrightarrow[CS_2]{AlCl_3} PhR + SbBrI_2 \quad (49)$$

$R = Pr^i, Bu^i, Pen^i$

Aryl groups other than phenyl can also be transferred from triarylstibines to acyl chlorides or alkyl bromides (equations 50 and 51)[57].

$$Ar_3Sb + 3RC(=O)Cl \xrightarrow[CS_2]{AlCl_3} 3ArC(=O)R + SbCl_3 \quad (50)$$

Ar = 4-Tol; $R = Me, Et, Pr^i$
Ar = 1-Np; R = Me, Et

$$Ar_3Sb + 3RBr \xrightarrow[CS_2]{AlCl_3} 3ArR + SbBr_3 \quad (51)$$

Ar = 4-Tol; $R = Pr^i, Bu^n, Bu^i$
Ar = 1-Np; $R = Pr^i, Bu^n$

In 1973 it was discovered that palladium(II) acetate can promote the transfer of a phenyl group from triphenylstibine to the unsubstituted olefinic carbon atom of styrene (equation 52)[58]. The reaction is carried out by refluxing equimolar amounts of the stibine, styrene, and palladium compound in a mixture of acetic acid and dioxane; the yield of stilbene is 67% (based on the palladium compound). In addition a 108% yield of biphenyl is obtained.

$$Ph_3Sb + PhCH{=}CH_2 \xrightarrow{[Pd(OAc)_2]} \textit{trans}\text{-}PhCH{=}CHPh \quad (52)$$

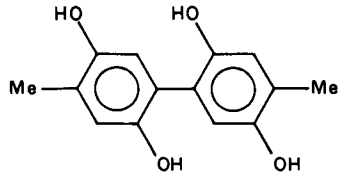
A similar reaction was reported 4 years later[59]. Thus, when equimolar amounts of triphenylstibine and palladium(II) acetate are allowed to react with a 10-fold excess of oct-1-ene in acetonitrile at 25 °C, a 70% yield of biphenyl and a 113% yield of phenylated octenes are obtained. When ethyl acrylate is used instead of oct-1-ene, the products are biphenyl and ethyl cinnamate. Triphenylantimony dichloride can also cause phenylation of olefins in the presence of palladium(II) compounds, but details of these reactions have not been published. It has been concluded that the phenylation reactions involve the intermediate formation of phenylpalladium species. Later papers[60] have described the

stereospecific phenylation of alkenylsilanes of the type (*E*)- or (*Z*)-RCH=CHSiMe$_3$ (where R = Ph, Hex, or MeOCH$_2$) by means of phenylpalladium acetate generated *in situ* from various sources. These reactions are accompanied by inversion of the starting geometry with respect to the R and Me$_3$Si groups. The interaction of palladium(II) acetate and triphenylstibine can be used to generate the phenylpalladium acetate (equation 53).

$$Ph_3Sb + Pd(OAc)_2 \longrightarrow PhPdOAc + Ph_2SbOAc \qquad (53)$$

Goel *et al.*[61] have shown that palladium(II) compounds can promote the cleavage of the phenyl—antimony bond even in the absence of olefins. Thus, when palladium(II) acetate is heated with 1 or 2 mol of triphenylstibine in toluene at 100 °C for 5 h, biphenyl (70%), phenyl acetate (17%), and benzene (5%) are obtained. In a similar reaction between the stibine and palladium(II) chloride at temperatures above 100 °C, the products are benzene, biphenyl, and chlorobenzene. No reaction occurs when triphenylstibine alone is refluxed in toluene. When triphenylstibine and palladium(II) chloride are allowed to react in toluene under carbon monoxide at temperatures above 150 °C, small amounts of benzene and biphenyl are formed in addition to benzoyl chloride, benzophenone, benzaldehyde, and anthraquinone. A later paper[62] described the formation of benzoic acid when triphenylstibine and a palladium(II) salt are heated at 180–200 °C in an atmosphere of carbon dioxide; the yields of the acid are 15–40% (based on palladium). Much higher yields (up to six times) are obtained when the reactions are carried out in an atmosphere of carbon monoxide, nitric oxide, and nitrogen (in a ratio of 1:1:3). Small amounts of benzophenone and anthraquinone are also formed. All of the reactions described in this paragraph are presumed to involve phenyl–palladium species.

As mentioned in Section II.C.2, phenylation by triphenylstibine may occur when the latter compound reacts with quinones[36]. Thus, when 1,4-benzoquinone and the stibine are allowed to react in refluxing diethyl ether and the reaction mixture is then treated with hydrochloric acid, the main products are hydroquinone (92%) and triphenylantimony dichloride (94%), but about 8% 2-phenylhydroquinone is also obtained. In refluxing benzene, however, the phenylated quinone is the main product. 1,4-Naphthoquinone and the stibine give mainly the corresponding hydroquinone in either solvent, but some 2-phenyl derivative is also obtained. 2,5-Diphenyl-1,4-benzoquinone in refluxing xylene yields 60% of triphenyl-1,4-benzoquinone; in addition, a 13% yield of biphenyl is produced by the decomposition of the triphenylstibine. 2,5-Di-*tert*-butyl-1,4-benzoquinone reacts with triphenylstibine in refluxing benzene only in the presence of benzoyl peroxide; under these conditions 23% of 2,5-di-*tert*-butyl-3-phenyl-1,4-benzoquinone is produced. The behaviour of *p*-toluquinone in refluxing benzene is distinctly different from that of the other quinones studied in this investigation. In addition to *p*-toluquinol (2-methylbenzene-1,4-diol) and diphenylstibinic acid, the biphenyl derivative (7) is obtained.



(7)

The formation of the various reaction products identified in this study was explained by mechanisms that involve free radicals.

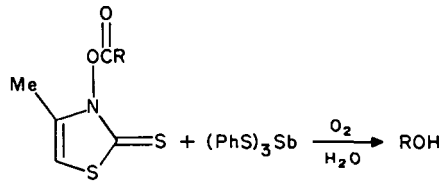
F. Miscellaneous

Although antimony trifluoride has been widely used for converting trichloromethyl-substituted aromatic compounds to the corresponding trifluoro derivatives, it has been reported that not all the chlorines are replaced by fluorine when the trichloromethyl group is deactivated by adjacent electron-withdrawing substituents[63]. Antimony pentafluoride is a more vigorous fluorinating agent, but it may also replace the aromatic hydrogens with fluorine atoms.

Phenylantimony tetrafluoride has been found to be a powerful reagent for converting benzotrichloride to benzotrifluoride. Thus, the interaction of the tetrafluoride and benzotrichloride at 50–55 °C for 2 h gives a 91% yield of benzotrifluoride and no chlorodifluoromethylbenzene. Pentafluoroethylbenzene can be made by similar reactions (equation 54). Diphenylantimony trifluoride is also able to effect the replacement of chlorine atoms in compounds containing trichloromethyl groups. It is, however, less efficient than phenylantimony tetrafluoride, and mixtures of trifluoromethyl and chlorodifluoromethyl derivatives may be obtained.

$$PhCCl_2CF_3 \xrightarrow{PhSbF_4} PhCF_2CF_3 \xleftarrow{PhSbF_4} PhCCl_2CCl_3 \qquad (54)$$

Mixed anhydrides of carboxylic acids and certain thiohydroxamic acids react with tris(phenylthio)stibine at room temperature to give high yields of nor-alcohols (equation 55)[64]. The reaction appears to follow a simple radical chain mechanism in which



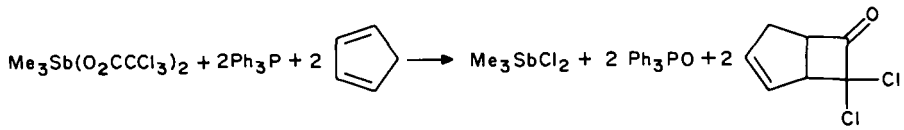
(55)

R = primary, secondary, tertiary

a carbon radical attacks the stibine and forms an oxygen-sensitive organoantimony compound (equation 56). Aerial oxidation and subsequent hydrolysis of the oxidized substance presumably produced the nor-alcohol and antimony(III) oxide; the latter compound can, in fact, be recovered almost quantitatively from the reaction mixture.

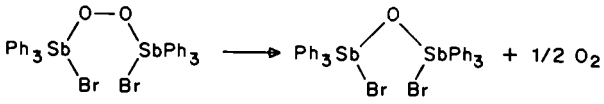
$$R\cdot + (PhS)_3Sb \longrightarrow RSb(SPh)_2 \qquad (56)$$

Trimethylantimony bis(trichloroacetate) reacts with triphenylphosphine to produce dichloroketene, which can be trapped by 1,3-cyclopentadiene (equation 57)[65]. The yield of the bicyclic compound is 33%.



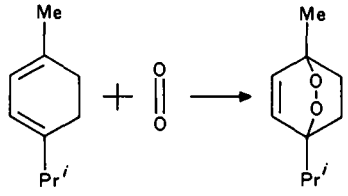
(57)

It has been suggested that singlet oxygen is generated during the decomposition of peroxybis(triphenylantimony) dibromide in chlorobenzene at 45 °C (equation 58)[66]. Thus, when the peroxy compound is allowed to decompose in the presence of tetramethylethy-



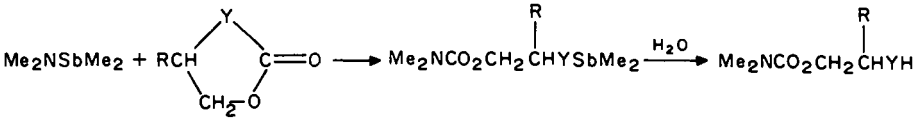
(58)

lene or α-terpinene, little or no evolution of oxygen is observed. Instead, the alkene yields 3-hydroperoxy-2,3-dimethylbut-1-ene, while the terpinene gives ascridole (equation 59).

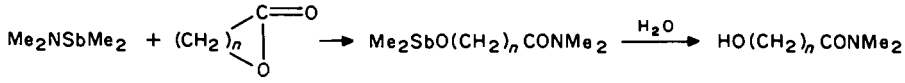


(59)

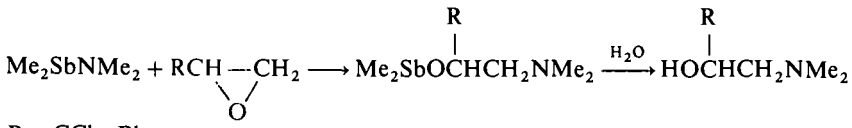
A number of carbamates, amides, and amines containing the OH or SH group have been prepared by the addition of dimethylaminodimethylstibine to cyclic carbonates (or thiolocarbonates), lactones, or epoxides and subsequent hydrolysis of the resulting adducts (equations 60–62)[67].



Y=O,S (60)



(61)



R = CCl_3, Ph (62)

Triphenylantimony dicarboxylates react with a number of primary amines to give reasonably good yields of amides (equation 63)[68]. These amides can also be prepared by using a catalytic amount of triphenylstibine oxide or a triphenylantimony dicarboxylate (equation 64). The catalytic effect of the antimony compounds is ascribed to the fact that triphenylstibine oxide readily reacts with carboxylic acids to yield dicarboxylates (equation 65).

$$Ph_3Sb(O_2CR^1)_2 + 2R^2NH_2 \longrightarrow 2R^1CONHR^2 + Ph_3SbO + H_2O \quad (63)$$

R^1 = Me, CF_3, Ph, $CH_2NHCO_2CH_2Ph$; R^2 = Bu^s, Hex, *c*-Hex, Ph

$$R^1CO_2H + R^2NH_2 \longrightarrow R^1CONHR^2 + H_2O \quad (64)$$

$$Ph_3SbO + 2R^1CO_2H \longrightarrow Ph_3Sb(O_2CR^1)_2 + H_2O \quad (65)$$

Trimethyl-, triethyl-, tributyl-, and trioctyl-stibines are effective catalysts for the preparation of alkyltin trihalides (containing up to 18 carbon atoms) by the type of reaction shown in equation 66[69]. The yields range from 62 to 100%. The mechanism of the alkylation reaction is not known, but it has been suggested that the stibines form weak complexes with the alkyl halides and thereby facilitate a carbenoid-like insertion of the tin(II) halide into the carbon—halogen bond (equations 67 and 68).

$$RX^1 + SnX^2_2 \longrightarrow RSnX^1X^2_2 \quad (66)$$

$X^1, X^2 = Cl, Br$

$$R_3Sb + RX \longrightarrow R_3Sb{\cdot}RX \quad (67)$$

$$R_3Sb{\cdot}RX + SnX_2 \longrightarrow R_3Sb + RSnX_3 \quad (68)$$

Trimethylstibine has also been found to be an effective catalyst for the formation of alkylead triiodides by the interaction of alkyl iodides and lead(II) iodide (equation 69)[70]. No mechanism has been suggested for this reaction.

$$RI + PbI_2 \xrightarrow{140\,^\circ C} RPbI_3 \quad (69)$$

$R = Et, Pr^n, Pr^i, Bu^n, Bu^t$

III. ORGANOBISMUTH(III) COMPOUNDS

A. Introduction

Organobismuth(III) compounds have found relatively little use in organic synthesis, which can be attributed to their chemical and physiological properties. Trialkylbismuthines are readily oxidized; the lower members are spontaneously flammable in air. The dialkylhalobismuthines are not only spontaneously flammable in air but also decompose on standing even in the absence of air and moisture. The diarybismuth compounds are powerful sternutators (sneezing agents). Thus, Ph_2BiCl, Ph_2BiBr, and Ph_2BiCN are said to be more powerful in this respect than the chemical warfare agent Ph_2AsCl[71]. The triarylbismuth compounds, however, are stable, crystalline solids which can be handled with ease. The six *s* electrons in bismuth(III) compounds do not readily undergo *s–p* hybridization but remain in the *s* orbitals. They are often referred to as an inert pair. For this reason, triarylbismuthines are poor nucleophiles or donors. They do not add to aldehydes or ketones, but Ph_3Bi does react with acetyl or benzoyl chloride to give acetophenone or benzophenone in low yields[72]. Tri-1-naphthylbismuthine and benzoyl chloride, in the presence of $AlCl_3$ or $FeCl_3$, give 1-naphthyl phenyl ketone in low yield[73].

B. Reaction of Trialkyl- and Triaryl-bismuthines with Other Elements or Elemental Halides

Because of the relatively low C—Bi bond energy, trialkyl- and triaryl-bismuthines react with several metals and with a number of metal or metalloid halides with cleavage of one or more C—Bi bonds and the alkylation or arylation of the metal or metalloid. Thus, Ph_3Bi and powdered antimony, when heated at 300 °C for 1 h, give an 89.2% yield of Ph_3Sb[74]. A number of elements, mercury, indium, tin, arsenic, and sulphur, undergo transmetallation with $(C_6F_5)_3Bi$ (equation 70)[75].

$$n(C_6F_5)_3Bi + 3M \longrightarrow 3(C_6F_5)_nM + Bi \quad (70)$$

Several elements have been arylated by the reaction of Ar_3Bi and an elemental chloride

(equation 71–74)[76].

$$Ar_3Bi + PCl_3 \longrightarrow Ar_2BiCl + ArPCl_2 \quad (71)$$

$$Ar_3Bi + AsCl_3 \longrightarrow Ar_2BiCl + ArAsCl_2 \quad (72)$$

$$Ar_3Bi + HgCl_2 \longrightarrow Ar_2BiCl + ArHgCl \quad (73)$$

$$2Ar_3Bi + TlCl_3 \longrightarrow 2Ar_2BiCl + Ar_2TlCl \quad (74)$$

An interesting reaction involves the transfer of an isopropenyl group from bismuth to thallium(III) (equation 75)[77]. The yield is 98%. Triphenylbismuthine reacts with mercury arenesulfinates to yield a phenylmercury arenesulfinate (equation 76)[78]. The resulting compounds are difficult to separate. Selenium dioxide and triarylbismuthines react to give areneselenic acids in excellent yields (equation 77)[79]. Tetraborane and Me_3Bi react to give a 5% yield of 2-MeB_4H_9[80]. Much higher yields of the same product are obtained when Me_2Hg or Me_3Ga is used rather than Me_3Bi.

$$2(CH_2{=}CMe)_3Bi + 3TlCl_3 \xrightarrow{-40\,^\circ C} (CH_2{=}CMe)_2TlCl + 2BiCl_3 \quad (75)$$

$$Ph_3Bi + 3Hg(O_2SAr)_2 \longrightarrow 3PhHg(O_2SAr) + Bi(O_2SAr)_3 \quad (76)$$

$$2Ar_3Bi + 9SeO_2 + 3H_2O \longrightarrow 6ArSeO_2H + Bi_2(SeO_3)_3 \quad (77)$$

$Ar = Ph, 2\text{-}ClC_6H_4, 3\text{-}ClC_6H_4, 4\text{-}ClC_6H_4$

The reaction between Ph_3Bi and palladium(II) compounds in the presence of olefins has been described. The use of triphenyl compounds of the type Ph_3M, where M = N, P, As, Sb, and Bi, with $Pd(OAc)_2$ in the presence of styrene was studied, and the product with Ph_3P, Ph_3As, Ph_3Sb, and Ph_3Bi was *trans*-stilbene and (except for Ph_3P) biphenyl[58]. The maximum yield of *trans*-stilbene occurs with Ph_3As and the minimum yield with Ph_3Bi. With Ph_3Bi the principal product is biphenyl. In the absence of $Pd(OAc)_2$, Ph_3Bi and styrene give benzene and a small amount of biphenyl, but no *trans*-stilbene. The reaction of Ph_3P, Ph_3As, Ph_3Sb, Ph_3Bi (and also Ph_2Se and Ph_2Te) and $Pd(OAc)_2$ in the presence of oct-1-ene or ethyl acrylate was studied[59]. In all cases the olefin is phenylated, with the maximum yield occurring with Ph_3Sb; biphenyl is also formed. With oct-1-ene, a variety of different phenylated compounds are produced. With $CH_2{=}CHCO_2Et$ the single phenyl compound $PhCH{=}CHCO_2Et$ is formed. The reaction involves transfer of one or more phenyl groups from the Group V element to palladium followed by transfer of the phenyl group from palladium to the olefin. Triethyltin hydride reacts with Ph_3Bi when heated at 140 °C for 75 h to give triethylphenyltin[81].

C. Miscellaneous Reactions

Alcohols[82a] and amines[82b] can be phenylated by a mixture of Ph_3Bi and $Cu(OAc)_2$. These reactions undoubtedly involve the intermediacy of organobismuth(V) compounds and are discussed in Sections IV.E and IV.J.

Kauffmann's group has made extensive investigations of the use of organometallic compounds of the heavier Main Group elements in organic synthesis. A review of this research has appeared[17]. The compound $(Ph_2Bi)_2CH_2$ is obtained in 52% yield from Ph_2BiNa and CH_2Cl_2 (equation 78)[83]. It reacts with PhLi as shown in equation 79. The resulting lithium compound reacts with aldehydes or ketones in thf solution at − 78 °C to give addition products (equation 80). Hydrolysis of the addition products with $HClO_4$ gives an alkene (equation 81). When the addition product from Ph_2CO and Ph_2BiCH_2Li is hydrolysed, an alcohol is formed. Further reaction of this alcohol with 10.4 M $HClO_4$

gives 1, 1-diphenylethene in 61% yield (equation 82).

$$2Ph_2BiNa + CH_2Cl_2 \xrightarrow{NH_3} (Ph_2Bi)_2CH_2 + 2NaCl \quad (78)$$

$$(Ph_2Bi)_2CH_2 + PhLi \rightleftharpoons Ph_2BiCH_2Li + Ph_3Bi \quad (79)$$

$$Ph_2BiCH_2Li + R^1R^2CO \longrightarrow Ph_2BiCH_2\overset{\displaystyle OLi}{\overset{|}{C}}R^1R^2 \quad (80)$$

$R^1 = R^2 = Ph$; $R^1 = Ph$, $R^2 = H$; $R^1 = Hex$, $R^2 = H$

$$Ph_2BiCH_2\overset{\displaystyle OLi}{\overset{|}{C}}R^1R^2 \xrightarrow{HClO_4} Ph_2BiOH + CH_2{=}CR^1R^2 \quad (81)$$

$$Ph_2BiCH_2C(OLi)Ph_2 + H_2O \longrightarrow Ph_2BiCH_2C(OH)Ph_2 \xrightarrow{HClO_4}$$

$$Ph_2C{=}CH_2 + Ph_2BiOH \quad (82)$$

Trialkyl- and triaryl-bismuthines have been used as catalysts and co-catalysts for the polymerization of olefins and a number of patents have been issued on their use for these purposes. Masuda and coworkers used Ph_3Bi as a co-catalysts with transition metal compounds for the polymerization of alkynes. Thus, $TaCl_5$ and Ph_3Bi (1:1) produce polymers of $Me_3SiC{\equiv}CMe$ with an $\bar{M}_w$ value up to 4×10^6, the highest value known among substituted acetylenes[84]. Similarly, $ClC{\equiv}CPh$[85] or $BrC{\equiv}CPh$[86] are polymerized in high yields by Ph_3Bi and $MoCl_5$ or WCl_6. Another use of Ph_3Bi has been as a co-catalyst for the metathesis of olefins. Ichikawa *et al.*[87] have studied the metathesis of hept-2-ene to give but-2-ene and dec-5-ene. The catalysts were Ph_3Bi and WCl_6.

IV. ORGANOBISMUTH(V) COMPOUNDS

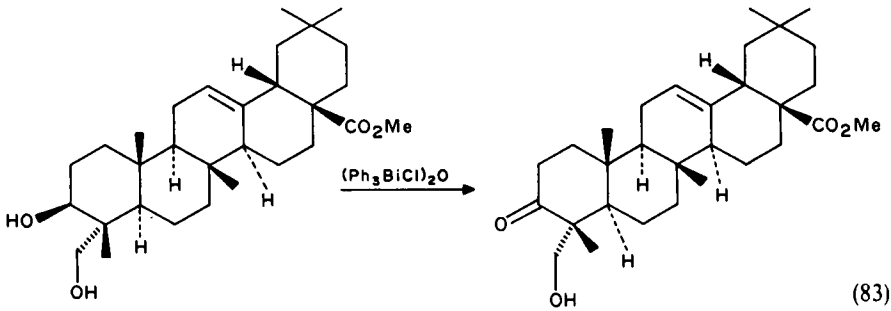
A. Introduction

Only a few inorganic compounds of bismuth(V) are known[88]. In contrast, a large number of organobismuth(V) compounds of the type Ar_3BiX_2, where X is a halogen (other than iodine) or another electronegative group, are well known. Other organobismuth(V) compounds include those of the types Ar_4BiX and Ar_5Bi. These bismuth(V) compounds have found considerable use in organic synthesis in recent years. Summaries of this research have recently been published[89]. Organobismuth(V) reagents have served as oxidizing agents for the conversion of primary or secondary alcohols to the corresponding aldehydes or ketones, for the oxidation of mercaptans to disulfides, for the *O*-arylation of alcohols, enols, or phenols to aryl or diaryl ethers, for the *N*-arylation of amines (primary and secondary) to secondary or tertiary amines, for the *C*-arylation of phenols, enols, and alcohols, and for the oxidation and/or arylation of a number of miscellaneous organic compounds.

B. Oxidation of Alcohols

The oxidation of EtOH, Pr^nOH, and Pr^iOH by $Ph_3Bi(OH)_2$ was first noted by Challenger and Richards[90]. Triphenylbismuthine was obtained in all cases, but no

yields of the oxidation products were given. Realizing from this preliminary work that organobismuth(V) compounds might prove to be valuable reagents for the oxidation of alcohols to aldehydes or ketones, Barton and coworkers initiated an in-depth study of this problem. The first organobismuth(V) reagent used for this purpose was μ-oxobis-(chlorotriphenyl)bismuth, $(Ph_3BiCl)_2O$, readily prepared by the action of alkali on Ph_3BiCl_2[91]. The oxidations are carried out in CH_2Cl_2 solution in the presence of an excess of base (K_2CO_3 or $NaHCO_3$) at room temperature or 60 °C. Triphenyl bismuthine is obtained in all cases. Both primary and secondary alcohols are readily oxidized to carbonyl compounds in large yields. Among the primary alcohols are a number of allylic and benzylic alcohols. Thus, cinnamyl alcohol gives cinnamaldehyde in 83% yield, and 4-nitrobenzyl alcohol gives 4-nitrobenzaldehyde in 87% yield. Since Barton and coworkers have published extensively on the chemistry of natural products, it is not surprising that many of the alcohols used are naturally occurring compounds. For example, the oxidation of methyl hederagenin to methyl hederagonate is one of the oxidations achieved (equation 83). Although the yield from this reaction is only 36%, this yield is a significant improvement over that previously reported[92].



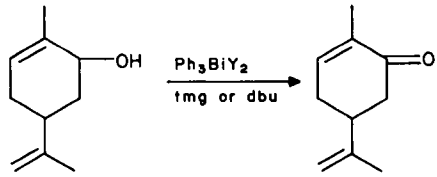
(83)

Other alcohols from natural products readily oxidized by $(Ph_3BiCl)_2O$ include geraniol, vitamin A alcohol, crotyl alcohol, cholest-1-en-3β-ol, cholest-4-en-3β-ol, 3β-cholestanol, tigogenin, testosterone, α-amyrin, and cholestan-3β,6β-diol[91]. The rate of oxidation is found to increase by the use of a negative group Y in the organobismuth compounds $(YC_6H_4)_3BiCl_2$ (Y = Me, H, Cl) when these compounds are used as the oxidizing agents. However, variation in X (X = Cl, Br, NO_2) in the compounds Ph_3BiX_2 has no effect on the reaction rate[93]. Since all of these reactions were carried out in the presence of K_2CO_3 or $NaHCO_3$, this result suggested that the active oxidizing agent might be Ph_3BiCO_3. Accordingly, Ph_3BiCO_3 was synthesized and found to be a remarkably effective oxidant, not only for primary and secondary alcohols, but also for a variety of other functional groups[93,94]. The reaction is fairly selective. Thus, cholest-4-en-3β-ol (1 equivalent) in the presence of thiophenol (1 equivalent) is oxidized to cholest-4-en-3-one without oxidation of the thiol (thiols, however, *can* be oxidized to disulfides by Ph_3BiCO_3; see Section IV C). Similarly, 8-methylselenotetradecan-7-ol gives the corresponding 8-methylselenotetradecan-7-one without oxidation of the selenium. Although oxidation of ephedrine results in C—C bond cleavage to give benzaldehyde, oxidation of *N*-acetylephedrine gives *N*-acetyl-α-methylaminopropiophenone (equation 84).

$$PhCH(OH)CHMeN(Me)Ac \xrightarrow{Ph_3BiCO_3} PhCOCHMeN(Me)Ac \qquad (84)$$

In additon to Ph_3BiCO_3, several other Ph_3BiX_2 compounds (X = OAc, O_2CPh, and O_2CCF_3) have been found to oxidize alcohols when used in conjunction with the strong

bases 1, 1, 3, 3-tetramethylguanidine (tmg) or dbu. Thus, (−)-carveol is readily oxidized to (−)-carvone at room temperature by any of these bismuth compounds in the presence of either of the above bases:



(85)

The presence of a strong base seems to be necessary for these reactions to give maximum yields of aldehydes or ketones. Under neutral or acidic conditions, or in the presence of a weaker base such as Et_3N, the yields of oxidation products are usually smaller, and *O*-arylation to give ethers is a competing reaction. Even when Ph_3BiCO_3 is used as the oxidizing agent, the addition of tmg or dbu accelerates the rate of oxidation in at least one case (cinnamyl alcohol to cinnamaldehyde)[93].

In addition to compounds of the type Ar_3BiX_2, compounds of the types Ar_5Bi and Ar_4BiX have been used for oxidizing alcohols to aldehydes and ketones. Razuvaev *et al.*[95] first noted that Ph_5Bi oxidizes isopropyl alcohol (equation 86).

$$Ph_5Bi + Pr^iOH \longrightarrow Ph_3Bi + Me_2CO + 2PhH \tag{86}$$

Benzyl alcohol is oxidized to benzaldehyde in 45% yield by Ph_5Bi[96]. 3β-Cholestanol is oxidized to the corresponding ketone in 70% yield, and 2,2-dimethylpropan-1-ol is similarly oxidized to the aldehyde in 65% yield[97]. In at least one case, however, both phenylation and oxidation occur. Thus, estradiol and Ph_5Bi give 2,4-diphenylestrone (14%), 4-phenylestrone (13%), and 2,4-diphenylestradiol (12%)[96]. Tetraarylbismuth compounds also oxidize alcohols to aldehydes or ketones in the presence of a strong base. Thus, 3β-cholestanol is oxidized to cholestanone in 92% yield by $Ph_4BiOTos$ in the presence of 2-*tert*-butyl-1, 1, 3, 3-tetramethylguanidine (btmg). This result is similar to those obtained with Ph_3BiX_2 compounds, although the reaction rate with the Ph_4BiX compound appears to be faster.

It appears, therefore, that organobismuth(V) compounds are excellent reagents for the oxidation of primary and secondary alcohols to aldehydes and ketones. The yields are generally high, the reactions are carried out under mild conditions, and a large excess of the oxidizing agent is not required. Although all three types of organobismuth(V) reagents (Ph_3BiX_2, Ph_4BiX, and Ph_5Bi) can be used, the Ph_3BiX_2 compounds appear to be the reagents of choice because of their ease of preparation and their stability. Both $(Ph_3BiCl)_2O$ (with the addition of K_2CO_3 or $NaHCO_3$) and Ph_3BiCO_3 are readily available reagents. The latter compound is easily prepared from Ph_3BiCl_2 in acetone by the addition of K_2CO_3 in water[94]. However, it is probably not necessary to isolate Ph_3BiCO_3; it was demonstrated that it could readily be prepared *in situ* (the oxidation of androst-4-en-3β,17β-diol by Ph_3BiCl_2 and K_2CO_3). In another case (the oxidation of 3β-cholestanol) Ph_3BiCl_2 and BTMG give the product in 88% yield[97]. Other Ph_3BiX_2 compounds ($X = O_2CCF_3$, OAc, and O_2CPh) are equally effective. Isopropyl alcohol has been oxidized to Me_2CO in 98% yield by $Ph_3Bi(OAc)_2$ and K_2CO_3 in $CHCl_3$[98]. A review (in Portugese) of the use of organobismuth(V) compounds for the oxidation of alcohols has been published[99], and a patent on this procedure has also been issued[100].

C. Oxidation of Compounds Other than Alcohols

Thiols are readily oxidized to the corresponding disulfides by Ph_3BiCO_3. Thus, PhSH, 2-TolSH, and 4-TolSH give the corresponding disulfides in 70, 90 and 89% yields, respectively, when treated with Ph_3BiCO_3[93,94]. The reaction of thiols, ArSH, with Ph_5Bi

is different in that mixed sulfides, ArSPh, are obtained. Thus, PhSH, 2-TolSH, and 4-TolSH give the corresponding sulfides in 65, 47 and 32% yields, respectively[96]. Thiophenol and $Ph_4BiO_2CCF_3$, when heated in PhH in an argon atmosphere for 24 h, give a mixture of Ph_2S_2 and Ph_2S. This oily mixture is dissolved in diethyl ether and treated with $LiAlH_4$ to give to 70% yield of Ph_2S[101]. In a similar manner, $(2\text{-Tol})_2S$ can be prepared in 80% yield. Finally, PhSH and Ph_3BiCl_2 in the presence of NaH give a 99% yield of Ph_2S_2. Although the thiono group in xanthates and dialkylaminothionocarbamates is not oxidized by Ph_3BiCO_3, the oxidation of the thiono group in 1,2:5,6-di-*O*-isopropylidene-3-(*N*-4-nitrophenylthionocarbamato)-α-D-glucofuranose to the corresponding disulfide in 81% yield has been achieved[94,102]. The oxidation of sodium dithiocarbamates to thiuram disulfides has also been mentioned (equation 87)[103]:

$$R_2NC(S)SNa \xrightarrow{Ph_3BiCl_2} (R_2NC(S)S)_2 + Ph_3Bi \qquad (87)$$

The nitrogen in compounds such as indole, pyrrolidine, aniline, and dimethylaniline is unaffected by organobismuth(V) reagents. However, hydrazo compounds are oxidized to azo compounds and hydrazones to diazo compounds (equations 88 and 89)[93,94].

$$PhNHNHPh \xrightarrow{Ph_3BiCO_3} PhN{=}NPh \qquad (88)$$

$$Ph_2C{=}NNH_2 \xrightarrow{Ph_3BiCO_3} Ph_2CN_2 \qquad (89)$$

Although benzophenone hydrazone is oxidized to diphenyldiazomethane in 97% yield, benzophenone phenylhydrazone, benzophenone 2,4-dinitrophenylhydrazone, and benzophenone semicarbazone are unaffected by Ph_3BiCO_3. Phenylhydroxylamine is oxidized to nitrosobenzene by Ph_3BiCO_3, but the yield is only 22%, and the free radical diphenylnitroxide is obtained in 64% yield. If $(4\text{-Tol})_3BiCO_3$ is used, phenyl-4-tolylnitroxide is obtained in 50% yield.

D. Oxidative Cleavage of Vicinal Glycols

The usual reagents for the oxidative cleavage of vicinal glycols, to yield two molecules of aldehyde or ketone, are lead tetraacetate in anhydrous solvents or periodic acid in aqueous solution. In their first paper on the use of organobismuth(V) compounds as synthetic reagents, Barton *et al.*[91] reported that *meso*-hydrobenzoin and 1,2:5,6-di-*O*-isopropylidene-D-mannitol are converted to benzaldehyde and 2,3-isopropylidene-D-glyceraldehyde by $(Ph_3BiCl)_2O$ in 80 and 70% yields, respectively. When Ph_3BiCO_3 is used as the oxidizing agent, *cis*-cyclohexane-1,2-diol, *meso*-hydrobenzoin, and 1,2:5,6-di-*O*-isopropylidene-D-mannitol yield the corresponding carbonyl compounds in 100, 97 and 89% yields, respectively[93,94]. Dodonov *et al.*[98] obtained 1.65 mol of acetone per mole of $Ph_3Bi(OAc)_2$ when pinacol and the bismuth compound, in the presence of K_2CO_3, were heated in toluene solution.

Barton and coworkers[93,94] suggested that the oxidative cleavage of glycols occurs by a different mechanism than the oxidation of simple alcohols. This suggestion is based on the fact that cleavage of 1,2-glycols by Ph_3BiCO_3 gives a virtually quantitative yield of Ph_3Bi, compared with about a 50% yield when simple alcohols are oxidized. It therefore seemed possible that a catalytic cycle, using small amounts of Ph_3Bi and a suitable oxidizing agent, might be employed. Accordingly they first tried to oxidize hydrobenzoin by the use of H_2O_2 (and $NaHCO_3$) or Bu^{t}OOH in the presence of small amounts of Ph_3Bi. Although successful with hydrobenzoin, the reaction fails with other glycols. Excellent results are

obtained, however, when nbs is used as the oxidizing agent[104]. *N*-Bromoacetamide can also be used. The reaction is rapid, and the yields are high. Pinacol gives a 100% yield of acetone. The cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol occurs without racemization. In contrast to lead tetraacetate, the addition of an organic base does not lead to a faster reaction rate, but actually hinders the reaction. The procedure used is simple: nbs in MeCN containing 1% water is added dropwise over 1.5 h to a stirred solution of the glycol and 0.01–0.1 equivalent of Ph_3Bi in moist MeCN containing K_2CO_3. The reaction is run in the dark. After filtration of the reaction mixture, the solvent is removed and the product recovered by distillation or column chromatography. The method may be successful where other methods fail. Thus, *trans*-decalin-9,10-diol is not cleaved by Ph_3BiCO_3 and btmg nor by periodic acid, whereas with $Pb(OAc)_4$ the rate of cleavage is 100 times slower than the cleavage of the *cis*-isomer. In contrast, Ph_3Bi and NBS cleave both isomers at approximately the same rate and with the same yields.

The choice of organobismuth reagents for the cleavage of 1,2-glycols has been further investigated[105]. The glycols used were *meso*-hydrobenzoin, *cis*- and *trans*-decalin-9,10-diol, and benzopinacol, and the bismuth reagents were Ph_3BiCO_3 (in both the presence and absence of btmg), Ph_3BiCl_2 (in the presence of btmg) and Ph_3Bi (in the presence of nbs and K_2CO_3). With one exception the yields are fairly comparable (ranging from 50 to 100%). The exception is *trans*-decalin-9,10-diol, where Ph_3BiCO_3 fails to oxidize the diol, and Ph_3BiCl_2 gives the diketone in only 6% yield (after 3 h), whereas Ph_3Bi (0.1 equivalent), nbs, and K_2CO_3 give the diketone in 77% yield after 3.7 h. This result suggested an entirely different mechanism for the cleavage of vicinal glycols by the two types of organobismuth reagents, Ph_3BiX_2 or Ph_3Bi, in the presence of NBS.

David and Thiéffry[106] showed that stannylene derivatives of vicinal glycols are readily cleaved by a number of oxidizing agents, including $Ph_3Bi(OAc)_2$, to give the corresponding aldehydes. Thus, DL-*erythro*-$PhCH_2CH_2CHOHCHOHCH_2Ph$ was converted to the stannylene derivative by reaction with Bu_2SnO. Reaction of this compound with $Ph_3Bi(OAc)_2$ in CH_2Cl_2 at 40 °C gave the two aldehydes $PhCH_2CHO$ and $PhCH_2CH_2CHO$ in 66 and 90% yields, respectively. Since Ph_3BiCO_3 is an excellent reagent for the oxidative cleavage of vicinal glycols, there seems to be no advantage in preparing the stannylene derivatives.

E. Arylation of Alcohols

As described previously, primary and secondary alcohols (in the absence of a copper catalyst) are oxidized to aldehydes and ketones by organobismuth(V) reagents, Ar_5Bi, Ar_4BiX, and Ar_3BiX_2. With the last two types of reagents the presence of a fairly strong base generally leads to a maximum yield of oxidation product. Under neutral or acidic conditions, or in the presence of a weak base such as Et_3N, both oxidation and *O*-arylation may occur. Dodonov *et al.*[98,107] have studied the reaction of alcohols and $Ph_3Bi(OAc)_2$ in the presence and absence of bases. In the absence of a base the yields of oxidation products are variable, depending on the alcohol used and the reaction conditions employed. However, in the presence of K_2CO_3, oxidation to aldehyde or ketone is essentially the only reaction. Thus, Pr^iOH, $Ph_3Bi(OAc)_2$, and K_2CO_3 give a 98% yield of Me_2CO when heated in $CHCl_3$ (equation 90). If Et_3N is used instead of K_2CO_3, the yield of Me_2CO is only 68%, and in the absence of a base a mixture of products, Me_2CO, Pr^iOPh, and Pr^iOAc, is obtained. Cyclohexanol gives trace amounts of phenoxycyclohexane as the sole reaction product when heated with $Ph_3Bi(OAc)_2$ in CH_2Cl_2 solution[108].

$$Pr^iOH + Ph_3Bi(OAc)_2 \xrightarrow{K_2CO_3} Me_2CO + 2PhH + PhBi(OAc)_2 \qquad (90)$$

3β-Cholestanol reacts with a number of compounds of the type Ph_4BiX [X = O_2CCF_3,

OTos, OAc, OSO_2CF_3, 2,4,6$(NO_2)_3C_6H_2O$, O_2CCCl_3, O_2CCH_2Cl, O_2CCHPh_2] under neutral or acidic conditions[97]. Both oxidation to cholestanone and *O*-phenylation occur with each of the above reagents. It has also been reported that the following alcohols undergo *O*-phenylation when allowed to react with $Ph_4BiO_2CCF_3$ in the absence of a catalyst: octadecan-1-ol (76%), 2,2-dimethylpropan-1-ol (61%), and geraniol (57%)[109].

Different results are obtained in the presence of a copper catalyst[110]. Simple primary and secondary alcohols (EtOH, BuOH, Pen^{i}OH, and Pr^{i}OH) give the corresponding alkyl aryl ethers in yields of 62–97% when allowed to react with $Ph_3Bi(OAc)_2$ and a copper catalyst at room temperature for periods of 6–24 h (equation 91).

$$Ph_3Bi(OAc)_2 + ROH \xrightarrow{CuCl_2} PhOR + AcOH + Ph_2BiOAc \qquad (91)$$

The copper catalysts used are $CuCl_2$, CuCl, $Cu(OAc)_2$, and copper, all of which are effective. However, with $CuCl_2$ and CuCl, some chlorobenzene is formed at the expense of the ether. Metallic copper or $Cu(OAc)_2$ would seem to be preferable. The amount of catalyst is not particularly critical. Thus, Pr^{i}OH, $Ph_3Bi(OAc)_2$, and $Cu(OAc)_2$, all in 1 molar amounts, give the ether in 97% yield, but reducing the amount of $Cu(OAc)_2$ to 0.01 mol still gives an 86% yield of product. *tert*-Butyl alcohol is phenylated to Bu^{t}OPh but the yield is only 9%.

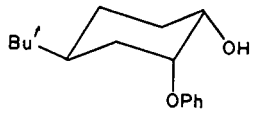
Although the phenylation of simple alcohols by the above procedure is fairly effective, its use in the synthesis of more complex ethers has not been thoroughly investigated. 3β-Cholestanol and $Ph_3Bi(OAc)_2$ give the corresponding phenyl ether in 36% yield without a catalyst and in 39% yield when 0.1 equivalent of $Cu(OAc)_2$ is added[109]. Both reactions are carried out in refluxing CH_2Cl_2 for 8 h. However, in refluxing benzene for 24 h, the yield of ether increases to 50%.

Ph_3Bi forms ethers with primary and secondary alcohols, in the presence of 2 molar equivalents of $Cu(OAc)_2$, at a very slow rate (several days at room temperature)[82a]. Other products of the reaction are PhH and AcOH. Thus, Ph_3Bi (1 equivalent) and $Cu(OAc)_2$ (2 equivalents) in Pr^{i}OH give PhH, Pr^{i}OPh, and AcOH (2.29, 0.52, and 0.46 mol per mole of Ph_3Bi, respectively). The reaction is carried out in a sealed ampoule. The same yields are obtained when the reaction is carried out at 50 °C for 6 h. If, however, the reaction is carried out in air at 50 °C for 6 h, the yield of Pr^{i}OPh is increased significantly whereas the amounts of PhH and AcOH are markedly decreased. Similar results to those obtained with Pr^{i}OH are found with the primary alcohols, EtOH, BuOH, and Pen^{i}OH.

F. Monoarylation of Glycols

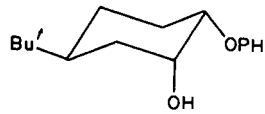
In contrast to simple alcohols, glycols are monophenylated by $Ph_3Bi(OAc)_2$ in refluxing CH_2Cl_2 in the absence of a catalyst[106]. In a preliminary investigation, it was reported that $PhCH_2CHOHCHOHCH_2CH_2Ph$ gives a mixture of $PhCH_2CH(OPh)CHOHCH_2CH_2Ph$ and $PhCH_2CHOHCH(OPh)CH_2CH_2Ph$ in quantitative yield, and that *trans*-cyclohexane-1,2-diol gives *trans*-2-phenoxycyclohexanol in 88% yield. Following these findings, the studies were extended to a wide variety of glycols[108,111]. Simple vicinal glycols give monophenyl compounds in yields of 85–92%. In some cases oxidative cleavage of the glycol occurs. Thus, *meso*-PhCHOHCHPhOH gives PhCHOPhCHPhOH in only 37% yield, and $Ph_2COHCPh_2OH$ gives no phenylation product. The reaction is not limited to vicinal glycols. Thus, the glycols $CH_2OH(CH_2)_nCH_2OH$ give the monophenyl compounds in the following yields: $n = 1$, 87%; $n = 2$, 80%; $n = 3$, 50%; and $n = 4$, 40%. (*Z*)-$CH_2OHCH{=}CHCH_2OH$ is monophenylated in 75% yield. Alicyclic diols are also readily monophenylated. Thus, *cis*- and *trans*-cyclopentane-1,2-diols give the *cis* and *trans* monoethers in 41 and 51% yields, respectively; *cis*- and *trans*-cyclohexane-1,2-diols give the monoethers in 87 and 88%

yields, respectively. With compounds where either a secondary or a tertiary hydroxy group can be phenylated, the product is that in which the secondary hydroxy group is phenylated, e.g. *trans*-1-phenylcyclohexane-1,2-diol gives *trans*-2-phenoxy-1-phenylcyclohexanol. The phenylation of several conformationally rigid 1,2-glycols were then investigated. With *trans*-4-*tert*-butyl-*cis*-cyclohexane-1,2-diol, two isomers (**8** and **9**) are obtained, that in which the axial OH group is phenylated predominating in a ratio of 73:2. Similar results are obtained with a variety of other cyclohexane-1,2-diols and a number of pyranosides.



73%

(8)



2%

(9)

The procedure used is reasonably simple. The diol (1 mmol) and $Ph_3Bi(OAc)_2$ (1 mmol) in 5 ml of CH_2Cl_2 are refluxed until the reaction is complete as shown by TLC. The reaction mixture is evaporated to dryness and the phenyl ether separated from the residue by column chromatography on a silica gel column. The method would seem to be valuable for the preparation of a wide variety of phenyl ethers that are otherwise difficult to obtain.

The glycol arylation reaction has been further investigated by Barton *et al.*[109]. They found that neighboring groups other than hydroxy could promote phenylation. Thus, 2-phenoxyethanol and 2-methoxyethanol are phenylated in 92 and 86% yields, respectively. This result is surprising as earlier workers did not detect diphenylation in any of the glycols they investigated[108,111]. Phenylation of these two ethers, however, is slower than phenylation of ethylene glycol. As might be expected, the sulfur atom in 2-mercaptoethanol is oxidized whereas the hydroxyl group is phenylated. Thus, the reaction produces a mixture of bis(2-phenoxyethyl) disulfide (22%) and 2-hydroxyethyl 2-phenoxyethyl disulfide (58%). Although not mentioned by David and Thiéffry, Barton *et al.* found that the phenylation of glycols always requires an induction period and is remarkably dependent on the solvent used. Thus, with 2,2-dimethylpropane-1,3-diol, the monoether is obtained in 91% yield when the reactants are refluxed in CH_2Cl_2 for 4 h. The reaction time is reduced to 1.5 h when the flask is irradiated with a 300-W sun-lamp. No reaction occurs at room temperature or when the reactants are refluxed in the dark, no reaction occurs in Me_2CO, PhH, $BrCH_2Cl$, $CHCl_3$, CH_2Br_2, or thf, and only a small yield is obtained in $ClCH_2CH_2Cl$.

No explanation for this remarkable solvent effect has been suggested. However, the addition of small amounts of $Cu(OAc)_2$ (0.1 equivalent) has a dramatic effect. There is no longer an induction period, irradiation is not necessary, and the reaction occurs readily at room temperature in $CHCl_3$, PhH, $BrCH_2Cl$, and thf. In contrast, $Co(OAc)_2$, $Ni(OAc)_2$, and $FeCl_3$ have no effect on the reaction.

It has been mentioned previously that *cis*-cyclohexane-1,2-diol is converted to the monophenyl ether in 87% yield by treatment with $Ph_3Bi(OAc)_2$[111]. Since this isomer is *meso*, monophenylation destroys the plane of symmetry, and two enantiomers are produced, i.e. the product is a racemic mixture. Brunner *et al.*[112] carried out the monophenylation reaction in the presence of a number of chiral pyridine oxazolines. Copper acetate was used as the catalyst. The yield of monoether was reduced from 87% to 35–45% in the presence of the chiral agent. In order to determine the enantiomeric excess formed in the reaction, the phenoxy alcohol was converted to the corresponding urethane by treatment with MeNCO and the enantiomeric excess determined by gas chroma-

tography. The optical induction was found to vary between 13.0 and 30.2% with the eight different chiral pyridine oxazolines used. A similar study was carried out with *meso*-butane-2, 3-diol, but using only one of the chiral pyridine oxazolines. In order to determine the optical induction, the product was treated with Pr^iNCO rather than MeNCO. The optical induction was found to be 17%.

G. The Arylation of Phenols

The reaction between phenols and organobismuth(V) reagents can lead to a variety of products, depending on the organobismuth compound used, the substrate, and the reaction conditions (particularly the presence or absence of a base). Often a mixture of products is obtained. However, by a careful choice of reagents and reaction conditions, it is usually possible to obtain, in fairly high yield, either one of two products, the diaryl ether (*O*-arylation) or the *O*-arylphenol (*C*-arylation). Table 1 shows the results obtained in the phenylation of 2-naphthol under various reaction conditions. Under basic conditions, compounds of the types Ar_3BiX_2 and Ar_4BiX give the *C*-phenylated product. The same product is obtained by using Ph_3BiCO_3 or Ph_5Bi without the addition of a base. The reaction is fairly rapid and is frequently carried out at room temperature. The yields, particularly with Ph_3BiX_2 and Ph_4BiX compounds, are excellent. The reaction between 2-naphthol and Ph_3BiX_2 or Ph_4BiX compounds in the absence of a base yields predominantly or exclusively phenyl 2-naphthyl ether. The reaction proceeds at a much faster rate and the yields are larger in the presence of a copper catalyst.

The reaction has been extended to a number of substituted phenols[113]. It involves stirring a mixture of the phenol, $Ph_3Bi(OAc)_2$ (1.2 equivalents), and metallic copper (0.1 equivalent) in CH_2Cl_2 solution at room temperature in an argon atmosphere. The results are given in Table 2. The yield of ether is based on equation 92.

$$Ph_3Bi(OAc)_2 + ArOH \xrightarrow{Cu} ArOPh + HOAc + Ph_2BiOAc \qquad (92)$$

TABLE 1. Phenylation of 2-naphthol by organobismuth(V) reagents under neutral or basic conditions

Reagent	Base[a]	Catalyst[b]	*O*-Phenylation (%)	*C*-Phenylation (%)	Ref.
$Ph_4BiO_2CCF_3$[c]	–	–	50		113
$Ph_4BiO_2CCF_3$[d]	–	–	77	2	114
Ph_4BiOAc	–	–	26	25	115
Ph_3BiCO_3	–	–		76	116
Ph_3BiCO_3	+	–		76	102
Ph_4BiOAc	+	–		90	115
$Ph_4BiO_2CCF_3$	+	–		90	115
Ph_3BiCl_2	+	–		90	114
$Ph_3Bi(OAc)_2$[e]	–	+	84		113
$Ph_4BiO_2CCF_3$[f]	–	+	80		113
$Ph_4BiOTos$	+	–	0	90	117
Ph_5Bi	–	–		61	96

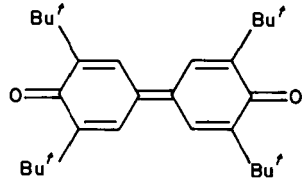
[a]The base used was usually btmg or tmg, but NaH was equally effective.
[b]The copper catalysts were $Cu(OAc)_2$ or copper. Copper metal may have given slightly better results.
[c]Benzene at room temperature for 24 h under argon.
[d]Refluxing benzene for 140 h.
[e]After 5 h under argon at room temperature in CH_2Cl_2.
[f]In benzene under argon at room temperature for 24 h.
[g]Yield after 1 h at room temperature in thf.

TABLE 2. *O*-Phenylation of phenols by $Ph_3Bi(OAc)_2$ catalysed by copper metal

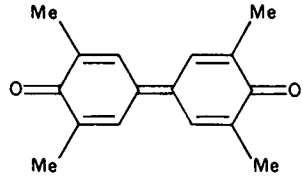
Phenol	Reaction time (h)	Yield of aryl phenyl ether (%)
Phenol	5	88
O-Phenyl-	24	73
2,6-Di-Me-	3	67
3,5-Di-OMe-	4	90
4-*t*-Bu-	5	80
2,4-Di-*t*-Bu-	3	26
2,4,6-Tri-*t*-Bu-	24	0
3,5-Di-*t*-Bu-	4	90
4-Carbomethoxy-	5	90
4-Nitro-	15	97

Although the number of phenols that have been *O*-arylated to yield ethers is limited, this would seem to be an excellent synthetic method. Except for the highly hindered di-*o*-substituted compounds, the yields are high. The ether is also free of *C*-phenylated product[113]. Although the reaction rate is increased markedly by the use of a copper catalyst, ethers have been obtained from phenols and organobismuth(V) reagents without the use of a copper catalyst. Thus, 2,6-dimethylphenol, when refluxed with $Ph_4BiOCOCF_3$ in benzene solution for 72 h, gives a 58% yield of 2,6-dimethylphenyl phenyl ether[114,118]; 2,3,5,6-tetramethylphenol gives a 57% yield at 2,3,5,6-tetramethylphenyl phenyl ether (after 24 h refluxing), and estrone gives a 75% yield of estrone phenyl ether after 18 h refluxing[114]. Presumably, the rate of all of the above reactions could be markedly increased by the addition of a copper catalyst. As noted in Table 1, the reaction of 2-naphthol with either Ph_3BiCO_3 or Ph_5Bi leads to *C*-phenylation. In this regard these two bismuth(V) reagents react in a similar manner to the reaction of Ph_3BiX_2 and Ph_4BiX reagents under basic conditions. Accordingly, the reactions of Ph_3BiCO_3 and Ph_5Bi will be considered under the reactions of phenols and organobismuth(V) reagents under basic conditions.

The reaction between phenols and compounds of the type Ph_3BiX_2 or Ph_4BiX under basic conditions (and also Ph_3BiCO_3 and Ph_5Bi without base) is complicated. The products obtained depend considerably on the substrate and on the organobismuth reagent used. Often a mixture of products is obtained. In addition to *O*-arylation and mono-*C*-arylation, di-*C*-arylation and oxidation to dienones may occur. For example, phenol and Ph_3BiCl_2 with the addition of btmg give 2-hydroxybiphenyl (30%), 2,6-diphenylphenol (7%), diphenyl ether (8%), and biphenyl (50%)[119]. Phenol and Ph_5Bi give diphenyl ether in 42% yield[95]. The reaction between 2,6-di-*tert*-butylphenol and Ph_3BiCl_2 in the presence of btmg gives the diphenoquinone **10**. The same product is obtained from 2,6-di-*tert*-butylphenol and Ph_3BiCO_3[119]. 2,6-Dimethylphenol and Ph_3BiCO_3 give a

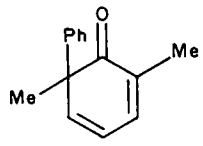


(10)



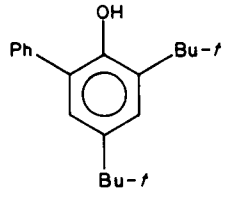
(11)

diphenoquinone (**11**). The same phenol and Ph_5Bi give 6-phenyl-2,6-dimethylcyclohexa-2,4-dienone (**12**)[96].

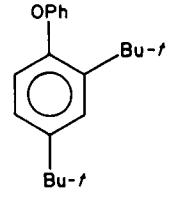


(12)

The reaction between 2,4-di-*tert*-butylphenol and $Ph_4BiO_2CCF_3$ in the presence of btmg (at room temperature in CH_2Cl_2 for 20 h) gives an 81% yield of the 6-phenyl derivative (**13**) and a 3% yield of the phenyl ether (**14**). The same 6-phenyl compound (in

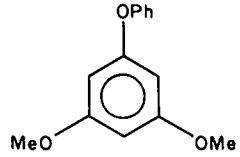


(13)

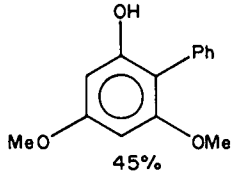


(14)

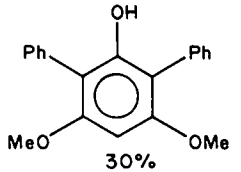
65% yield but no ether) is obtained when Ph_5Bi is used as the phenylating agent[119]. 3,5-Dimethoxyphenol, Ph_3BiCl_2, and btmg give a mixture of ether and phenylated phenols (**15–17**).



10%
(15)

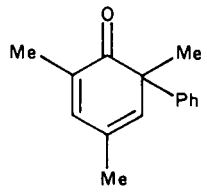


45%
(16)

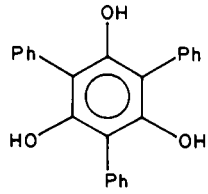


30%
(17)

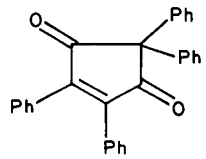
2,4,6-Trimethylphenol and Ph_5Bi give the phenylated dienone **18**. 2,6-Dimethyl-4-*tert*-butylphenol and Ph_5Bi give a similar dienone in 51% yield[96]. 1-Naphthol and Ph_5Bi give 2-phenyl-1-naphthol in 48% yield, but the same phenol and Ph_3BiCO_3 give an intractable mixture of products. In contrast, phloroglucinol and Ph_3BiCO_3 give the phenylated products **19** and **20**, while phloroglucinol and Ph_5Bi give a complex mixture of



(18)



(19)



(20)

products[96,114]. The reaction between estradiol and Ph_5Bi gives a mixture of 2,4-diphenylestrone (14%), 4-phenylestrone (13%), and 2,4-diphenylestradiol (12%).

From the results given above, the use of organobismuth(V) compounds of the types Ph_3BiX_2 and Ph_4BiX under basic conditions, or Ph_3BiCO_3 and Ph_5Bi under neutral conditions, for the arylation of phenols, particularly those containing electron-repelling groups, would seem to be of limited value. Barton *et al.*[116] prepared several 4-substituted triarylbismuth carbonates, $(4\text{-}RC_6H_4)_3BiCO_3$ (R = Me, OMe, and NO_2), and investigated their reaction with 2-naphthol. In each case 1-aryl-2-naphthols were obtained in satisfactory yields (69–76%). This would seem to be an excellent method for the preparation of this class of compounds.

The reaction of organobismuth(V) reagents with phenols containing electron-attracting groups in the *para* position differs markedly from their reaction with phenols containing electron-repelling groups. Thus, $4\text{-}O_2NC_6H_4OH$ reacts with Ph_5Bi or $Ph_4BiOTos$ (under basic conditions) to yield the stable product $4\text{-}O_2NC_6H_4OBiPh_4$[114]. When this product is refluxed in toluene solution for 4 h in an argon atmosphere, a 98% yield of $4\text{-}O_2NC_6H_4OPh$ is obtained. The reaction of Ph_3BiX_2 (X = Cl or O_2CCF_3) under basic conditions yields the stable product $4\text{-}O_2NC_6H_4OBiPh_3X$. However, thermal decomposition of these compounds in refluxing PhH gives only a 2% yield of $4\text{-}O_2NC_6H_4OPh$ when X = Cl and zero yield when $X = O_2CCF_3$[119]. When other phenols containing electron-attracting groups in the *para* position ($4\text{-}YC_6H_4OH$, Y = CO_2Me, CN, or CF_3) are refluxed in solution (toluene or thf) with Ph_3BiCl_2 and btmg, the corresponding ethers are obtained in satisfactory yields (70–91%). Since 4-nitrophenyl phenyl ether is obtained in 97% yield from $4\text{-}NO_2C_6H_4OH$ and $Ph_3Bi(OAc)_2$ in the presence of copper, there would seem to be no advantage in performing this reaction under basic conditions.

The reaction of phenols containing electron-attracting groups in the *meta* position with organobismuth(V) reagents under basic conditions yields products in which both *O*- and *C*-arylation has occurred. Thus, $3\text{-}O_2NC_6H_4OH$, Ph_3BiCl_2, and btmg in toluene at room temperature for 16 h give $3\text{-}O_2NC_6H_4OPh$ (54%), $2\text{-Ph-}5\text{-}O_2NC_6H_3OH$ (13%), and $2,6\text{-}Ph_2\text{-}3\text{-}O_2NC_6H_2OH$ (9%). Similarly, $3,5\text{-}Cl_2C_6H_3OH$ gives $3,5\text{-}Cl_2C_6H_3OPh$ (60%), $2\text{-Ph-}3,5\text{-}Cl_2C_6H_2OH$ (16%), and $2,6\text{-}Ph_2\text{-}3,5\text{-}Cl_2C_6HOH$ (12%). Presumably, both of these phenols would give only the corresponding phenyl ether if allowed to react with $Ph_3Bi(OAc)_2$, under neutral conditions, particularly in the presence of a copper catalyst.

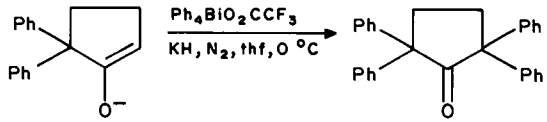
H. Arylation of Enols and Enolate Anions

The arylation of ketones by organobismuth(V) reagents can lead to *C*-arylation of the carbon adjacent to the carbonyl group and/or to *O*-arylation of the enolic hydroxy group. The *C*-arylation was first noted when quinine was oxidized to quininone by Ph_3BiCO_3. The yield of ketone, however, is only 34%, and it is accompanied by a diastereomeric mixture of α-phenylated ketones in 75% yield[101,102]. With $(4\text{-Tol})_3BiCO_3$ a 90% yield of the analogous mixture of α-tolyl ketones is obtained. Similarly, treatment of 1,2-

diphenylethanol with Ph_3BiCO_3 gives a triphenylated ketone (equation 93)[101].

$$PhCH_2CH(OH)Ph \xrightarrow[CH_2Cl_2]{Ph_3BiCO_3} Ph_2CHCOPh \quad (93)$$

Following these results, the reaction of a number of ketones and 1,3-dicarbonyl compounds were investigated with several different organobismuth(V) reagents (Ph_3BiCl_2, Ph_3BiCO_3, $Ph_4BiO_2CCF_3$, and Ph_5Bi) under various reaction conditions[101]. In one series of reactions a number of ketones were dissolved in thf in the presence of KH (1.1–12 equivalents) and then treated with Ph_3BiCO_3 (2–8 equivalents) in an argon atmosphere. The products were those in which the carbon atoms α to the carbonyl group were phenylated. Thus, acetophenone gave 2,2,2-triphenylacetophenone, dibenzyl ketone gave pentaphenylacetone and cyclohexanone gave 2,2,6,6-tetraphenylcyclohexanone[101,120]. Among the natural products phenylated by this procedure is cholestan-3-one, which gives 2,2-diphenylcholestan-3-one. All of these phenylated products are obtained in satisfactory yields (60–93%). In addition to Ph_3BiCO_3, other organobismuth(V) reagents can be used for the polyphenylation of ketones. The cyclohexanone anion (from cyclohexanone and KH) in thf solution in an argon atmosphere gives an 80% yield of 2,2,6,6-tetraphenylcyclohexanone when treated with $Ph_4BiOTos$[121]; 2,2-diphenylcyclopentanone anion in a nitrogen atmosphere gives a 74% yield of 2,2,5,5-tetraphenylcyclopentanone with $Ph_4BiO_2CCF_3$ (equation 94).



(94)

Pentaphenylbismuth also gives good yields of polyphenylated products. Thus, 2-phenylethanol and Ph_5Bi in PhH solution gives a 69% yield of triphenylacetaldehyde (equation 95)[101].

$$PhCH_2CH_2OH \xrightarrow[PhH,\,argon]{Ph_5Bi} Ph_3CCHO \quad (95)$$

The 1,3-dicarbonyl compounds that are phenylated by organobismuth(V) reagents include acetylacetone, ethyl acetoacetate, ethyl cyclohexanone-2-carboxylate, ethyl cyclopentanone-2-carboxylate, diethyl malonate, and dimedone. The products obtained usually depend on the reaction conditions as well as the bismuth compound used. Thus, acetylacetone gives the results shown in Scheme 8.

$$\xrightarrow[CH_2Cl_2,\,reflux]{Ph_3BiCO_3} \underset{33\%}{MeCOCHPhCOMe} + \underset{40\%}{MeCOCPh_2COMe}$$

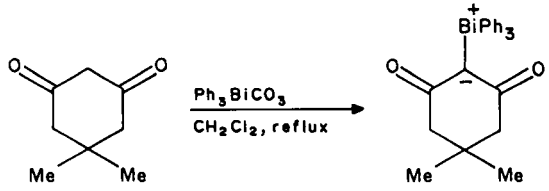
$$acac \xrightarrow[\substack{btmg,\,PhH,\\ reflux}]{Ph_3BiCl_2} \underset{74\%}{MeCOCPh_2COMe}$$

$$\xrightarrow[PhH,\,reflux]{Ph_4BiO_2CCF_3} \underset{34\%}{MeCOCHPhCOMe}$$

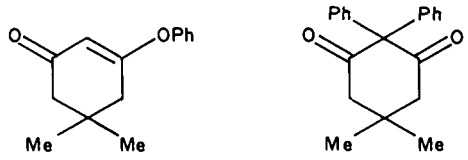
SCHEME 8

Similar results are obtained with ethyl acetoacetate, where it is possible to obtain either the mono- or di-phenylated products, $MeCOCHPhCO_2Et$ or $MeCOCPh_2CO_2Et$. In

addition, when Ph_3BiCO_3 (2.1 equivalents) in CH_2Cl_2 is used, a 21% yield of Ph_2CHCO_2Et is obtained. Dimedone and Ph_3BiCO_3 in refluxing CH_2Cl_2 give an unexpected product, a bismuth ylide (equation 96). However, with $Ph_4BiO_2CCF_3$ in PhH alone, or in PhH with the addition of CF_3CO_2H, the *O*-phenylated product **21** is produced in 56 and 88% yields, respectively. The same bismuth reagent and btmg gives the *C*-phenylated product **22**.

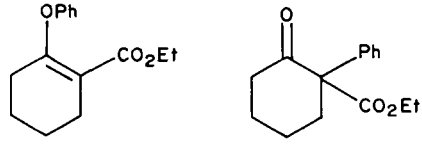


(96)



(21) **(22)**

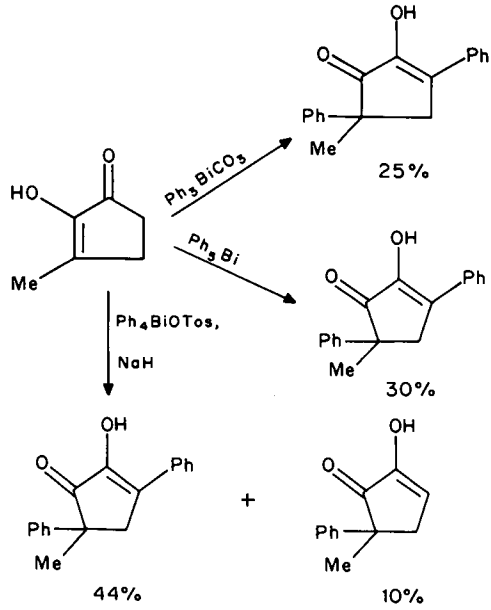
Ethyl cyclohexanone-2-carboxylate with $Ph_4BiOCOCF_3$ gives the *O*-phenylated product **23** in 30% yield, but the yield is increased to 57% under acidic conditions (CCl_3CO_2H). However, the same ester with $Ph_4BiO_2CCF_3$ or Ph_3BiCl_2, both under basic conditions, or with Ph_3BiCO_3 or Ph_5Bi under neutral conditions, yields the *C*-phenylated product **24** in yields as high as 90%.



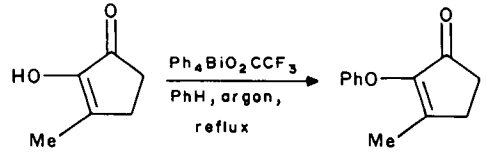
(23) **(24)**

Another interesting result has been obtained with the diosphenol 2-hydroxy-3-methylcyclopent-2-enone. With Ph_5Bi or Ph_3BiCO_3 under neutral conditions, or with $Ph_4BiOTos$ under basic conditions (NaH), a diphenylated product is obtained (Scheme 9). However, when $Ph_4BiO_2CCF_3$ under neutral conditions is used, the *O*-phenylated product is obtained in 84% yield (equation 97).

Barton *et al.*[113] also investigated the effect of a copper catalyst on the phenylation of enols. The results are not dramatic. Thus, ethyl cyclohexanone-2-carboxylate and $Ph_4BiO_2CCF_3$ in PhH after 20 h at 50 °C give a 27% yield of the 2-phenyl derivative, but only a 40% yield on the addition of 0.1 equivalent of $Cu(OAc)_2$ (after 40 h). The *O*-phenylation of dimedone by $Ph_3Bi(O_2CCF_3)_2$ in the presence of 0.1 equivalent of copper occurs at a faster rate than that previously found using $Ph_4BiO_2CCF_3$ alone. The *O*-phenylation of 2-hydroxy-3-methylcyclopent-2-enone by $Ph_3Bi(OAc)_2$ or $Ph_3Bi(O_2CCF_3)_2$ also occurs at a faster rate in the presence of 0.1 equivalent of copper.



SCHEME 9

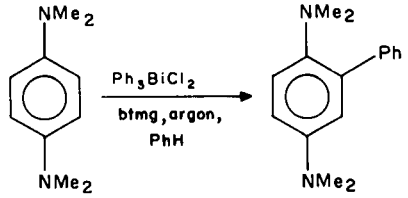


(97)

The phenylation of ketones and dicarbonyl compounds would therefore appear to be an excellent method for obtaining polyphenylated derivatives. By careful choice of the bismuth reagent and of reaction conditions, a single product can usually be obtained.

I. Arylation of Anions Other than Enolate Ions

2-Nitropropane reacts with Ph_5Bi in benzene solution in an argon atmosphere to give a 25% yield of α-nitrocumene[96,101]. The same product is obtained in an 80% yield from Ph_3BiCO_3 under basic conditions (KH in thf solution) and from $Ph_4BiOTos$ and btmg (86%) or from Ph_3BiCl_2 and btmg (77%)[117]. A 40% yield of Ph_4C is obtained from Ph_3CH and potassium in $MeOCH_2CH_2OMe$ when treated with Ph_3BiCO_3. Phenyl 4-tolyl sulfone is obtained from either 4-toluenesulfinic acid or its sodium salt with several different organobismuth(V) reagents. The phenylation of indole by $Ph_4BiO_2CCF_3$ in refluxing PhH gives 3,*N*-diphenylindole (2%) and 3-phenylindole (43%); indole and $Ph_4BiOTos$ give 3-phenylindole (36%). Under basic conditions (NaH), indole and $Ph_4BiOTos$ give 3-phenylindole (3%) and 3,3-diphenyl-3*H*-indole (61%). In a similar manner, 3-methylindole is phenylated to 3-methyl-3-phenyl-3*H*-indole by Ph_3BiCl_2 and NaH (51%) or by $Ph_4BiOTos$ and btmg (95%). Another interesting phenylation reaction involves *N*,*N*,*N*′,*N*′-tetramethylphenylene-1,4-diamine which yields the 2-phenyl derivative when treated with Ph_3BiCl_2 and btmg (19%), $Ph_4BiOTos$ and btmg (8%), or Ph_3BiCO_3 (16%) (equation 98).



(98)

In yet another phenylation reaction, Ptitsyna *et al.*[122] found that Ph_4BiBF_4 reacts with Ph_3P to give Ph_4PBF_4 in 90% yield.

J. Arylation of Amines

Barton and coworkers[93,94] originally reported that both aniline and *N,N*-dimethylaniline are not oxidized by Ph_3BiCO_3 at room temperature. Dodonov *et al.*[123], however, found that primary aliphatic and aromatic amines and secondary aliphatic amines are readily phenylated by $Ph_3Bi(OAc)_2$ at room temperature in the presence of $Cu(OAc)_2$. No reaction occurs in the absence of the copper catalyst. Diphenylamine gives Ph_3N in only 3% yield after heating at 50 °C for 74 h. The primary amines, $PrNH_2$, Bu^tNH_2, Bu^tNH_2, and $PhNH_2$, are used in a 5–10-fold excess in order to obtain only the secondary amine; 0.02 equivalent of $Cu(OAc)_2$ is used. The yields of secondary amines vary from 69 to 82%, according to equation 99.

$$Ph_3Bi(OAc)_2 + 2RNH_2 \xrightarrow{Cu(OAc)_2} PhNHR + Ph_2BiOAc + RNH_2{\cdot}AcOH \quad (99)$$

All of the reactions are carried out at room temperature for periods that vary from 60 to 180 h. The secondary amines readily phenylated to tertiary amines are Et_2NH and Bu_2NH. Following this preliminary report by Dodonov *et al.*, Barton *et al.*[124] reported that metallic copper is a superior catalyst to $Cu(OAc)_2$ for the phenylation of both aliphatic and aromatic amines. Thus, $PhNH_2$, $Ph_3Bi(OAc)_2$ (1.1 equivalents) and 0.1 equivalent of copper in CH_2Cl_2 give a 96% yield of Ph_2NH after 2 h at room temperature. A number of other primary aromatic amines, $ArNH_2$ (Ar = 4-Tol, 4-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$, and 2-$O_2NC_6H_4$) are similarly arylated in yields of over 90%. However, 4-$O_2NC_6H_4NH_2$ gives both 4-$O_2NC_6H_4NHPh$ (74%) and 4-$O_2NC_6H_4NPh_2$ (23%) after only 2 h at room temperature. With an excess of $Ph_3Bi(OAc)_2$ (2.2 equivalents) after 16 h, a 90% yield of 4-$O_2NC_6H_4NPh_2$ is obtained. By increasing the amount of $Ph_3Bi(OAc)_2$ and prolonging the reaction time, secondary aromatic amines can be readily converted to tertiary amines. Thus, 4-$MeOC_6H_4NHPh$ and 2.2 equivalents of $Ph_3Bi(OAc)_2$ stirred for 72 h give a 78% yield of 4-$MeOC_6H_4NPh_2$; Ph_2NH and $Ph_3Bi(OAc)_2$ (1.1 equivalents) after 48 h give a 23% yield of Ph_3N. In addition to $Ph_3Bi(OAc)_2$, a number of other organobismuth(V) compounds (Ph_3BiY_2, Ph_4BiY, and Ph_5Bi) were tested as reagents for the *N*-phenylation of amines. Of these, $Ph_3Bi(O_2CCF_3)_2$ appears to be the best. Thus, 4-$O_2NC_6H_4NH_2$ gives only a 26% yield of 4-$O_2NC_6H_4NHPh$ with $Ph_3Bi(OAc)_2$ after 0.75 h, but a 98% yield with $Ph_3Bi(O_2CCF_3)_2$ after the same time period. Neither Ph_5Bi nor Ph_3BiCO_3 gives any phenylated amine, but $Ph_4BiO_2CCF_3$ is only slightly less effective than $Ph_3Bi(O_2CCF_3)_2$.

The primary aliphatic amines $BuNH_2$ and *c*-$HexNH_2$ are readily phenylated by $Ph_3Bi(OAc)_2$ and copper. With $BuNH_2$ and 1.1 equivalents of $Ph_3Bi(OAc)_2$ after 4 h, a mixture of BuNHPh (60%) and $BuNPh_2$ (20%) is obtained, but with 2.2 equivalents of $Ph_3Bi(OAc)_2$ after 3 h, only $BuNPh_2$ (70%) is formed. Bu^tNH_2 is not phenylated after stirring for 48 h. The only secondary aliphatic amine investigated was Et_2NH, which yields Et_2NPh in 32% yield when treated with $Ph_3Bi(O_2CCF_3)_2$ for 24 h. An amino

ester $PhCH_2CH(NH_2)CO_2Et$ yields a mixture of $PhCH_2CH(NHPh)CO_2Et$ (70%) and $PhCH_2CH(NPh_2)CO_2Et$ with $Ph_3Bi(OAc)_2$ after 24 h. Another amino compound, benzophenone hydrazone, is phenylated in 90% yield after 24 h (equation 100).

$$Ph_2C{=}NNH_2 \xrightarrow[CH_2Cl_2]{Ph_3Bi(OAc)_2} Ph_2C{=}NNHPh \qquad (100)$$

Morpholine is phenylated by $Ph_3Bi(O_2CCF_3)_2$, but only in 32% yield. However, imines, enamines, oximes, amides, semicarbazones, and tmg were found to be inert to $Ph_3Bi(OAc)_2$ and copper. Although Barton *et al.*[117] reported that Ph_3BiCO_3 fails to phenylate amines, *N*-phenylhydroxylamine is phenylated by this reagent under neutral conditions or in the presence of btmg. The initial product of the reaction was not isolated but reduced and acetylated to give *N,N*-diphenylacetamide (equation 101).

$$PhNHOH + Ph_3BiCO_3 \longrightarrow [Ph_2NOH] \xrightarrow[Fe]{Ac_2O} AcNPh_2 \qquad (101)$$

Since both alcohols and primary amines are readily phenylated by organobismuth(V) reagents in the presence of copper, the phenylation of $HOCH_2CH_2NH_2$ by $Ph_3Bi(OAc)_2$ (but in the absence of copper) was attempted[109]. The reaction products were $PhNHCH_2CH_2OH$ (51%), $Ph_2NCH_2CH_2OH$ (8%), and $PhNHCH_2CH_2OPh$ (17%). This was only a preliminary report, however, and further study might reveal that under other conditions a single product could be obtained.

The arylation of both aliphatic and aromatic primary amines by organobismuth(V) reagents in the presence of a copper catalyst would seem to be an excellent method for preparing secondary amines containing one or two aryl groups. With aliphatic amines, in order to avoid a mixture of secondary and tertiary amines, an excess of the primary amine must be used. In order to obtain pure tertiary amines, $RNAr_2$, an excess of the bismuth reagent and longer reaction times must be employed. Triarylamines have been obtained only in small yields.

During their study of the phenylation of amines by organobismuth(V) reagents of the type $Ph_3Bi(O_2CR)_2$ in the presence of a copper catalyst, Barton *et al.*[82b] sometimes observed yields of phenylated amines in excess of 100%, based on equation 102. This

$$Ph_3Bi(O_2CR^1)_2 + R^2NH_2 \xrightarrow{Cu^{II}} R^2NHPh + R^1CO_2H + Ph_2BiO_2CR^1 \qquad (102)$$

result suggested that organobismuth(III) compounds might act as phenylating agents for amines in the presence of copper salts. Accordingly, they attempted the arylation of several primary aryl amines, and also two primary and two secondary aliphatic amines and two other amino compounds, *N,N*-diphenylhydrazine and benzophenone phenylhydrazone. The reactions were carried out with Ph_3Bi (1.2 equivalents) and $Cu(OAc)_2$ (0.5 equivalent) in CH_2Cl_2 at room temperature for periods ranging from 18 to 24 h. All of the compounds were successfully monophenylated. $BuNH_2$ gives a mixture of BuNHPh (60%) and $BuNPh_2$ (38%), but *c*-$HexNH_2$ gives only the monophenylated amine in 76% yield. Two secondary alicyclic amines, piperidine and 1,2,3,4-tetrahydroiso quinoline, give the *N*-phenylated tertiary amines in 56 and 90% yields, respectively. Among the aromatic primary amines, $4\text{-}O_2NC_6H_4NH_2$ and $2,4,6\text{-}Me_3C_6H_2NH_2$ are monophenylated in only 6 and 25% yields, respectively, but other amines, $ArNH_2$ (Ar = 4-$MeOC_6H_4$, 4-Tol, and Ph), are monophenylated in 82, 60, and 48% yields, respectively. Although the above yields were obtained with 0.5 equivalent of $Cu(OAc)_2$, better yields were obtained with stoichiometric amounts of $Cu(OAc)_2$. Thus, $4\text{-}MeOC_6H_4NH_2$ gives $4\text{-}MeOC_6H_4NHPh$ in 25, 42, 60, and 59% yields as the amount of $Cu(OAc)_2$ is increased from 0.5 to 1.0, 1.5, and 2.0 equivalents. These reactions are

carried out with the rigid exclusion of oxygen and suggest that the actual phenylating agent is an organobismuth(V) compound, formed by the oxidation of Ph_3Bi by copper(II). However, $Cu(OAc)_2$ and Ph_3Bi do not react in CH_2Cl_2 after 24 h. Preliminary experiments suggest that the presence of the amine is also necessary for the oxidation of the Ph_3Bi by copper(II).

V. REFERENCES

1. H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
2. G. Wittig and G. Geissler, *Justus Liebigs Ann. Chem.*, **580**, 44 (1953); A. W. Johnson, *Ylid Chemistry*, Academic Press, New York, 1966, Ch. 4.
3. M. C. Henry and G. Wittig, *J. Am. Chem. Soc.*, **82**, 563 (1960).
4. J. J. Monagle, *J. Org. Chem.*, **27**, 3851 (1962).
5. S. Herbstman, *J. Org. Chem.*, **30**, 1259 (1965).
6. A. M. Pinchuk, Z. I. Kuplennik, and Zh. N. Belaya, *Zh. Obshch. Khim.*, **46**, 2242 (1976).
7. Z. I. Kuplennik, Zh. N. Belaya, and A. M. Pinchuk, *Zh. Obshch. Khim.*, **51**, 2711 (1981).
8. D. Lloyd and M. I. C. Singer, *Chem. Ind. (London)*, 787 (1967).
9. (a) D. Lloyd and M. I. C. Singer, *Chem. Ind. (London)*, 1277 (1968).
   (b) B. H. Freeman, D. Lloyd, and M. I. C. Singer, *Tetrahedron*, **28**, 343 (1972).
10. C. Glidewell, D. Lloyd, and S. Metcalfe, *Tetrahedron*, **42**, 3887 (1986).
11. Y. Huang, Y. Shen, and C. Chen, *Tetrahedron Lett.*, **27**, 2903 (1986).
12. H. Schmidbaur and G. Hasslberger, *Chem. Ber.*, **111**, 2702 (1978).
13. T. Kauffmann, A. Hamsen, R. Kriegesmann, and A. Vahrenhorst, *Tetrahedron Lett.*, 4395 (1978).
14. T. Kauffmann, K.-J. Echsler, A. Hamsen, R. Kriegesmann, F. Steinseifer, and A. Vahrenhorst, *Tetrahedron Lett.*, 4391 (1978).
15. T. Kauffmann, H. Ahlers, R. Joussen, R. Kriegesmann, A. Vahrenhorst, and A. Woltermann, *Tetrahedron Lett.*, 4399 (1978).
16. T. Kauffmann, *Top. Curr. Chem.*, **92**, 109 (1980).
17. T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **21**, 410 (1982).
18. H.-J. Tilhard, H. Ahlers, and T. Kauffmann, *Tetrahedron Lett.*, **21**, 2803 (1980).
19. T. Kauffmann, R. Joussen, N. Klas, and A. Vahrenhorst, *Chem. Ber.*, **116**, 473 (1983).
20. E. Wiberg and K. Mödritzer, *Z. Naturforsch., Teil B*, **12**, 128, 131 (1957).
21. A. B. Burg and L. R. Grant, *J. Am. Chem. Soc.*,**81**, 1 (1959).
22. A. N. Nesmeyanov, A. E. Borisov, and N. V. Novikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 815 (1967).
23. K. Issleib and A. Balszuweit, *Z. Anorg. Allg. Chem.*, **418**, 158 (1975).
24. P. Choudhury and A. L. Rheingold, *Inorg. Chim. Acta*, **28**, L127 (1978).
25. A. L. Rheingold, P. Choudhury, and M. F. El-Shazly, *Synth. React. Inorg. Met.-Org. Chem.*, **8**, 453 (1978).
26. Y. Z. Huang, Y. Shen, and C. Chen, *Tetrahedron Lett.*, **26**, 5171 (1985).
27. K. Issleib and A. Balszuweit, *Z. Anorg. Allg. Chem.*, **419**, 87 (1976).
28. P. Choudhury, M. F. El-Shazly, C. Spring, and A. L. Rheingold, *Inorg. Chem.*, **18**, 543 (1979).
29. K.-H. Linke and W. Brandt, *Angew. Chem., Int. Ed. Engl.*, **14**, 643 (1975); *Z. Anorg. Allg. Chem.*, **433**, 119 (1977).
30. C. Löwig and E. Schweizer, *Justus Liebigs Ann. Chem.*, **75**, 315 (1850).
31. G. O. Doak and L. D. Freedman, *Organometallic Compounds of Arsenic, Antimony, and Bismuth*, Wiley–Interscience, New York, 1970, (a) pp. 371–373; (b) Ch. VII.
32. K. Akiba, A. Shimizu, H. Ohnari, and K. Ohkata, *Tetrahedron Lett.*, **26**, 3211 (1985).
33. T. Chivers, M. N. S. Rao, and J. F. Richardson, *J. Chem. Soc., Chem. Commun.*, 186 (1983); N. Burford, T. Chivers, M. N. S. Rao, and J. F. Richardson, *Inorg. Chem.*, **23**, 1946 (1984).
34. R. T. Boeré, C. L. French, R. T. Oakley, A. W. Cordes, J. A. J. Privett, S. L. Craig, and J. B. Graham, *J. Am. Chem. Soc.*,**107**, 7710 (1985).
35. L. S. Boulos and A. A. El-Kateb, *Chem. Ind. (London)*, 864 (1983).
36. A. Alberola, A. M. Gonzalez, and F. J. Pulido, *Rev. Roum. Chim.*, **29**, 441 (1984).
37. A. B. Bruker and N. M. Nikiforova, *Zh. Obshch. Khim.*, **18**, 1133 (1948); *Chem. Abstr.*, **43**, 1737 (1949).
38. J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 1467 (1961).

39. S. Bittner, Y. Assaf, P. Krief, M. Pomerantz, B. T. Ziemnicka, and C. G. Smith, *J. Org. Chem.*, **50**, 1712 (1985).
40. A. G. Davies and S. C. W. Hook, *J. Chem. Soc. C*, 1660 (1971).
41. G. A. Razuvaev, T. G. Brilkina, E. V. Krasilnikova, T. I. Zinovjeva, and A. I. Filimonov, *J. Organomet. Chem.*, **40**, 151 (1972).
42. R. Hiatt, C. McColeman, and G. R. Howe, *Can. J. Chem.*, **53**, 559 (1975).
43. V. G. Tsvetkov, Yu. A. Aleksandrov, V. N. Glushakova, N. A. Skorodumova, and G. M. Kol'yakova, *Zh. Obshch. Khim.*, **50**, 256 (1980).
44. K. Akiba, H. Ohnari, and K. Ohkata, *Chem. Lett.*, 1577 (1985).
45. Y. Huang, Y. Shen, and C. Chen, *Synthesis*, 651 (1985).
46. E. J. Kupchik and P. J. Calabretta, *Inorg. Chem.*, **4**, 973 (1965).
47. Y. Matsumura, M. Shindo, and R. Okawara, *Inorg. Nucl. Chem. Lett.*, **3**, 219 (1967).
48. J. Otera and R. Okawara, *J. Organomet. Chem.*, **16**, 335 (1969).
49. J. Otera, T. Kadowaki, and R. Okawara, *J. Organomet. Chem.*, **19**, 213 (1969).
50. H. Schmidbaur and K.-H. Mitschke, *Chem. Ber.*, **104**, 1837, 1842 (1971).
51. S. Chatterjee, *J. Inst. Chem. (India)*, **49**, 263 (1977); *Chem. Abstr.*, **89**, 24467w (1978).
52. J. L. Wardell and D. W. Grant, *J. Organomet. Chem.*, **149**, C13 (1978); **188**, 345 (1980).
53. R. Nomura, A. Takabe, and H. Matsuda, *Chem. Express*, **1**, 375 (1986); *Chem. Abstr.*, **106**, 101439n (1987).
54. M. S. Malinovsky and S. P. Olifirenko, *Zh. Obshch. Khim.*, **25**, 122 (1955).
55. M. S. Malinovsky and S. P. Olifirenko, *Zh. Obshch. Khim.*, **25**, 2437 (1955).
56. M. S. Malinovsky and S. P. Olifirenko, *Zh. Obshch. Khim.*, **26**, 118 (1956).
57. M. S. Malinovsky and S. P. Olifirenko, *Zh. Obshch. Khim.*, **26**, 1402 (1956).
58. R. Asano, I. Moritani, Y. Fujiwara, and S. Teranishi, *Bull. Chem. Soc. Jpn.*, **46**, 2910 (1973).
59. T. Kawamura, K. Kikukawa, M. Takagi, and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **50**, 2021 (1977).
60. K. Kikukawa, K. Ikenaga, F. Wada, and T. Matsuda, *Tetrahedron Lett.*, **25**, 5789 (1984); K. Ikenaga, K. Kikukawa, and T. Matsuda, *J. Org. Chem.*, **52**, 1276 (1987).
61. A. B. Goel, H. J. Richards, and J. H. Kyung, *Inorg. Chim. Acta*, **76**, L95 (1983); A. B. Goel, *Inorg. Chim. Acta*, **86**, L77 (1984).
62. A. B. Goel, H. J. Richards, and J. H. Kyung, *Tetrahedron Lett.*, **25**, 391 (1984).
63. L. M. Yagupol'skii, N. V. Kondratenko, and V. I. Popov, *Zh. Org. Khim.*, **13**, 613 (1977).
64. D. H. R. Barton, D. Bridon, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1066 (1985); *Tetrahedron Lett.*, **27**, 4309 (1986); D. H. R. Barton and S. Z. Zard, *Pure Appl. Chem.*, **58**, 675 (1986); *Janssen Chim. Acta*, **4**, 3 (1986).
65. T. Okada and R. Okawara, *J. Organomet. Chem.*, **42**, 117 (1972).
66. J. Dahlmann and K. Winsel, *Z. Chem.*, **14**, 232 (1974).
67. J. Koketsu, S. Kokjma, and Y. Ishii, *J. Organomet. Chem.*, **38**, 69 (1972).
68. R. Nomura, T. Wada, Y. Yamada, and H. Matsuda, *Chem. Lett.*, 1901 (1986).
69. E. J. Bulten, *J. Organomet. Chem.*, **97**, 167 (1975); *U.S. Pat.* 3824264 (1974).
70. G. Chobert and M. Devaud, *J. Organomet. Chem.*, **153**, C23 (1978).
71. H. McCombie and B. C. Saunders, *Nature (London)*, **159**, 491 (1947).
72. F. Challenger and L. R. Ridgway, *J. Chem. Soc.*, **121**, 104 (1922).
73. F. Kh. Solomakhina and Z. M. Manulkin, *Tr. Tashk. Farm. Inst.*, **3**, 390 (1962); *Chem. Abstr.*, **61**, 3143 (1964).
74. W. J. Considine and J. J. Ventura, *J. Organomet. Chem.*, **3**, 420 (1965).
75. G. B. Deacon and I. K. Johnson, *Inorg. Nucl. Chem. Lett.*, **8**, 271 (1972).
76. F. Kh. Solomakhina, *Tr. Tashk. Farm. Inst.*, **1**, 321 (1957); *Chem. Abstr.*, **55**, 15389 (1961).
77. A. E. Borisov, M. A. Osinova, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1507 (1963).
78. G. B. Deacon, G. D. Fallon, and P. W. Felder, *J. Organomet. Chem.*, **26**, C10 (1971).
79. S. I. A. El Sheikh, M. S. Patel, B. C. Smith, and C. B. Waller, *J. Chem. Soc., Dalton Trans.*, 641 (1977).
80. F. M. Miller and D. M. Ritter, *Inorg. Chem.*, **9**, 1284 (1970).
81. N. S. Vyazankin, G. A. Razuvaev, and S. P. Korneva, *Zh. Obshch. Khim.*, **34**, 2787 (1964).
82. (a) A. V. Gushchin, T. G. Brilkina, and V. A. Dodonov, *Zh. Obshch. Khim.*, **55**, 2630 (1985). (b) D. H. R. Barton, J.-P. Finet, and J. Khamsi, *Tetrahedron Lett.*, **28**, 887 (1987).
83. F. Steinseifer and T. Kauffmann, *Angew Chem., Int. Ed. Engl.*, **19**, 723 (1980); T. Kauffmann, F. Steinseifer, and N. Klas, *Chem. Ber.*, **118**, 1039 (1985).

84. T. Masuda, E. Isobe, T. Hamano, and T. Higashimura, *Macromolecules*, **19**, 2448 (1986).
85. T. Masuda, M. Yamagata, and T. Higashimura, *Macromolecules*, 17, 126 (1984).
86. M. Yamagata, T. Masuda, and T. Higashimura, *J. Polym. Sci., Polym. Chem. Ed.*, **22**, 2275 (1984).
87. K. Ichikawa, O. Watanabe, and K. Fukuzumi, *Transit. Met. Chem.*, **1**, 183 (1976).
88. G. G. Long, L. D. Freedman, and G. O. Doak, in *Kirk-Othmer Encyclopedia of Chemical Technology*, (Ed. M. Grayson) *3rd ed.*, John Wiley and Sons, New York, Vol. 3, 1978, p. 921.
89. D. H. R. Barton and J.-P. Finet, *Pure Appl. Chem.*, **59**, 937 (1987); *Actual. Chim.*, 5 (1986); *Chem. Abstr.*, **106**, 195508j (1986).
90. F. Challenger and O. V. Richards, *J. Chem. Soc.*, 405 (1934).
91. D. H. R. Barton, J. P. Kitchin, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1099 (1978).
92. W. A. Jacobs, *J. Biol. Chem.*, **63**, 631 (1925).
93. D. H. R. Barton, D. J. Lester, W. B. Motherwell, and M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.*, 705 (1979).
94. D. H. R. Barton, J. P. Kitchin, D. J. Lester, W. B. Motherwell, and M. T. B. Papoula, *Tetrahedron*, **37**, *Suppl.*, 73 (1981).
95. G. A. Razuvaev, N. A. Osanova, and V. V. Sharutin, *Dokl. Akad. Nauk SSSR*, **225**, 581 (1975).
96. D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, D. J. Lester, W. B. Motherwell, and M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.*, 827 (1980).
97. D. H. R. Barton, J.-P. Finet, W. B. Motherwell, and C. Pichon, *J. Chem. Soc., Perkin Trans. 1*, 251 (1987).
98. V. A. Dodonov, A. V. Gushchin, and T. C. Brilkina, *Zh. Obshch. Khim.*, **55**, 73 (1985).
99. D. H. R. Barton, W. B. Motherwell, B. da Silva, and M. Teresa, *Rev. Port. Quim.*, **26**, 177 (1984); *Chem. Abstr.*, **104**, 108623k (1984).
100. D. Barton and W. Motherwell, *Fr. Demande*, 2441602 (1980); *Chem. Abstr.*, **94**, 209082p (1981).
101. D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, W. B. Motherwell, M. T. B. Papoula, and S. P. Stanforth, *J. Chem. Soc., Perkin Trans. 1*, 2667 (1985).
102. D. H. R. Barton, D. J. Lester, W. B. Motherwell, and M. T. B. Papoula, *J. Chem. Soc., Chem. Commun.*, 246 (1980).
103. E. J. Kupchik and C. T. Theisen, *J. Organomet. Chem.*, **11**, 627 (1968).
104. D. H. R. Barton, W. B. Motherwell, and A. Stobie, *J. Chem. Soc., Chem. Commun.*, 1232 (1981).
105. D. H. R. Barton, J.-P. Finet, W. B. Motherwell, and C. Pichon, *Tetrahedron*, **42**, 5627 (1986).
106. S. David and A. Thiéffry, *Tetrahedron Lett.*, **22**, 2885 (1981).
107. V. A. Dodonov, T. G. Brilkina, and A. V. Gushchin, *Zh. Obshch. Khim.*, **51**, 2380 (1981).
108. S. David and A. Thiéffry, *Tetrahedron Lett.*, **22**, 5063 (1981).
109. D. H. R. Barton, J.-P. Finet, and C. Pichon, *J. Chem. Soc., Chem. Commun.*, 65 (1986).
110. V. A. Dodonov, A. V. Gushchin, and T. G. Brilkina, *Zh. Obshch. Khim.*, **55**, 2514 (1985).
111. S. David and A. Thiéffry, *J. Org. Chem.*, **48**, 441 (1983).
112. H. Brunner, U. Obermann, and P. Wimmer, *J. Organomet Chem.*, **316**, C1 (1986).
113. D. H. R. Barton, J.-P. Finet, J. Khamsi, and C. Pichon, *Tetrahedron Lett.*, **27**, 3619 (1986).
114. D. H. R. Barton, N. Y. Bhatnagar, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, D. J. Lester, W. B. Motherwell, M. T. B. Papoula, and S. P. Stanforth, *J. Chem. Soc., Perkin Trans. 1*, 2657 (1985).
115. D. H. R. Barton, B. Charpiot, and W. B. Motherwell, *Tetrahedron Lett.*, **23**, 3365 (1982).
116. D. H. R. Barton, N. Y. Bhatnagar, J.-P. Finet, and W. B. Motherwell, *Tetrahedron*, **42**, 3111 (1986).
117. D. H. R. Barton, J.-P. Finet, C. Giannotti, and F. Halley, *J. Chem. Soc., Perkin Trans. 1*, 241 (1987).
118. D. H. R. Barton, J.-C. Blazejewski, B. Charpiot, and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 503 (1981).
119. D. H. R. Barton, N. Y. Bhatnagar, J.-P. Finet, J. Khamsi, W. B. Motherwell, and S. P. Stanforth, *Tetrahedron*, **43**, 323 (1987).
120. D. H. R. Barton, M. T. B. Papoula, J. Guilhem, W. B. Motherwell, C. Pascard, and E. T. H. Dau, *J. Chem. Soc., Chem. Commun.*, 732 (1982).
121. D. H. R. Barton, B. Charpiot, K. U. Ingold, L. J. Johnston, W. B. Motherwell, J. C. Scaiano, and S. Stanforth, *J. Am. Chem. Soc.*, **107**, 3607 (1985).
122. O. A. Ptitsyna, M. E. Gurskii, and O. A. Reutov, *Izv. Akad. Nauk SSR, Ser. Khim.*, 229 (1973).
123. V. A. Dodonov, A. V. Gushchin, and T. G. Brilkina, *Zh. Obshch. Khim.*, **55**, 466 (1985).
124. D. H. R. Barton, J.-P. Finet, and J. Khamsi, *Tetrahedron Lett.*, **27**, 3615 (1986).

Part 4
Biological Synthesis

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 10

Biological and environmental methylation of metals

PETER J. CRAIG

School of Chemistry, Leicester Polytechnic, P.O. Box 143, Leicester LE1 9BH, UK

I. INTRODUCTION

A considerable number of organometallic species have been detected in the natural environment in recent years. A number of these are non-methyl compounds which have entered the environment after manufacture and use (e.g. butyltin compounds by diffusion

TABLE 1. Elements forming methyl derivatives in the environment

Metals	Metalloids
Mercury	Arsenic
Lead	Antimony
Tin	Selenium
Thallium	Phosphorus
Cobalt	(Sulphur)*
	Tellurium
	Germanium

*Not usually regarded as metallic

from anti-fouling paints on boats). Only a few methyl compounds are now manufactured and used (e.g. some methyltin compounds are used as oxide film precursors on glass). The general environmental properties and fate of organometallic compounds was the subject of a recent book[1] and individual organometallics in the environment have also been assessed[2–10].

This chapter is concerned with the formation of organometallic species in the natural environment from inorganic precursors. Essentially this means the formation of methyl compounds, as no other alkyl group is known naturally to form bonds to a metal in the environment, and the area covered is environmental methylation (or biomethylation). It is now well established that certain organometallic compounds are formed in the environment, unequivocally so for mercury, arsenic, selenium, tellurium, and tin, and deduced on the basis of analytical evidence for lead, germanium, antimony, and thallium. A list of elements for which methylation in the environment may occur is given in Table 1. The speciation details differ in each case and are discussed in the sections on the separate elements.

The chief point of interest in methylation is the change in properties resulting from the attachment of methyl groups to the inorganic element or compound. Lipid solubility, volatility, and persistence of metals in biological systems may be increased in the methyl derivatives. Most organometallics are more toxic than the inorganic compounds from which they are formed (e.g. for mercury and tin), but sometimes the reverse is the case (particularly for arsenic). The formation of volatile forms of the metal by methylation in many cases provides increased mobility in the biogeochemical cycle for that element. For example, methylmercury is much more stable than inorganic mercury in humans in terms of its half-life or persistence. Hence the organic form is a much more effective deliverer of the toxic metal to sensitive regions of the organism and is therefore more toxic. In terms of transportation in the biosphere, methylation of mercury produces more volatile forms than the inorganic mercury(II) precursors and the methyl forms, together with mercury (0), are particularly important in the environmental mobility of this element. In a similar way, lipid-soluble methylarsenic compounds confer very different stabilities and transport possibilities compared to the element's compounds with inorganic ligands.

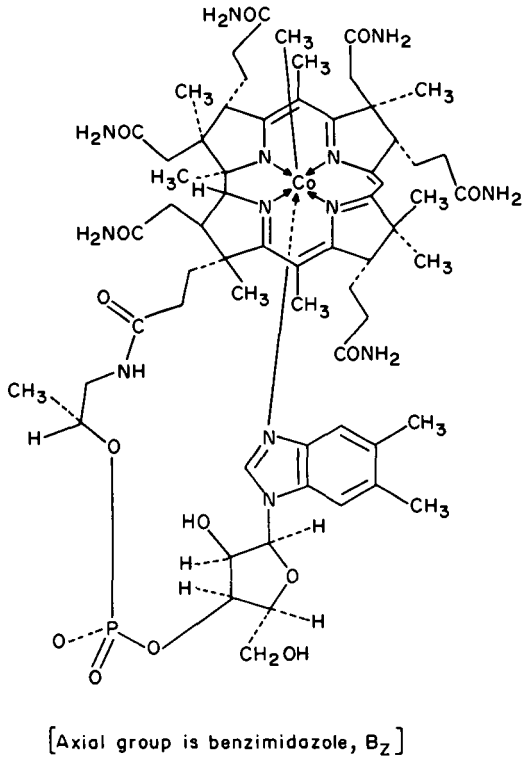
The mechanisms of formation of methyl-substituted metals in the natural environment are still not fully understood. A considerable number of laboratory model experiments to simulate methylation have been undertaken, but it is not clear to what extent these replicate the exact processes occurring in the environment. They do show, however, that environmental methylation is a chemically feasible process and that there are several explanations for the existence of methylated metals in the environment. It is still not clearly understood in the case of metals such as mercury or tin whether or not the process occurs within the cell as part of a biochemical process (with the metal being misread for the correct

atom), or whether or not methylation occurs outside the cell using methyl-donating metabolites excreted from the cell. The end result, however, is a methyl metal in both cases.

The general routes for environmental methylation have been reviewed on a number of occasions[11-17] and only a brief outline will be given here. For elements in environmentally stable high oxidation states, and without available lone-pair electrons, the methyl group will be transferred from the methylating agent as a methyl carbanion group (CH_3^-). This carbanion group will normally arise from the presence of the natural biological methylating species methylcobalamin, the methyl derivative of vitamin B_{12} [i.e. $(CH_3)CoB_{12}$] containing a methyl—cobalt bond. This facilitates methyl transfer to certain species, e.g. mercury(II), as shown in the equation

$$(CH_3)CoB_{12} + Hg^{2+} \xrightarrow{H_2O} CH_3Hg^+ + (H_2O)CoB_{12}{}^+ \qquad (1)$$

In this case there is no change in the oxidation state of mercury. Methylcobalamin appears to be the only methyl carbanion transfer agent in biochemistry and it has therefore been closely associated with mercury methylation where there is no change in oxidation state. The role of methylcobalamin in biochemistry is discussed elsewhere[18], but its salient features as a methyl transfer agent for metals lies in the ability of the methyl—cobalt bond to break under mild conditions in aqueous media. A structure for methylcobalamin is given in Figure 1.



[Axial group is benzimidazole, B_Z]

FIGURE 1. Structure of methylcobalamin coenzyme, $(CH_3)CoB_{12}$ (charges not shown)

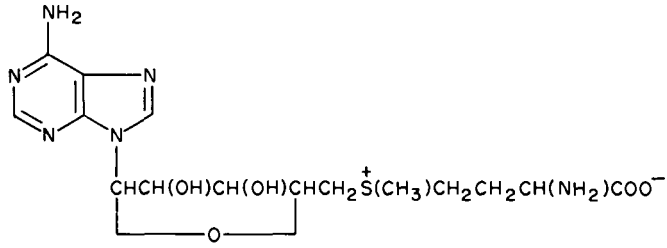


FIGURE 2. *S*-Adenosylmethionine

Biochemical methyl transfer as the methyl carbonium ion (CH_3^+) is more common in nature, and is relevant to metals where oxidation is possible (e.g. arsenic and tin). The most common source of the methyl carbonium ion is *S*-adenosylmethionine (Figure 2), which has been identified in arsenic methylation. *S*-Adenosylmethionine (SAM) is an activated form of methionine [$CH_3SCH_2CH_2CH(NH_2)COOH$] and can methylate metals by a process of oxidative addition:

$$CH_3^+(\text{from SAM}) + As^{III}(OH)_3 \longrightarrow CH_3As^{V}(OH)_3^+ \longrightarrow CH_3As^{V}O(OH)_2 + H^+ \quad (2)$$

In the case of arsenic, more than one methyl group may be added and there are a succession of such oxidative additions, each followed by a reduction so as eventually to produce $(CH_3)_3AsO$ or $(CH_3)_3As$[19].

Clearly not all methyl-substituted metal species, once formed, are stable in the environment. Only stable species will have any practical importance in terms of methylation. The chief agents against which stability should be measured are water, light, and oxygen. In sediments, natural coordinating groups would be expected to enhance the stability of the metal—carbon bond, and here light is usually absent (and so too, in many cases, is oxygen). Coordination by naturally occurring oxygen, sulphur, or nitrogen ligands leads to greater stability of the organometallic compound in sediments. In the atmosphere, the presence of light in combination with free radicals would be expected to limit considerably the lifetimes of organometallic species over those predicted on the basis of bond enthalipies alone. Model studies in the laboratory are often used to predict the lifetimes of organometallics in the environment, but the severely modifying characteristics of each natural environmental have to be borne in mind.

Tables 2 and 3 indicate the stability of methyl-substituted metals towards water and oxygen, respectively, and provide guidelines as to which organometallics are likely actually to be found (after formation) in the natural environment.

Organometallics therefore have a limited stability in the atmosphere, not only because of direct attack of light or oxygen on the metal—carbon bond but also owing to other factors. The additional presence of other free radicals or minute surface areas on particles considerably facilitates decay processes. Estimated half-lives for tetramethyllead [$(CH_3)_4Pb$] in the atmosphere are about 10 h in summer and 34 h in winter[20]. This is not to underestimate the importance of methylation in increasing the volatility of the metal and enabling it to be transferred from the water layer to the atmosphere. Even after decay in the atmosphere, the reduced inorganic metal may persist in aerosol form and be subject to long-range transport. This might not be possible without the initial organometallic phase.

Tables 2 and 3 lead to an expectation of the species to be found in the natural environment, and indeed most of the stable species are known. It should be noted that few examples of methyl-substituted transition metals are found in the environment, although

TABLE 2. Stability of organometallic species in water (data from Reference 1)

Organometallic	Stability comments
R_2Hg, R_4Sn, R_4Pb	Only slightly soluble, stable, diffuse to atmosphere. Higher alkyls less stable and less volatile. Species generally hydrophobic and variously volatile
CH_3HgX	Stable, slightly soluble depending on X
$(CH_3)_nSn^{(4-n)+}$	Soluble, methyltin unites stable but made hexa- and penta-coordinate by H_2O, OH^-. Species are solvated, partly hydrolysed to various hydroxo species. At high pH polynuclear bridged hydroxo species form for $(CH_3)_2Sn^{2+}$
$(CH_3)_3Pb^+$	Soluble, hydrolysis as methyltins above. Also dismutates to $(CH_3)_4Pb$ and $(CH_3)_2Pb^{2+}$ at 20 °C
$(CH_3)_2Pb^{2+}$	Soluble as for $(CH_3)_3Pb^+$ above. Disproportionates to $(CH_3)_3Pb^+$, Pb^{2+} and CH_3^+ slowly. These reactions cause eventual total loss of $(CH_3)_3Pb^+$ and $(CH_3)_2Pb^{2+}$ from water
$(CH_3)_2As^+$	Hydrolyses to $(CH_3)_2AsOH$ then to slightly soluble $\{(CH_3)_2As\}_2O$
CH_3As^{2+}	Hydrolyses to $CH_3As(OH)_2$ then to soluble $(CH_3AsO)_n$
$(CH_3)_2AsO(OH)$	Stable and soluble (330 g dm^{-3}). Acidic, $pK_a = 6.27$, i.e. cacodylic acid, dimethylarsonic acid. Detected in oceans
$CH_3AsO(OH)_2$	Stable and soluble. Strong acid, $pK_1 = 3.6$, $pK_2 = 8.3$; methylarsinic acid. Detected in oceans
$(CH_3)_3S^+$, $(CH_3)_3Se^+$	Stable and slightly soluble
$(CH_3)_nSiCl_{4-n}$	Hydrolyses and condenses but methylsilicon groupings retained
$(CH_3)_nGe^{(4-n)+}$	Stable, soluble, have been discovered in oceans. Hydrolyse but $(CH_3)_nGe$ moiety preserved
$(CH_3)_2Tl^+$	Very stable, soluble, but has not been detected as a natural environmental product
Other species:	
Stable and insoluble: R_4Si, $(R_2SiO)_n$, $CH_3HgSeCH_3$, most C_6H_5Hg derivatives, $(CH_3)_2S$, $(CH_3)_2Se$, $(CH_3)_4Ge$, $(CH_3)_3B$	
Unstable: CH_3Pb^+ (has not been detected in the environment), R_2Zn, R_2Cd, R_3Al, R_3Ga, $(CH_3)_6Sn_2$, $(CH_3)_6Pb_2$, $(CH_3)_5Sb$, CH_3Tl^{2+}, CH_3Cd^+, $(CH_3)_2Cd$, $(CH_3)_2Sb^+$, CH_3Sb^{2+}	

they can easily be stabilized in the laboratory. The extra outer-shell electrons available in transition metals may lead to a destabilization of other bonds present, including any metal—carbon bonds (for a discussion of bond stability in this area, see ref. 21). However, many naturally occurring ligands apparently capable of stabilizing transition metal—methyl bonds do occur in the aqueous natural environment. The question of the occurrence of transition metal methyls is an open one. No deliberate and systematic search appears to have been made to date.

It should also be noted that methyl-substituted metals are more stable than the ethyl or similar analogues because they do not possess a β-hydrogen atom (i.e. a hydrogen atom bonded to the second carbon atom from the metal). β-Hydrogen atoms are susceptible to chemical or biological attack or migration and lead to greatly reduced stability in compounds that, possess this feature (e.g. ethyls) compared with those that do not (e.g. methyls). Ethyl derivatives may be formed via the environment or not, but if they are formed they are not likely to be stable for long, and this alone may account for their non-appearance in the environment.

In the following sections, the methylation properties of the important individual elements are discussed.

TABLE 3. Stability of methylmetals to oxygen[a,b] (data from Reference 1)

Stable	Unstable[c]
$(CH_3)_2Hg$	CH_3PbX_3
$(CH_3)_4Si$, $\{(CH_3)_2SiO\}_n$, $(CH_3)_nSi^{(4-n)+}$, $(CH_3)_6Si_2$	CH_3Tl^+
$(CH_3)_4Ge$, $(CH_3)_nGe^{(4-n)+}$, $(CH_3)_6Ge_2$	$(CH_3)_2Zn$(CH_3Zn^+ also)
$(CH_3)_4Sn$	$(CH_3)_2Cd$ (CH_3Cd^+ also)
$(CH_3)_4Pb$[d]	$(CH_3)_3B$
CH_3HgX(C_6H_5- and C_2H_5- also stable)	$(CH_3)_3Al$
$(CH_3)_{4-n}SnX_n$	$(CH_3)_3Ga$
$(CH_3)_3PbX$	$(CH_3)_3In$
$(CH_3)_2PbX_2$	$(CH_3)_3Tl$
$[(\pi\text{-}CH_3C_5H_4)Mn(CO)_3]$[d]	$(CH_3)_5As$
$[CH_3Mn(CO)_4L]$[e]	$(CH_3)_3As$
$(CH_3)_2AsO(OH)$	$(CH_3)_3Sb$
$CH_3As(O)(OH)_2$	$(CH_3)_3Bi$
$(CH_3)_2S$	$(CH_3)_2AsH$
$(CH_3)_2Se$	CH_3AsX_2
$CH_3HgSeCH_3$	CH_3SbX_2
$(CH_3)CoB_{12}$ (solid state)	$(CH_3)_{4-n}SnH_n$[f]
$(CH_3)_3SbO$	$(CH_3)_6Sn_2$ (at room temperature gives $\{(CH_3)_3Sn\}_2O$)
$(CH_3)_2SbO(OH)$	$(CH_3)_6Pb_2$ (to methyllead products)
$CH_3SbO(OH)_2$	$(CH_3)_5Sb$
$(CH_3)_2Tl^+$, $(CH_3)_2Ga^+$	$(CH_3)_3AsO$
$(CH_3)_3S^+$	$(CH_3)_3P$
$(CH_3)_3Se^+$	$(CH_3)_4SiH_{4-n}$
$(CH_3)_3PO$	$(CH_3)_4GeH_{4-n}$

[a]At room temperature. Assume similar but lesser environmental stability for ethyls.
[b]That is, against rapid (seconds, minutes) oxidation.
[c]Variously unstable because of empty low-lying orbitals on the metal, polar metal—carbon bonds and/or lone electron pairs on the metal.
[d]Gasoline additive.
[e]To exemplify ligand-complexed transition metal organometallics. Many of these synthetic compounds are stable to oxygen but none have been found in the natural environment.
[f]But apparently stable in dilute form and detected in the environment.

II. ARSENIC METHYLATION

A. Introduction

Arsenic has been shown unequivocably to become methylated in the natural environment. Although methylarsenic compounds are used as herbicides or cotton desiccants (10^3–10^4 tonnes per annum worldwide), methylation of inorganic arsenic and the detection of naturally methylated arsenic has been conclusively demonstrated. The use of methylarsenics, therefore, does not account for most of the observed environmental methylarsenic compounds. The terrestrial arsenic cycle is characterized by the predominance of simple methylated compounds (e.g. methanearsonic acid ($CH_3AsO(OH)_2$) dimethylarsinic acid ($(CH_3)_2AsO(OH)$) trimethylarsine oxide, and mono-, di-, and trimethylarsine). In the marine environment, arsenic chemistry is dominated by a series of complex methylarsenic species, e.g. arsenobetaine and methylarsenic ribosyl species.

The fascinating organometallic chemistry of arsenic in recent years has been reflected by

a number of excellent reviews discussing these aspects. Some of the more recent ones are mentioned at the end of this section.

B. Methylarsenic in Non-marine Micro-organisms and Terrestrial Higher Organisms

The early work of Gosio[22] showed that a number of mould species could produce a volatile arsenic compound from arsenite (AsO_3^{3-}). Challenger[23] then identified this gas as trimethylarsine [$(CH_3)_3As$], with methanearsonic and dimethylarsinic anions as intermediates. Challenger[1,2,3] proposed the basic mechanism shown in Figure 3, in which

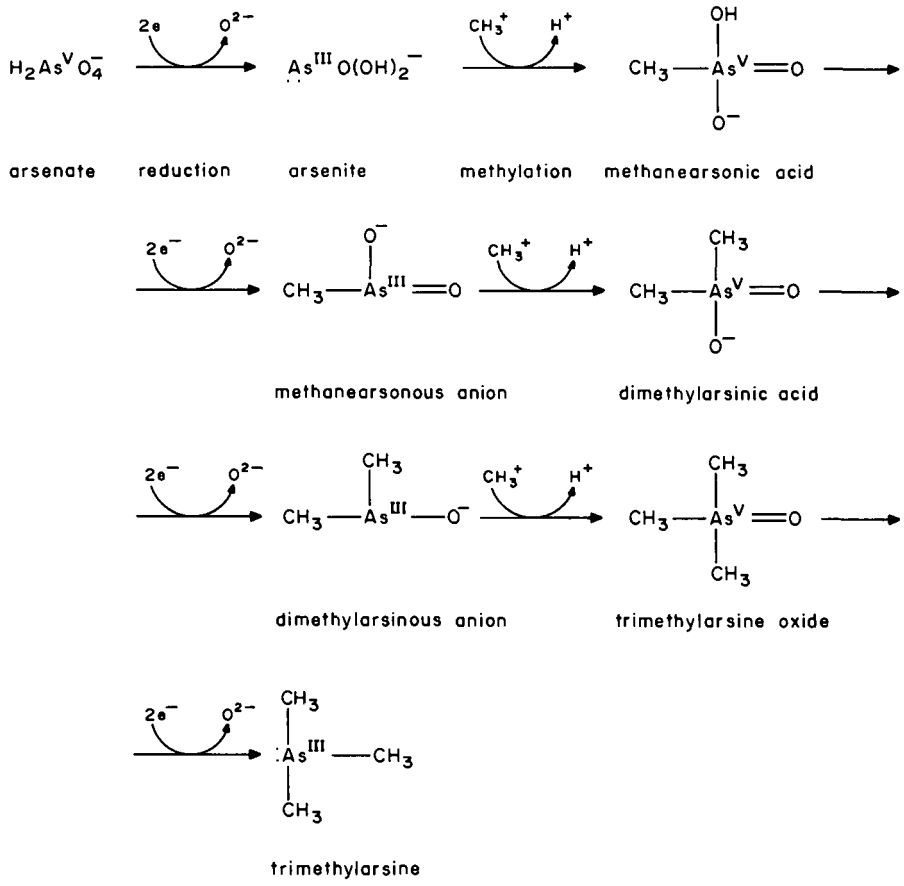


FIGURE 3. Arsenic methylation in moulds and fungi (from Ref. 1; modified after Challenger, Ref. 23).

aerobic methylation occurs by transfer of methylcarbonium anions from naturally occurring *S*-adenosylmethionine to a lone electron pair of arsenic(III), i.e. oxidative addition or rather a succession of oxidations and reductions. Species capable of this process include *S. brevicaulis* and *C. humicola*[24]. Others may produce $(CH_3)_3As$ from partially methylated

arsenic. Similarly, mixed methylorganoarsines (R = phenyl, butyl) may be produced from benzenearsonic acid or butylarsonic acid[25–27]. These results are notable owing to the use of aromatic arsonic acids as animal food additives.

Both bacterial and fungal methylation of inorganic arsenic have been observed. Wong *et al.*[28] showed that river or lake sediments or pure cultures of *Aeromonas* sp., *Flavobacterium* sp. or *E. coli* produce $(CH_3)_3As$, $(CH_3)_2AsH$, $(CH_3)_2AsO(OH)$, $CH_3AsO(OH)_2$, and $(CH_3)_3AsO$. The yields were low, and the experiments involved high concentrations of arsenic, suggesting that although methylation occurred it may not do so in environments where arsenic concentrations are more normal. Similarly high levels of arsenic were used in work on freshwater algae, which produced $CH_3AsO(OH)_2$ and $(CH_3)_2AsO(OH)$ by methylation[29]. However, these two species are commonly found in freshwater, suggesting that arsenic biomethylation by freshwater micro-organisms is a feasible process. Similarly, mixed microbial communities in soils also produce volatile arsines when the soils are treated with methylarsenicals, but this could be due to a combination of reduction and/or dismutation[30]. It should be pointed out that under purely anaerobic conditions, biomethylation of arsenic appears to proceed only to dimethylarsine[31].

The ability to methylate arsenic seems to be common in higher animals[32]. It is likely that methylation is not due simply to intestinal bacteria[33]. The products are methanearsonic acid, dimethylarsinic acid, and trimethylarsine oxide, which may be synthesized in the liver from arsenite or from arsenate via the former. These products are found in eggshells and human and animal urine, although methylation of the original inorganic compound was not complete. Freshwater fish and some terrestrial higher plants are also able to synthesize the methylarsenic acids[34].

C. Uses of Methylarsenic Species

There are small-scale uses of organic arsenic compounds for veterinary and medical applications, but methyl compounds are used on a larger scale only as herbicides and cotton desiccants. Use of mono- or di-sodium salts of methanearsonic acids as post-emergence grass herbicides in cotton production occurs on a large scale (e.g. about 10 400 tonnes annually in the USA). Dimethylarsinic acid (cacodylic acid) is used as a cotton defoliant prior to harvesting (about 260 tonnes per year in the USA)[35]. This leads to a brief consideration of the fate of methylarsenic species in the natural environment, i.e. demethylation and other degradation process.

D. Demethylation of Arsenic—Metabolism

The uses of methylarsenic species alluded to above are not responsible for, nor do they account for, the observation of methylarsenics in the oceans and in marine organisms, not do they mitigate against the basic model demonstrations of methylation in laboratories. Methanearsonic acid and dimethylarsinic acid are very stable to both chemical and biological attack. They are not demethylated by either plants[36] or animals[37]. The organoarsenic compounds found in seafood pass through the human body with almost no change or loss[38]. The methylarsenic acids are of low toxicity (e.g. LD_{50} 700–2600 mg kg^{-1} in rats); the methyl arsenic compounds in seafood are effectively non-toxic. This contrasts with the high toxicity (LD_{50}) of inorganic arsenic, viz. As_2O_3 (20), arsenite (14), and arsenate (20 mg kg^{-1}) defined as previously[35]. A lobster meal can, in fact, provide a dose of arsenic of about 30 mg, which would be a near fatal dose were it inorganic arsenic.

To date, only bacteria have been shown to be able to demethylate organoarsenic compounds[39,40]. The methylarsenic acids are oxidized to arsenate, and also further methylated to free methylarsines. Demethylation (i.e. oxidation to arsenate) also appears

to be the most important route for loss of methylarsenics in soils. Numerous bacterial species have been shown to have this property, e.g. *Achromobacter* sp., *Flavobacterium* sp., and *Pseudomonas* sp., usually at a rate of ca 3–5% per 48 h incubation[41].

As noted in the following section, marine algae are able to convert arsenate to arsenite and methylarsenic compounds to organic arsenic. Excretion products of algae and aquatic animals are solely methanearsonate and dimethylarsinate, accounting for the presence of these species in seawater. Arsenite, possibly a demethylation product, is also excreted by algae. This may simply be due to reduction of arsenate taken in, rather than reduction of any methylarsenic forms.

E. Methylarsenic Species in Marine Waters and Organisms

Arsenobetaine and arsenocholine have not been found in marine algae, but are the dominant forms of arsenic in marine invertebrates and fish. The trimethyl(carboxymethyl)arsonium zwitterion (arsenobetaine, $(CH_3)_3As^+CH_2COO^-$) is ubiquitous in marine animals consumed by man, at ca the mg kg^{-1} levels[41]. Present evidence suggests the conversion of arsenate to dimethyl(ribosyl)arsine oxides by algae, followed by a microbially mediated transformation of dimethyl(ribosyl)arsine oxides to arsenocholine and then arsenobetaine or its immediate precursors in sediments, i.e. food not water is the source of the arsenic[42–44]. Arsenobetaine has not been detected in seawater.

The ultimate origin of the methylarsenic species present in marine animals lies in the bacterial transformation of arsenate and arsenite in seawater. Arsenate ($2\,\mu g\,dm^{-3}$) predominates over arsenite in seawater, but the latter is always present at a greater concentration than predicted by thermodynamics[45–47]. The arsenate is transformed by algal micro-organisms in seawater to arsenite, methanearsonic acid [$CH_3AsO(OH)_2$] and dimethylarsinic acid [$(CH_3)_2AsO(OH)$, cacodylic acid], all of which are found in seawater via algal excretion[48–50]. As noted, arsenobetaine is not found in seawater[45,51]. The mechanism of the methylation is likely to be that suggested originally by Challenger[52,53] for the methylation of inorganic arsenic by, e.g., yeasts. Repeated reduction ($As^V \rightarrow As^{III}$) followed by methylation by *S*-adenosylmethionine in the algal cell converts arsenate to the acids above[54]. Edmonds and Francesconi suggested[55] that reduction of dimethylarsinic acid and the methylation of the resulting methylarsenic(III) compound to a trimethylarsine derivative observed with micro-organisms does not occur

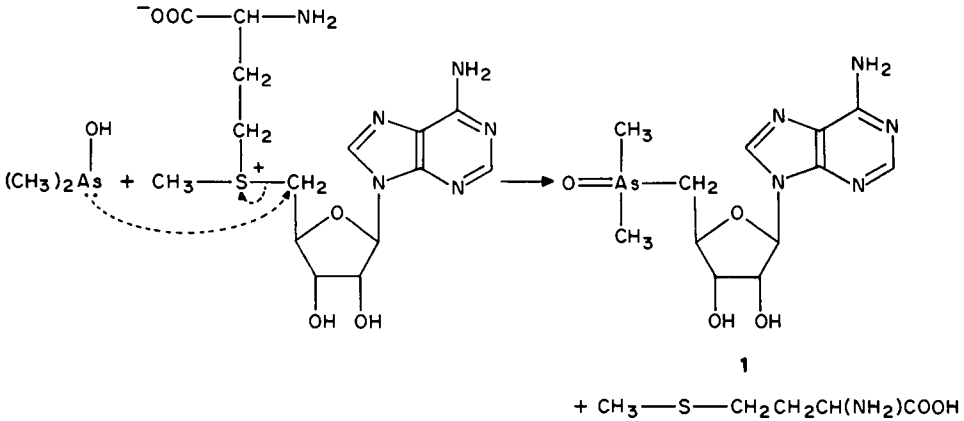
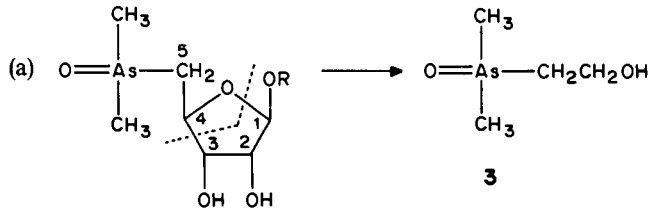


FIGURE 4. Arsenic methylation in algae (from Ref. 55)



2

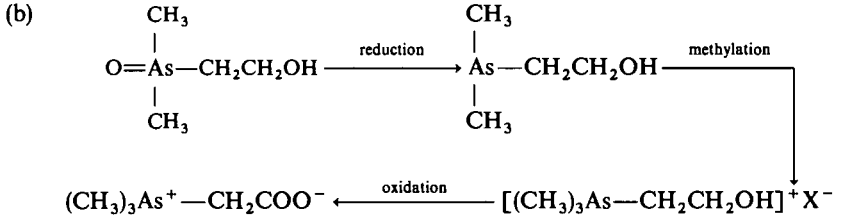
2a R = —$CH_2CH(OH)CH_2OH$

2b R = —$CH_2CH(OH)CH_2SO_3H$

2c R = —$CH_2CH(OH)CH_2OSO_3H$

2d R = —$CH_2CH(NH_2)CH_2SO_3H$

2e R = —$CH_2CH(OH)CH_2O\overset{\overset{O}{\|}}{P}OCH_2CH(OH)CH_2OH$ (OH)



arsenobetaine

FIGURE 5. Arsenoribosides found in algae (from Ref. 55)

in the biosynthesis of arsenoribosides; instead, in algae (Figure 4), the adenosyl group of *S*-adenosylmethionine is transferred to the trivalent arsenic. The key intermediate is **1**, which, however, has not yet been detected in algae. Hydrolytic removal of the adenine residue followed by glycosylation of available algal metabolites would then give rise to the arsenoribisodes (Figure 5a)[55]. It is likely that algae are ultimately the primary producers responsible for the production of the arsenobetaine found in marine animals. Marine algae contain large amounts of arsenic[41]. Arsenic concentrations are usually higher in brown algae (10–40 mg kg^{-1} wet weight) than in red or green algae (1–12 mg kg^{-1} wet weight) (such arsenic is non-toxic; compare the approximately 100 mg lethal oral dose of As_2O_3 for a human). Although some brown algae of the family Saragassaceae were reported to contain inorganic arsenic[56–58], most (ca 90–100%) of the arsenic in algae appears to be in the form of dimethyl(5-ribosyl)arsine oxides (arsenoribosides) (Figure 5a), five of which (**2a–e**) differing only in the aglycone grouping have been identified[58–61]. Irgolic[62] suggested that the reported arsenolipids[63,64] present in some algae may be derived from the arsenoribose **2e** by acylation of the two free hydroxyl groups of the terminal glycerol residue.

Arsenobetaine has not yet been identified in algae. Conversion of arsenoribosides to arsenobetaine involves cleavage of the C-3—C-4 bond of the sugar ring (Figure 5),

oxidation of the CH_2OH group thus formed to a carboxyl group, reduction of the arsine oxide, and methylation of the resulting arsine. Edmonds and Francesconi[55] suggested that a microbially mediated stage, probably occurring within sediments, is responsible for the production of arsenobetaine from the algal arsenoribosides.

This mechanism is supported by the observation of **3** as an anaerobic decomposition product from the kelp *Ecklonia radiata* in a laboratory model study[65]. This compound appears to be a significant intermediate in the formation of arsenobetaine, although the route suggested in Figure 5b has not been demonstrated so far. It is therefore not known if transformation of dimethyl(2-hydroxyethyl)arsine oxide (**3**) to arsenobetaine occurs in sediments with the arsenobetaine formed becoming available to the food chain through detritus feeders, or whether dimenthyl(2-hydroxyethyl)arsine oxide is released to the water column, absorbed by marine animals, and then rapidly converted to arsenobetaine.

The conversion of **3** to arsenobetaine involves reduction followed by methylation to a quaternary arsenic compound (Figure 5b). It is interesting that quaternary arsonium compounds (tetramethylarsonium compounds) have now been observed as natural products.

Trimethyl(ribosyl)arsonium compounds do not appear to have been detected in the few species of algae examined so far. However, such arsenic compounds may exist in algae at very low concentrations and may decompose to arsenocholine in a reaction analogous to the decomposition of dimethyl(ribosyl)arsine oxide (Figure 5b). Arsenocholine could then be oxidized to arsenobetaine. For trimethyl(ribosyl)arsonium compounds to account for the great predominance of arsenobetaine, a very high degree of selectivity favouring the passage and accumulation of breakdown products of ribosylarsonium compounds through the food web would be required. This implies that further separate methylation of dimethylribosides is a more likely route to arsenobetaine than accumulation of trimethylribosides. Alternatively, it has been considered that the trimethylamine oxide ($(CH_3)_3AsO$) may arise from decomposition of arsenobetaine. However, a microbially mediated stage, probably occurring within sediments, is necessary for the generation of arsenobetaine from arsenoribosides[67].

It should be pointed out that fish exposed to arsenate in solution in water do convert small amounts of the arsenate to methylarsenic compounds, but not to arsenobetaine[68–70]. In such cases $(CH_3)_3AsO$ is the product, with the gut flora being the most likely agents for the conversion[71].

The extent of retention of arsenobetaine, accounting for the observed concentrations, is not yet known. It does not appear to have any known function in marine animals. However, the non-toxicity and ubiquity of the methylarsenic species present in marine animals has led to suggestions that arsenic might be an essential trace element for marine animals or man.

The fascinating natural organic chemistry of arsenic has been dealt with at greater length in a number of reviews. Papers based on the Proceedings of the 1987 and 1989 Japanese Arsenic Scientists' Society held at Kagoshima and Tokyo, Japan, have now been published as single issues of *Applied Organometallic Chemistry*; many of these papers deal with methylation and demethylation of arsenic[72–80].

III. LEAD METHYLATION

A. Methylation

Between 3000 and 4000 tonnes of lead annually are used to produce alkyl and mixed alloy leads (tetraalkylleads; TAL) for use as gasoline additives. Of this, about 90% is accounted for by the methyl-and mixed methylethyl-lead species. Lead is added to petroleum (gasoline) in order to prevent premature combustion of the mixture (knocking).

The use of these organic lead compounds is inherently dispersive; about 75% of the additive is emitted from the vehicle exhaust mainly, but not entirely, as inorganic lead compounds. Estimates have been made that between 0.1 and 2% of the lead added is emitted unchanged, i.e. as methyl-, ethyl-, or methylethyl-lead compounds, and this is the chief source of organic lead in the atmosphere. There are also losses in various forms of unburnt fuel from two-stroke engines and evaporative losses during the handling of leaded fuel. It was estimated that approximately 7000 tonnes of organic lead were released to the atmosphere in the western world in 1975.[1] Although it may be expected that such losses will continue to be reduced owing to the use of non-leaded petrols, the point still remains that much methyllead has been released in the TAL form into the atmosphere over a number of years[81].

Clearly, then, the detection, observation, or measurement of methyllead species in the natural environment will, in many cases, not be evidence of the formation of methyllead in the environment from inorganic lead by biomethylation. In addition, some of the model experiments demonstrating the methylation of inorganic lead under environmental or quasi-environmental conditions have not proved repeatable over time or by other groups of workers. There is still no decisive evidence of lead methylation in the environment.

It should also be pointed out that observation of tetramethyllead (TML) arising from incubations of $(CH_3)_3Pb$ derivatives cannot usually be taken as evidence for biomethylations. Observation of a faster rate of TML production from a $(CH_3)_3Pb$ compound under environmental conditions (e.g. in a sediment with micro-organisms present) compared with TML production from the same $(CH_3)_3Pb$ species at the same concentration in a purely abiotic medium (e.g. distilled water) may simply be due to the disproportionation or dismutation of $(CH_3)_3Pb$ being accelerated chemically or physically by components in the environmental system. The presence of surface adhesion to clay or mineral and the presence of sulphide in the environmental system have been shown to increase the rate of dismutation. In fact, one study did not find any difference in rate between TML production when $(CH_3)_3PbOAc$ was incubated in sterilized and unsterilized lake sediments; in both cases about 4% of TML was evolved over the same period[82].

The ability of sulphide present in media to convert trialkyllead species to TML by dismutation has been demonstrated[83,84]:

$$2R_3P^+ + S^{2-} \longrightarrow (R_3Pb)_2S \longrightarrow R_4Pb + R_2PbS \qquad (3)$$

Clearly this reaction has to be taken into account before claims can be made that conversion of $(CH_3)_3Pb^+$ to TML has involved the environmental addition of a methyl group from elsewhere (i.e. biomethylation). In general in this section, such tri- to tetra-conversions will be discounted as real evidence for lead biomethylation.

The first report that sediment systems can convert inorganic lead(II) to TML was made in 1975[85]. Certain lake sediments produced more TML when lead(II) was added than without added lead(II). This extra TML production was not necessarily a biomethylation. Clearly the sediments contained TML anyway, and the extra TML may simply have been absorbed TML displaced by the stronger Lewis acid lead(II).

In a similar way, it was later reported that TML could be produced from lead(II) acetate after incubation with a micro-organism culture[85]. Although it is unlikely that the methyl groups could have arisen from the acetate methyl, there are circumstances where treatment of metal acetates leads to metal methyls. There is clearly a need for similar experiments of this type but they require the selection of a system in which any possibility of pre-existing lead is excluded and suitable lead(II) salts to be chosen as substrates, e.g. $Pb(NO_3)_2$. In another series of experiments, the conversion of inorganic lead(II) to TML in seeded water and sediment samples was noted[86-87].

There are a number of reports of TML being detected in fish tissue[88-91]. These may or may not constitute evidence for biomethylation. In a sophisticated series of experiments by

Harrison and Laxen[92], it was shown that unusually high TML to total lead ratios were found in maritime air masses identified by backward air mass trajectories. These high ratios were from areas where man-made lead would not be expected to be present. These results are circumstantial evidence towards biomethylation of inorganic lead to TML. Other results from different areas have confirmed the phenomenon of higher than expected TAL to inorganic lead ratios[93].

Another series of measurements on lead concentrations in pristine prehistoric Antartic ice[94] has given lead concentrations which, in order to be accounted for, require a natural input of lead in prehistoric times of the order of 10^5 tonnes per year to the atmosphere. Biomethylation of lead may have been responsible for this extra lead.

Various model experiments intended to determine if lead methylation in the environment is likely to occur have, on the whole, tended towards negative conclusions[95]. Craig and Rapsomanikis[96] have shown that the methyl donor iodomethane (CH_3I) will methylate inorganic lead(0), however. It is unlikely that carbonium ion donors such as CH_3I, used as models for *S*-adenosylmethionine or betaine in the environment or biochemistry, will react with divalent lead[97–99].

Methylation of lead(II) by $(CH_3)CoB_{12}$ has not been accomplished to date[100–103]. The methylation of lead(IV) (as Me_2Pb^{2+}) by $(CH_3)CoB_{12}$ does give TML[102]. Certain more active dimethylcobalt macrocyclic complexes [a model for $(CH_3CoB_{12}]$ will methylate inorganic lead [as $Pb(NO_3)_2$][104] to produce TML. The main problem regarding lead methylations is the great instability towards water of the initial monomethyllead complexes, CH_3Pb^+ or CH_3Pb^{3+}. Production of TML from inorganic lead requires the second methyl group to be added more rapidly than the rate at which the monomethyllead complexes decompose. If the precedent of mercury methylation with $(CH_3)CoB_{12}$ holds, this is unlikely. However, some lead methylation experiments, particularly with lead(0), do seem to have generated TML, so this problem does not seem chemically insuperable.

B. Decomposition of Alkyllead Compounds under Environmental Conditions

Atmospheric TAL species decompose to the tri- and di-alkyl and inorganic lead derivatives. Atmospheric half-lives are about 10 h (TML) and 2 h (tetraethyllead; TEL) in the summer months and about 34 h (TML) and 8 h (TEL) in the winter. This suggests that TEL and TML are not transported over long distances. Final decay is to inorganic lead(II), although the extent and time for the existence of the tri- and di-alkyl intermediate decay products is not known[105]. Fully alkylated lead compounds decay primarily to the trialkyllead species in water. The latter are stable in water, particularly the trimethyl species, which shows little decomposition over a 6-month period. Although TEL is very stable in water in the dark (2% decomposition over 77 days), it is likely that the presence of sunlight and other reactive chemical species in a natural water system would in practice lead to rapid decomposition of TAL derivatives[106]. Reasonable stability of alkyllead compounds in the biosphere appears to exist in view of the routine analyses of these compounds in rainwater, river water, fish, fruit, and animals.

C. Recent Work on Lead Methylation

Although some of the earlier work described above concerning lead methylation has tended not to be confirmed, a number of more recent papers do suggest that some methyllead species detected in the environment are in fact formed there. A recent report found that ionic alkyllead concentrations in the soft tissues of urban pigeons consisted mainly of triethylleads; in contrast, the major toxicant in mallard ducks from a rural sanctuary consisted of trimethyllead. An environmentally mediated methylation of

lead(II) which is more active in, but not confined to, aquatic environments was suggested to account for the trimethyllead in ducks[107].

Following on the earlier theme, TML has been observed to be produced from inorganic lead salts [$Pb(NO_3)_2$, $PbCl_2$, $Pb(OAc)_2$] incubated in biologically active sediments and water from the Tamar estuary, UK. TML production was a two-stage process involving an initial lag phase of about 100 h followed by exponential appearance of TML (accounting for about 0.03% of the total added lead)[108].

The recent Third Chemical Congress of the North American Continent (Toronto, 1988) included a Symposium on Organometallic Compounds in the Environment. Several reviews and papers on lead methylation based on presentations at this meeting have now been published[109–111]. The key question of inorganic lead(II) methylation is still a lively one. It will probably require an environmental incubation experiment giving comparatively large quantitites of methyllead in order for consensus acceptance that this phenomenon is an important process. Alternatively, a very decisive laboratory model experiment yielding positive results at a significant yield is still being sought. To date, many of the claims for lead methylation rest on closely argued deductions or implications rather than clear experimental demonstrations.

IV. TIN METHYLATION

A. Environmental Evidence for Methylation

This chapter covers areas other than the vast uses of organic (non-methyl) tin compounds in industrial products, e.g. stabilizers for PVC, biocides, antifouling agents. About 53×10^6 kg of organotin products annually are now used for a wide variety of purposes (see Chapter 11).

A small proportion of the organic compounds are in fact methyltin derivatives, e.g. $(CH_3)_nSn(SCH_2COO\text{-}t\text{-}C_8H_{17})_m$ ($n = 1, 2$; $m = 2, 3$). Similarly, CH_3SnCl_3 and $(CH_3)_2SnCl_2$ are used as precursors for forming tin oxide films on glasses. These uses do not account for the observation of methyltins in the environment or for the tin biomethylation experiments reported in recent years. The use of butyltin species as antifouling additives for marine paints has received much environmental interest in recent years. As non-methyl species they are outside the scope of this section, although mixed methylbutyltins have occasionally been detected in aqueous or sediment environments.

There are a number of detailed and recent reviews of the industrial uses of organotin compounds[112,113] and their environmental impact[114–118], which are also covered in Chapter 11. This section is solely concerned with aspects of the environment methylation of tin.

Methyltin compounds are widely observed in the natural aquatic environment[114,119–125]. The levels observed in waters are uniformly low, but much higher levels have been detected in the underlying sediment.

B. Model Experiments Demonstrating Methylation

Since methyltins are generally used far away from the sites where methyltins have been observed, it is presumed that the environmental methyltins were formed there. However occasional man-made methyltin contamination of the products is not impossible. Methylation mechanisms for tin methylation are not lacking. Wood and coworkers[126–128] have demonstrated the reaction of $(CH_3)CoB_{12}$ with $SnCl_2$ in aqueous solutions, showing the formation of methyltin products by NMR, and suggested a mechanism (Figure 6). This mechanism involves a postulated free-radical oxidation and

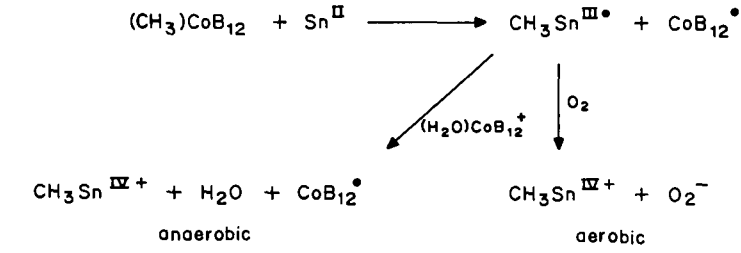


FIGURE 6. A mechanism for the methylation of tin by methylcobalamin (adapted from Refs. 126, 127)

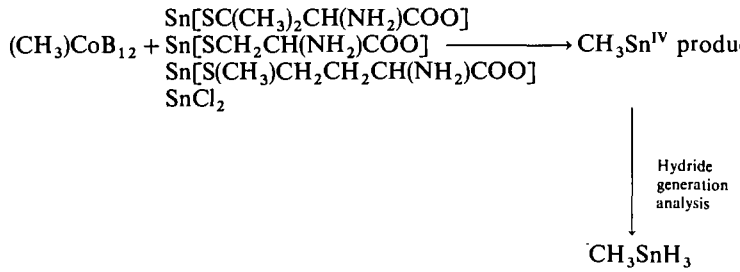


FIGURE 7. Reaction of methylcobalamin with various tin(II) compounds

conversion of tin(II) to tin(IV). Another group[129] has demonstrated the reaction of $(CH_3)CoB_{12}$ with dissolved and also insoluble tin(II) species. They showed by GC–AAS and GC–MS that the main products of the reactions were monomethyltin derivatives, although small amounts of dimethyltin species were also observed (Figure 7). It seems clear that $(CH_3)CoB_{12}$ can react with a variety of tin(II) compounds, but probably not with tin(IV).

There is evidence that the more normal *S*-adenosylmethionine-mediated methyl carbonium ion transfer to tin(II) may also take place[129]. This is an oxidative addition of CH_3^+ to tin(II) leading to a methyltin(IV) product. Successful oxidative additions to tin(II) have been shown to result in methyltin products in a number of cases[130,131] (Figure 8).

A classical method of demonstrating likely environmental methylation is to incubate an inorganic metallic precursor with a pure or mixed bacterial culture containing species likely to be capable of methyl transfer. Various populations of aquatic micro-organisms incubated with inorganic tin in water or sediments can methylate tin[132–134]. Some pure cultures have also effected methylations[135–137], including *Desulfovibrio* sp.[138].

A detailed study has been made of the incubation of various tin(II) compounds with a pure yeast culture[139]. A number of insoluble tin–amino acid complexes produced monomethyltin products which were detected and analysed by GC–AAS and GC–MS (Figure 9). Micro-solubilization of the substrates followed by conventional methylcarbonium oxidation seems the likeliest mechanistic pathway.

Lee and Weber have demonstrated in various model experiments a decrease in tin methylation (by iodomethane) under aerobic conditions[140]. Tin(II) tends to be rapidly oxidized in air and tin(IV) does not methylate in the environment. Sulphate-reducing bacteria are probably necessary for methylation of tin to occur in that this process generates or preserves tin(II), capable of *S*-adenosylmethionine-mediated oxidative addition. Methylation seems likeliest to occur in the anoxic zones of sediments rather than

$$M: + CH_3{:}I \longrightarrow M^{+\cdot} + CH_3 \cdot I^-$$
$$M^{+\cdot} + I^- \longrightarrow MI\cdot$$
$$MI\cdot + CH_3\cdot \longrightarrow CH_3MI$$
$$CH_3IM: + CH_3I \longrightarrow CH_3IM^{+\cdot} + CH_3\cdot + I^-$$
$$CH_3IM^{+\cdot} + I^- \longrightarrow CH_3MI_2\cdot$$
$$CH_3MI_2\cdot + CH_3\cdot \longrightarrow (CH_3)_2MI_2$$
$$CH_3I + MY_2 \xrightarrow{\text{slow}} [CH_3MY_2{}^{+\cdot}I^-] \xrightarrow{\text{fast}} CH_3MY_2I$$

In the case of CH_3SnY_2I, methyl products may be produced from the reductive disproportionation of $CH_3M^{IV}Y_2X$:

$$2CH_3SnY_2I \longrightarrow (CH_3)_2SnY_2 + SnY_2I_2$$
$$2CH_3PbY_2I \longrightarrow (CH_3)_2PbY_2 + PbY_2I_2$$

Fully methylated and trimethyl–metal species may then be produced from reductive disproportionation and dismutation reactions of $(CH_3)_2M^{2+}$, $(CH_3)_2MI_2$ or $(CH_3)_2MY_2$

$$2(CH_3)_2MI_2 \longrightarrow (CH_3)_3MI + MI_2 + CH_3I$$
$$4(CH_3)_3MI \longrightarrow 2(CH_3)_4M + 2(CH_3)_2MI_2$$
$$3(CH_3)_3MI \longrightarrow 2(CH_3)_4M + MI_2 + CH_3I$$

FIGURE 8. Oxidative addition of the methyl group to tin(II) (from Ref. 130)

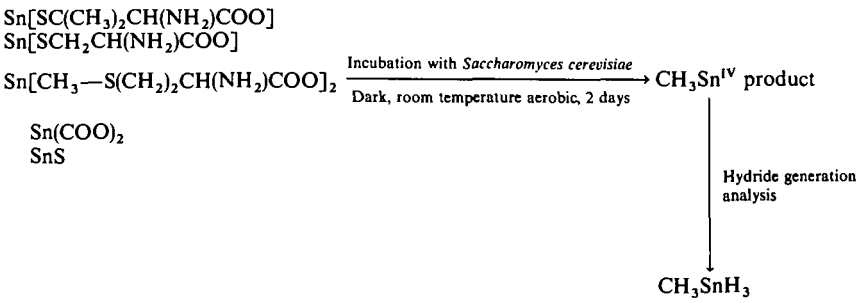


FIGURE 9. Tin(II) compounds methylated using yeast (from Ref.139)

in the oxic surface layers or in the water column above. In the sulphidic zone, tin(II) is capable of being methylated in solution and in the solid state[141].

The weight of evidence then is that (i) environmental methyl tin does exist, (ii) very plausible model experiments for its formation have been carried out and (iii) methylation is of tin(II) by oxidative addition (by *S*-adenosylmethionine or iodomethane or analogous carbonium ion donors).

C. Organotin Products

Apart from the specific example of alkylleads, organotin compounds represent the largest tonnage of manufactured organometallic compounds. Their uses are also much

more varied than the methyl- or ethyl-leads. The majority of the organotins are butyl, phenyl, cyclohexyl, and octyl compounds. Where methyltins are used (e.g. for rigid PVC stabilization and for oxide film precursors) they do, as mentioned, seem unable in both place and quantity alone to account for environmental methyltin products. Numerous reviews of the general industrial uses of organotin compounds, and of their environmental impact, now exist (e.g. refs 116, 117, 142–147).

V. MERCURY METHYLATION

A. Environmental Methylation and Methylating Factors

The initial evidence for environmental mercury formation arose when it was found that mercury was present in fish from Swedish fresh waters, usually more than 80% being in the form of methylmercury[148]. This general conclusion for fish has been reinforced on numerous occasions since. It should be noted that although a source of mercury has to be present, a source of methylmercury does not. The mercury is converted to methylmercury in the sediment, the water column, or the fish, or in all three. High levels of methylmercury have also been reported in marine fish. Levels and the percentage of methylmercury compared with that of total mercury in various environmental matrices and organisms have been summarized in a recent review[149]; in freshwater fish CH_3Hg usually comprises more than 90% of the total mercury.

It was first shown by Jensen and Jernelov 20 years ago[150] that inorganic mercury may be converted to methylmercury under environmental conditions. They showed that mercury(II) chloride was partially converted to the organic form by aquarium sediments. The yield was very low by normal chemical expectations (0.12%). However, because this form of mercury is efficiently absorbed by fish, and substantially retained as such within the fish, such yields may be both environmentally and toxicologically significant. There are reports of fish gut or liver contents being able to methylate mercury[151,152], although most methylation appears to take place in the sediments. It should also be noted that in Jensen and Jernelov's experiment[150], the amount of methylmercury present declined after 20 days. This suggested that an equilibrium between methylation and demethylation was occurring, an observation that has been confirmed by most workers in this area.

Methylation of inorganic mercury(II) has been shown to occur in sediments, in the water column[153], in soil[154], and in humic and fulvic materials[155]. Most mercury in aquatic environments is bound to fine-grained bottom sediments or suspended material and it is in the top-most layers of the sediments that methylation primarily takes place[156]. Verta[156] (Table 4) summarized the conditions associated with high and low methylmercury concentrations, assuming a source of mercury present in the system. Fish can be considered as the final sink for aquatic methylmercury.

TABLE 4. Factors associated with high and low rates of methylation of mercury in fish (data from Reference 156).

High concentrations	Low concentrations
Low pH	High pH
Oligotropic lake; low (phosphorus)	Eutrophic, high (phosphorus)
Low ionic strength; low (C_a)	High ionic strength, high
High humic concentrations	Low humic concentrations (C_a)
Large drainage area/lake volume ratio	
Deep lake with amall volume	
New, impounded reservoir	
Low O_2 saturation in reservoir	

Normally, methylmercury formation and demethylation are in equilibrium, leading to a constant value in the sediments (up to about 1.5% of the total mercury present). Methylation may occur in both aerobic and anaerobic zones, but maximum rates occur in the oxidizing anaerobic region with redox potentials in the -100 to $+150$ mV range[157,158]. Under acidic or neutral conditions, monomethylmercury (CH_3Hg^+) tends to be formed, but dimethylmercury may occur under basic pH conditions. Factors which affect the rate and extent of methylation in sediments include inorganic mercury concentration, redox potential, presence of micro-organisms, organic content, temperature, sulphide, and the speciation of the inorganic mercury (e.g. mercury(II) sulphide is very little methylated)[159].

B. Model Experiments Demonstrating Methylation

Mercury may be methylated and/or demethylated by a number of microorganisms (e.g. pseudomonads, aerobacters, enterobacters). Methylcobalamin has been demonstrated on numerous occasions to be capable of transferring a methyl carbanion to mercury(II) to produce methylmercury. Methylcobalamin exists naturally in the environment and its capability for methylation is undisputed, but the importance of its role in the actual environmental methylation of mercury has never really been quantified[160–170]. Those methylating agents (e.g. *S*-adenosylmethionine which oxidize metals to which they transfer a methyl group would seem incapable of methylating mercury(II). This would also apply to those potential methylators which are present in the aqueous environment as a result of various metabolic processes (Table 5)[171].

All of these molecules (except CH_3CoB_{12}) tend to add the methyl as an incipient methyl carbonium ion, thereby oxidizing the metal. The role but not the mechanism of methylation by humic substances has been observed. The role of bacteria then is still not clear, and whether or not mercury methylation is enzymatic or extra-cellular still has to be clarified. The methylcobalamin-mediated model (equation 4) is the process most studied in laboratories.

$$(CH_3)CoB_{12} + Hg^{2+} \xrightarrow{H_2O} CH_3Hg^+ + (H_2O)CoB_{12}{}^+ \qquad (4)$$

Several observations have suggested that a methyl carbanion ($CH_3{}^-$) may be being transferred in a cobalamin-based process. The methylating agent in tuna fish liver was shown to chromatograph with cobalamin and to be chemically similar[172,173]; also, methylation in saline regions where the mercury species $HgCl_4^{2-}$ is present occurs more slowly than for Hg^{2+}, suggesting a carbanion transfer as the environmental route[174]. However, as mercury(0) may be present in certain environments, the oxidative route appears to be feasible as has indeed been shown to be possible with iodomethane[175].

TABLE 5. Some methylating molecules present in the natural environment (data from Reference 171)

Intra-cellular methyl donors	Extra-cellular methyl donors
$(CH_3)CoB_{12}$	Methyl halides
$CH_3SCH_2CH_2CH(NH_2)COOH$	Methylene halides
$(CH_3)_2\overset{+}{S}CH_2CH_2COOH$	Methyl-substituted metals (transmethylation)
$(Aden)(CH_3)\overset{+}{S}CH_2CH_2CH(NH_2)COO^-$ [a]	Acetate
N_5-Tetrahydrofolic acid	

[a] *S*-Adenosylmethionine.

Several other non-cobalamin processes might also be possible, e.g. photolysis of natural mercury acetate or amino acid complexes to produce methyl transfer in the decay of the organic moiety[176–178]. As mentioned previously, humic and fulvic acids from sediments or leaf moulds can methylate mercury(II)[179]. Interestingly, abiotic methylation of some mercury compounds by $(CH_3)CoB_{12}$ proceeds at rates inversely proportional to mercury—ligand bond strengths, implying carbanion attack at a positive mercury centre[180].

It should be noted that, once formed, methylmercury may then undergo a slower further methylation to dimethylmercury. This may occur by a continuation of the initial methylation process or by disproportionation of the methylmercury itself, e.g. assisted by any sulphide ion present[181,182]:

$$2CH_3Hg^+ + S^{2-} \longrightarrow (CH_3Hg)_2S \longrightarrow (CH_3)_2Hg + HgS \qquad (5)$$

Conversion of relatively non-volatile, strongly bonding, and hydrophilic methylmercury to the covalent, volatile, and hydrophobic dimethylmercury may be a route to the general transport of mercury in the atmospheric environment. Certainly it has been shown to be a practical route for the transport of mercury[182] across the sediment–water atmosphere interfaces. In this context it is also interesting that methylmercurymethanethiol (CH_3HgSCH_3) may be found in shellfish[183].

C. General Conclusions on Mercury Methylation

An important environmental (as distinct from model) study of mercury methylation in the Ottawa River, Canada, points to the following general principles. In aqueous systems most of the total mercury (about 97%) and most of the methylmercury (98%) were located in the sediments. Biomass contained about 0.2% of total mercury in the system and 1.7% of methylmercury. Transport of mercury was accomplished mainly by movements in the water layer; bed sediment movement was responsible for less than 1% of mercury transport[184]. The pH of the sediment does not affect mercury methylation rates much, but a change from pH 7.0 to 5.0 doubles the rate of release of methylmercury. This may be responsible for higher methylmercury concentrations being found in fish from acid lakes[185]. It has been observed that the ratio of methylmercury in fish to the total mercury in the sediments increases as the pH declines[186].

The environmental production of methyl mercury is complex but it has been summarized recently[187] as follows. Most mercury in aquatic environments is bound to fine-grained bottom or suspended particles. It is mainly in the sediments that micro-organisms (directly or by methylating metabolites) convert a proportion of the inorganic mercury to methylmercury. Other micro-organisms may act so as to demethylate mercury and chemical demethylation is also possible. The net production rate for methylmercury is therefore a balance between methylation and demethylation. The mercury-transforming microorganisms vary, of course, according to the location and conditions, and the chemical nature (and hence methylation rate) of the inorganic or complexed mercury. The net rate of mercury production is a resultant of site, season, chemical environment, pH, redox potential, temperature, salinity, availability of nutrients, sulphide availability, aerobic–anaerobic behaviour, etc. General factors favouring methylmercury production include a good supply of organic nutrients, a lack of sulphides, and a lack of free oxygen. Not surprisingly, in any one location one or several of these factors may alter, leading to changes in the rate and extent of mercury methylation at that site. A large-scale study on the interaction and influence of clay minerals, oxides, and humic matter on mercury methylation and demethylation in freshwater sediments has recently been published[187]. Clays often interfere with methylation, but iron oxide often promotes this process. The effects of natural colloids are important and variable, but not altogether predictable.

With the general factors governing methylation now being largely appreciated,

although the detail of the methylating agents themselves as chemical entities is less clear, the environmental cycling process shown in Figure 10 may be used to describe the general role and interaction of mercury and methyl mercury species in the natural environment[188].

D. Other Sources of Mercury

Several more extensive studies on the role of mercury in the natural environment have appeared in recent years, so that this section has generally concentrated on the overall conclusions. A number of publications on the chemistry and environmental behaviour of mercury can be cited[189–200]; the recent study by Jackson[187] is particularly comprehensive.

VI. METHYLATION OF OTHER METALLIC ELEMENTS

A number of other metals and metalloids have been detected in the natural environment in their methyl forms (no other organic group having been added through an environmental process has been detected so far). This section covers those elements for which the organic derivative appears to have actually been formed in the environment.

Two methylated forms of germanium (CH_3Ge and $(CH_3)_2Ge$ derivatives) have been detected in natural waters[201–203], presumably from environmental methylation of inorganic germanium. In marine waters, it appeared that marine plankton or algal cultures were not responsible for the methylation (unlike the case for arsenic). In contrast, microbial methylation has been demonstrated to occur via sewage sludge organisms. Here the mono-, di-, and tri-methylgermanium species were found to be formed. It was suggested that production might occur exclusively during anaerobic digestion in the plant[201].

Several pristine rivers have been sampled for methylgermanium content, partly within a programme aimed at demonstrating the rivers as transport media for the organometallics to the oceans following continental production. Mono- and di-methylgermanium species were found at picomolar levels in rivers in the Amazon Basin, in the Congo, and in two Florida rivers. Dimethylgermanium was always present at a higher level[201]. This is the opposite situation to that obtaining for marine methylgermanium, where the monomethyl form was dominant (at the ng dm^{-3} level)[202–204]. Several possibilities were suggested to explain this, based on the view that initial continental formation of methylgermanium was followed by riverine transport to the oceans. There appears to be no discernible source of methylgermanium in the marine environment[201]. Laboratory experiments also suggest that there is negligible loss of methylgermanium from the oceans through evaporation, implying that atmospheric transport of methylgermanium is unimportant. In the oceans the methyl forms appear to be very stable and unreactive. As the methyl-germanium compounds were analysed by the hydride generation method, the environmental binding or form is not known. The proportion of organic to inorganic germanium is small (normally around 10%).

Methyl antimony species have also been found by similar means in natural waters (at the ng dm^{-3} level)[205–208]. The species detected so far (by hydride generation and standards) are the mono- and di-methylstibonic acids, $CH_3SbO(OH)_2$ and $(CH_3)_2SbOOH$. The analytical conditions allowed sequential reduction, and hence speciation to be deduced. The proportion of methyl to inorganic forms varies up to about 10%, with the monomethyl being the dominant organic form. To date, such methylantimony species have been detected in rivers in both Europe and the USA and also in several marine locations. So far there is little conclusive evidence regarding the methylation mechanism, but algae were thought not to be involved. It should be noted that the levels of methyl antimony species are much lower than those reported for methylarsenics in comparable environments, despite the fairly similar total metal concentrations for arsenic and

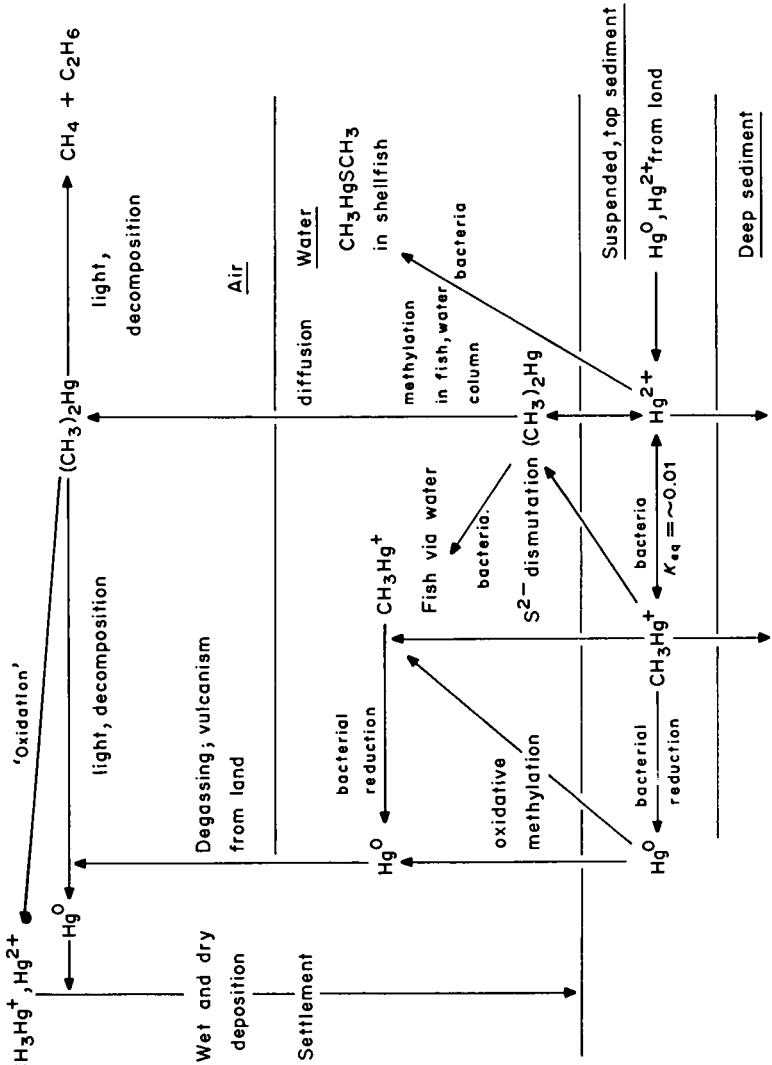


FIGURE 10. Mercury cycle in the environment (taken from Ref. 1)

antimony in aquatic systems and also the similarity of the arsenate(V) and antimonate(V) species.

Incubation experiments have also been carried out with thallium(I) acetate, under dark anaerobic conditions using a natural sediment. After up to 21 days, dimethylthallium ions, $(CH_3)_2Tl^+$, were found. This series of experiments has not been followed up and the question of the methyl source (e.g. the acetate group) has not been clarified[209,210].

The natural occurrence of methylcobalamin, $(CH_3)CoB_{12}$, is not considered here as an example of environmental methylation. Students of the biochemistry of this species are referred to appropriate sources (e.g. ref. 211). The methylation of phosphorus, sulphur, and selenium is considered to be outside the scope of this chapter and appropriate sources should be consulted (e.g. ref. 212 for sulphur and selenium and ref. 213 for phosphorus).

VII. REFERENCES

1. P. J. Craig (Ed.), *Organometallic Compounds in the Environment*, Longman, London, 1986.
2. *Proceedings, Oceans 86 Conference and Exposition, September 1986, Organotin Symposium*, IEEE, Piscatanay, NJ, 1986.
3. *Proceedings, Oceans 87, Conference and Exposition, September 1987.*
4. J. A. J. Thompson, M. G. Shaffer, R. C. Pierie, Y. K. Chau, J. J. Cooney, W. R. Cullen, and R. J. Maguire, *Organotin Compounds in the Aquatic Environment*, NRCC Report No. 22494, NRC Canada, Ottawa, Ontario, 1985.
5. J. S. Thayer, *Organometallic Compounds and Living Organisms*, Academic Press, New York, 1984.
6. R. M. Harrison and A. G. Allen, *Appl. Organomet. Chem.*, **3**, 49 (1989).
7. B. L. Lewis, M. O. Andrene, and P. N. Froelich, in *The Biological Alkylation of Heavy Metal Elements* (Eds. P. J. Craig and F. Glockling), Royal Society of Chemistry, London, 1988.
8. W. Maher and E. Butler, *Appl. Organomet. Chem.*, **2**, 191 (1988).
9. R. J. Maguire, *Appl. Organomet. Chem.*, **1**, 475 (1987).
10. J. O. Nriagu (Ed.), *The Biogeochemistry of Mercury in the Environment*, Elsevier North-Holland, Amsterdam, 1979.
11. W. P. Ridley, L. G. Dizikes, and J. M. Wood, *Science*, **197**, 329 (1977).
12. Y.-T. Fanchiang, W. P. Ridley, and J. M. Wood, *ACS Symp. Ser.*, **82**, 59 (1978).
13. J. M. Wood, *Naturwiss enschaften*, **62**, 357 (1975).
14. J. M. Wood and Y.-T. Fanchiang, in *Proceedings of the Third European Symposium on Vitamin B_{12} and Intrinsic Factor* (Ed. B. Zagalak) Water de Gruyter, Berlin, New York, 1979, Ch. 3, p. 539.
15. P. J. Craig, in *Handbook of Environmental Chemistry*, (Ed. O. Hutzinger), Vol. 1, Part A, Springer, Berlin, 1980, p. 169.
16. P. J. Craig, in *Pollution; Causes, Effects and Control* (Ed. R. M. Harrison), Royal Society of Chemistry, London, 1983, p. 277.
17. P. J. Craig, in *Comprehensive Organometallic Chemistry* (Eds. E. W. Abel, F. G. A. Stone and G. Wilkinson), Vol. 2, Pergamon Press, 1982, p. 979.
18. D. Dolphin, (Ed.) B_{12}, Wiley-Interscience, New York, 1982.
19. F. Challenger, *ACS Symp. Ser.*, **82**, 1 (1978).
20. G. W. Schaeffer and M. Emilius, *J. Am. Chem. Soc.*, **76**, 1203 (1954); M. Pourbaix, *Atlas of Electrochemical Equilibria*, Pergamon Press, New York, 1966, p. 476.
21. P. J. Craig, *Organometallic Compounds in the Environment*, Longman, London, 1986, pp. 9–29.
22. B. Gosio, *Chem. Ber.*, 1024 (1897).
23. F. Challenger, *Chem. Rev.*, **36**, 315 (1945).
24. D. P. Cox and M. Alexander, *Bull. Environ. Contam. Toxicol.*, **9**, 84 (1973).
25. W. R. Cullen, C. L. Froese, A. Liu, B. C. McBride, D. J. Patmore, and M. Reiner, *J. Organomet. Chem.*, **139**, 61 (1977).
26. B. C. McBride, H. Merilees, W. R. Cullen, and W. Pickett, *ACS Symp. Ser.*, **82**, 94 (1978).
27. W. R. Cullen, A. E. Erdman, B. C. McBride, and W. Pickett, *J. Microbiol. Methods*, **1**, 297 (1983).
28. P. T. S. Wong, Y. K. Chau, L. Laxon, and G. A. Bengert, *Trace Substances in Environmental Health—XI* (Ed. D. D. Hemphill), University of Missouri, Columbia, MO, 1977, pp. 100–105.

29. M. D. Baker, P. T. S. Wong, Y. K. Chau, C. LI. Mayfield, and W. E. Inniss, *Can. J. Fish Aquat. Sci.*, **40**, 1254 (1983).
30. R. S. Braman, *ACS Symp. Ser.*, **7**, 108 (1975).
31. B. C. McBride and R. S. Wolfe, *Biochemistry*, **10**, 4312 (1971).
32. R. S. Braman and C. G. Foreback, *Science*, **182**, 4118 (1973).
33. M. Vahter and B. Gustafsson, in *Proceedings of 3rd International Symposium on Arsenic and Nickel, Jena, GDR, July 1980* (Eds. M. Anke, H. J. Schneider, and C. Brucker), pp. 123–129.
34. M. Vahter and E. Marafante, *The Biological Alkylation of Heavy Metal Elements*, 1988, pp. 105–119.
35. M. O. Andreae, *Organometallic Compounds in the Environment*, 1986, pp. 198–228.
36. A. E. Hiltbold, *ACS Symp. Ser.*, **7**, 53 (1975).
37. J. T. Stevens, L. L. Hall, J. D. Farmer, L. C. DiPasquale, N. Chernoff, and W. F. Durham, *Environ. Health Perspect.*, **19**, 151 (1987).
38. A. Chapman, *Analyst (London)*, **51**, 548 (1926).
39. R. S. Braman, *ACS Symp. Ser.*, **7**, 108 (1975).
40. E. A. Woolson and B. Kearney, *Environ. Sci. Technol.*, **7**, 47 (1973).
41. M. Shariotpanahi, A. C. Anderson, and A. A. Abdelghani, *Trace Substances in Environmental Health—XV* (Ed. D. D. Hemphill), University of Missouri, Columbia, MO, 1981, pp. 383–387.
42. S. W. Fowler and M. Y. Unlu, *Chemosphere*, **7**, 711 (1978).
43. D. W. Klumpp, *Mar. Biol.*, **58**, 265 (1980).
44. R. J. Pentreath, Publication CM 1977/E:17, International Council for Exploration of the Sea, 1977.
45. M. O. Andreae, *Limmol. Oceanogr.*, **24**, 440 (1979).
46. M. O. Andreae, *Deep-Sea Res.*, **25**, 391 (1978).
47. D. L. Johnson and M. E. Q. Pilson, *J. Mar. Res.*, **30**, 140 (1972).
48. D. L. Johnson, *Nature (London)*, **240**, 44 (1972).
49. D. L. Johnson and R. M. Burke, *Chemosphere*, **7**, 645 (1978).
50. F. V. Vidal and V. M. V. Vidal, *Mar. Biol.*, **60**, 1 (1980).
51. K. A. Francesconi and J. S. Edmonds, *Appl. Organomet. Chem.*, **2**.
52. F. Challenger, *Chem. Rev.*, **36**, 315 (1945).
53. F. Challenger, *Adv. Enzymol.*, **12**, 429 (1941).
54. G. L. Cantoni, *Bull. Jpn. Chem. Soc.*, **74**, 2942 (1952).
55. J. S. Edmonds and K. A. Francesconi, *Appl. Organomet. Chem.*, **2**, 297 (1988).
56. D. L. Johnson and R. S. Braman, *Deep-Sea Res.*, **22**, 503 (1975).
57. J. N. C. Whyte and J. R. Engler, *Bot. Mar.*, **26**, 159 (1983).
58. J. S. Edmonds, M. Morita, and Y. Shibato, *J. Chem. Soc., Perkin Trans. 1*, 577 (1987).
59. J. S. Edmonds and K. A. Francesconi, *J. Chem. Soc., Perkin Trans. 1*, 2375 (1983).
60. J. S. Edmonds, K. A. Francesconi, P. C. Healy, and A. H. White, *J. Chem. Soc., Perkin Trans. 1*, 2989 (1982).
61. Y. Shibata, M. Morita, and J. S. Edmonds, *J. Agric. Biol. Chem.*, **51**, 391 (1987).
62. K. J. Irgolic, *Appl. Organomet. Chem.*, **2**, 303 (1988).
63. D. W. Klumpp and P. J. Peterson, *Mar. Biol.*, **62**, 297 (1981).
64. R. V. Cooney, R. O. Mumma, and A. A. Benson, *Proc. Natl. Acad. Sci. USA*, **75**, 4262 (1978).
65. J. S. Edmonds, K. A. Francesconi, and J. A. Hansen, *Experientia*, **38**, 643 (1982).
66. K. Shiomi, Y. Kakehashi, H. Yamonaka, and T. Kikuchi, *Appl. Organomet. Chem.*, **1**, 177 (1987).
67. J. S. Edmonds and K. A. Francesconi, *Nature (London)*, **289**, 602 (1981).
68. W. R. Penrose, *J. Fish. Res. Board Can.*, **32**, 2385 (1975).
69. A. A. Oladimeji, S. U. Quadri, G. K. H. Tam, and A. S. W. DeFreitas, *Ecotoxicol. Environ. Sci.*, **3**, 314 (1979).
70. J. S. Edmonds and K. A. Francesconi, *Sci. Total Environ.*, **64**, 317 (1987).
71. H. Norin, A. Christakopuros, and M. Sandstrom, *Chemosphere*, **14**, 313 (1985).
72. K. J. Irgolic, *Appl. Organomet. Chem.*, **2**, 303 (1988).
73. K. Talahashi, H. Yamauchu, N. Yamoto, and Y. Yamamura, *Appl. Organomet. Chem.*, **2**, 309 (1988).
74. M. Hirata, A. Hisanaga, A. Tanaka, and N. Ishimshi, *Appl. Organomet. Chem.*, **2**, 315 (1988).
75. M. Ishizaki, S. Ueno, T. Okuzaki, T. Suzuki, and N. Oyamada, *Appl. Organomet. Chem.*, **2**, 323 (1988).
76. T. Kaise, H. Yamauchi, T. Hirayama, and S. Fukui, *Appl. Organomet. Chem.*, **2**, 339 (1988).

77. A. A. Benson, M. Katayama, and F. C. Knowles, *Appl. Organomet. Chem.*, **2**, 349 (1988).
78. S. Maeda, S. Fujita, A. Ohki, I. Yoshifuku, S. Higashi, and T. Takeshita, *Appl. Organomet. Chem.*, **2**, 353 (1988).
79. K. Jin, T. Hayashi, Y. Shubata, and M. Monta, *Appl. Organomet. Chem.*, **2**, 365 (1988).
80. K. Hanaoka, H. Yamamoto, K. Kawashima, S. Tagawa, and T. Kaise, *Appl. Organomet. Chem.*, **2**, 371 (1988).
81. R. M. Harrison and A. G. Allen, *Appl. Organomet. Chem.*, **3**, 49 (1989).
82. P. J. Craig, *Environ. Technol. Lett.*, **1**, 17 (1980).
83. A. W. P. Jarvie, R. N. Markall, and H. R. Potter, *Nature* (*London*), **255**, 217 (1975).
84. K. Reisinger, M. Stoeppler, and H. W. Nurnberg, *Nature* (*London*), **291**, 228 (1981).
85. P. T. S. Wong, Y. K. Chau, and P. L. Luxon, *Nature* (*London*), **253**, 263 (1975).
86. U. Schmidt and F. Huber, *Nature* (*London*), **259**, 157 (1976).
87. J. P. Dumas, L. Pazdernik, S. Belloncik, D. Bouchard, and G. Vaillancourt, in *Proceedings of the 12th Canadian Symposium on Water Pollution Research*, 1977, p. 91.
88. J. A. J. Thompson and J. A. Crerer, *Mar. Pollut. Bull.*, **11**, 251 (1980).
89. G. R. Sirota and J. F. Uthe, *Anal. Chem.*, **49**, 823 (1977).
90. Y. K. Chau, P. T. S. Wong, G. A. Bengert, and O. Kramar, *Anal. Chem.*, **51**, 186 (1979).
91. R. D. Cruz, C. Lovouse, S. Georges, Y. Thomassen, J. D. Kinrade, L. R. P. Butler, J. Lye, and J. C. Van Loon, *Spectrochim. Acta, Part B*, **35**, 775 (1980).
92. R. D. Harrison and D. P. H. Laxen, *Nature* (*London*), **275**, 238 (1978).
93. C. N. Hewitt, S. J. de Mora, and R. M. Harrison, *Mar. Chem.*, **15**, 189 (1984).
94. C. F. Boulron and C. C. Patterson, *Geochim. Cosmochim. Acta*, 47, 1355 (1983).
95. A. W. P. Jarvie, A. P. Whitmore, R. N. Markall, and H. R. Potter, *Environ. Pollut., Ser. B*, **6**, 69 and 81 (1983).
96. P. J. Craig and S. Rapsomanikis, *Environ. Sci. Technol.*, **19**, 726 (1985).
97. I. Achmad, Y. K. Chau, P. T. S. Wong, A. J. Carty, and L. Taylor, *Nature* (*London*), **287**, 716 (1980).
98. A. W. P. Jarvie and A. P. Whitmore, *Environ. Technol. Lett.*, **2**, 197 (1981).
99. W. Snyder and J. M. Bentz, *Nature* (*London*), **296**, 228 (1982).
100. A. W. P. Jarvie, R. N. Markall, and H. R. Potter, *Nature* (*London*), **255**, 217 (1975).
101. R. T. Taylor and M. L. Hanna, *J. Environ. Sci. Health*, 201 (1976).
102. W. P. Ridley, L. J. Dizikes, and J. M. Wood, *Science*, **197**, 329 (1977).
103. C. Agnes, S. Bendle, H. A. O. Hill, F. R. Williams, and R. J. P. Williams, *J. Chem. Soc., Chem. Commun.*, 850 (1971).
104. S. F. Rhode and J. H. Weber, *Environ. Technol. Lett.*, **5**, 13 (1984).
105. R. M. Harrison, in *Organometallic Compounds in the Environment* (Ed. P. J. Craig), Longmans, London, 1986, pp. 175–178.
106. A. W. P. Jarvie, R. N. Markall, and H. R. Potter, *Environ. Res.*, **25**, 241 (1981).
107. D. S. Forsyth, W. D. Marshall, and M. C. Collette, *Appl. Organomet. Chem.*, **2**, 233 (1988).
108. A. P. Walton, L. Ebdon, and G. E. Millward, *Appl. Organomet. Chem.*, **2**, 87 (1988).
109. R. M. Harrison and A. G. Allen, *Appl. Organomet. Chem.*, **3**, 49 (1989).
110. P. T. S. Wong, Y. K. Chau, J. Yoromich, P. Hodson, and T. M. Whittle, *Appl. Organomet. Chem.*, **3**, 59 (1989).
111. J. S. Blais, G. M. Momplaisir, and W. D. Marshall, *Appl. Organomet. Chem.*, **3**, 89 (1989).
112. S. J. Blunden and A. Chapman, in *Organometallic Compounds in the Environment* (Ed. P. J. Craig), Longmans, London, 1986, p. 111.
113. *Environmental Health Criteria, No. 15, Tin and Organotin Compounds*, WHO, Geneva, 1980.
114. P. F. Seligman, J. G. Grovhoug, A. O. Valkirs, P. M. Stang, R. Fransham, M. O. Stallard, B. Davidson, and R. F. Lee, *Appl. Organomet. Chem.*, **3**, 31 (1989).
115. R. J. Maguire, *Appl. Organomet. Chem.*, **1**, 475 (1987).
116. *Proceedings, Oceans 86 Conference and Exposition, September 1986, Organotin Symposium*, IEEE, Piscatanay, NJ, 1986.
117. *Proceedings, Oceans 87 Conference and Exposition, September 1987, Organotin Symposium*, 1987.
118. J. A. J. Thompson, M. G. Shaffer, R. C. Pierie, Y. K. Chau, J. J. Cooney, W. R. Cullen, and R. J. Maguire, *Organotin Compounds in the Aquatic Environment*, NRCC Report No. 22494, NRC Canada, Ottawa, Ontario (1985).
119. S. Rapsomanikis and J. H. Weber, *Environ. Sci. Technol.*, **19**, 352 (1985).

120. O. F. X. Donard and J. H. Weber, *Environ. Sci. Technol.*, **19**, 1104 (1985).
121. O. F. X. Donard, S. Rapsomanikis, and J. H. Weber, *Anal. Chem.*, **58**, 772 (1986).
122. R. J. Maguire, R. J. Tkacz, Y. K. Chau, G. A. Bengert, and P. T. S. Wong, *Chemosphere*, **15**, 253 (1986).
123. T. A. Jackson, W. R. Blair, F. E. Brinckman, and W. P. Iverson, *Environ. Sci. Technol.*, **16**, 110 (1982).
124. L. Randall, J. S. Han, and J. H. Weber, *Environ. Technol. Lett.*, **7**, 571 (1986).
125. O. F. X. Donard, F. T. Short, and J. H. Weber, *Can. J. Fish. Aquat. Sci.*, **44**, 140 (1987).
126. L. J. Dizikes, W. P. Ridley, and J. M. Wood, *J. Am. Chem. Soc.*, **100**, 1010 (1978).
127. Y. T. Fanchiang and J. M. Wood, *J. Am. Chem. Soc.*, **103**, 5100 (1981).
128. W. P. Ridley, L. J. Dizikes, and J. M. Wood, *Science*, **197**, 329 (1977).
129. J. R. Ashby and P. J. Craig, 1989, *Appl. Organomet. Chem.*, **1**, 275 (1987).
130. P. J. Craig and S. Rapsomanikis, *Environ. Sci. Technol.*, **19**, 726 (1985).
131. W. F. Manders, G. T. Olsen, F. E. Brinckman, and J. M. Bellama, *J. Chem. Soc., Chem. Commun.*, 538 (1984).
132. Y. K. Chau, P. T. S. Wong, O. Kramer, and G. A. Bengert, in *Proceedings of the Third International Conference on Heavy Metals in the Environment*, CEP, Edinburgh, 1981, p. 641.
133. H. E. Guard, A. B. Cobet, and W. M. Coleman, *Science*, **213**, 770 (1981).
134. L. E. Hallas, J. C. Means, and J. C. Cooney, *Science*, **215**, 1505 (1982).
135. F. E. Brinckman, J. A. Jackson, W. R. Blair, G. J. Olsen, and W. P. Iverson, *Trace Metals in Seawater*, (NATO Conf. Ser., 4:9), Plenum Press, New York, 1983, p. 39.
136. Ref. 123, particularly p. 112.
137. S. L. Seidel, V. G. Hodge, and E. D. Goldberg, *Thallas. Jugosl.*, **16**, 209 (1980).
138. G. C. Gilmour, J. H. Tuttle, and J. C. Means, in *Estuarine Geochemistry* (Eds. A. C. Sigleo and A. Matton), Lewis, Chelsea, MI, 1985, p. 239.
139. J. R. Ashby and P. J. Craig, *Appl. Organomet. Chem.*, in press, 1989.
140. D. S. Lee and J. H. Weber, *Appl. Organomet. Chem.*, **2**, 435 (1988).
141. J. S. Thayer, G. T. Olson, and F. E. Brinckman, *Appl. Organomet. Chem.*, **1**, 73 (1987).
142. J. J. Zuckerman, R. P. Reisdorf, H. V. Ellis, and R. R. Wilkinson, *ACS Symp. Ser.*, **82**, 388 (1978).
143. R. Bock, *Residue Rev.*, **79**, (1981).
144. F. E. Brinckman, *J. Organomet. Chem. Library*, **12**, 343 (1981).
145. S. J. Blunden, L. A. Hobbs, and P. T. Smith, in *Environmental Chemistry* (Ed. H. J. M. Bowen), RSC Specialist Periodical Report, Vol. 3, Royal Society of Chemistry, London, 1984, p. 49.
146. C. J. Evans, *Tin Its Uses*, **100**, 3 (1974).
147. C. J. Evans, *Spec. Chem.*, **1**, 25 (1981).
148. G. Westoo, *Acta Chem. Scand.*, **20**, 2131 (1966).
149. Ref. 1, p. 65.
150. S. Jensen and A. Jernelov, *Nature (London)*, **223**, 753 (1969).
151. N. Imura, S.-K. Pon, M. Shimitzu, and T. Ukita, *New Methods in Environmental Chemistry and Toxicology*, in Collected Papers Res. Conf. New Methods Ecol. Chem. (Ed. F. Coulston), Int. Acad. Print. Co., Tokyo, 1973, p. 211.
152. N. Imura, S.-K. Pan, M. Shimitzu, T. Ukita, and K. Tonomura, *Ecotoxicol. Environ. Saf.*, **1**, 255 (1977).
153. G. Topping and I. M. Davies, *Nature (London)*, **290**, 243 (1981).
154. R. D. Rogers, *J. Environ. Qual.*, **6**, 463 (1977).
155. H. Nagase, Y. Ose, T. Sato, and T. Ishikawa, *Sci. Total Environ.*, **32**, 147 (1984).
156. M. Verta, *Aqua Fenn.*, **14**, 215 (1984).
157. R. Wollast, G. Billen, and F. T. Mackenzie, *Environ. Sci. Res.*, I (Ecol. Toxicol. Res.), 145 (1975).
158. P. D. Bartlett and P. J. Craig, *Water Res.*, **15**, 37 (1981).
159. Ref. 1, pp. 82–90.
160. J. M. Wood, F. S. Kennedy, and C. G. Rosen, *Nature (London)*, **220**, 173 (1968).
161. L. Bertilsson and H. Y. Neujahr, *Biochemistry*, **10**, 2805 (1971).
162. H. Yamamoto, T. Yokoyama, J.-L. Chen, and T. Kwan, *Bull. Chem. Soc. Jpn.*, **48**, 844 (1975).
163. P. J. Craig and S. F. Morton, *J. Organomet. Chem.*, **195**, 79 (1978).
164. R. E. DeSimone, M. W. Penley, L. Charbonneau, S. G. Smith, J. M. Wood, H. A. O. Hill, J. M. Pratt, S. Ridsdale, and R. J. P. Williams, *Biochim. Biophys. Acta*, **304**, 851 (1973).
165. V. C. W. Chu and D. W. Gruenwedel, *Z. Naturforsch., Teil C*, **31**, 753 (1976).
166. G. C. Robinson, F. Nome, and J. H. Fendler, *J. Am. Chem. Soc.*, **99**, 4969 (1977).

167. H. A. O. Hill, J. M. Pratt, S. Ridsdale, F. R. Williams, and R. J. P. Williams, *J. Chem. Soc., Chem. Commun.*, 341 (1970).
168. J. Lewis, R. H. Prince, and D. A. Stotter, *J. Inorg. Nucl. Chem.*, **35**, 341 (1973).
169. G. Agnes, S. Bendle, H. A. O. Hill, F. R. Williams, and R. J. P. Williams, *J. Chem. Soc., Chem. Commun.*, 850 (1971).
170. G. Tauzher, R. Dreos, G. Costo, and M. Green, *J. Organomet. Chem.*, **81**, 107 (1974).
171. F. E. Brinckman and G. J. Olson, in *The Biological Alkylation of Heavy Metals* (Eds. P. J. Craig and F. Glockling), Royal Society of Chemistry, London, 1988, p. 168.
172. N. Imura, S.-K. Pan, M. Shimitzu, and T. Ukita, *New Methods Environ. Chem. Toxicol.*, Int. Acad. Print. Co., Tokyo, 1973, p. 211.
173. N. Imura, S.-K. Pan, M. Shimitzu, T. Ukita, and K. Tonamura, *Ecotoxicol. Environ. Safety*, **1**, 255 (1977).
174. J. E. Blum and R. Bartha, *Bull. Environ. Contam. Toxicol.*, **25**, 404 (1980).
175. J. L. Maynard, *J. Am. Chem. Soc.*, **54**, 2108 (1932).
176. H. Akagi and E. Takobatake, *Chemosphere*, **3**, 131 (1973).
177. H. Akagi, Y. Fujita, and E. Takobatake, *Chem. Lett.*, **1**, 171 (1975).
178. K. Hayashi, S. Kawai, T. Ohno, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, 158 (1977).
179. H. Nagase, Y. Ose, and T. Ishikawa, *Sci. Total Environ.*, **32**, 147 (1984).
180. P. J. Craig and P. A. Moreton, *Environ. Pollut., Ser. B*, **10**, 141 (1985).
181. P. J. Craig and P. D. Bartlett, *Nature (London)*, **275**, 635 (1978).
182. P. J. Craig and P. A. Moreton, *Mar. Pollut. Bull.*, **15**, 406 (1984).
183. E. Fujita, *Kumamoto Igakkai Zasshi*, **43**, 47 (1969).
184. A. Kudo, D. R. Miller, H. Akagi, D. C. Mortimer, A. S. DeFreitas, H. Nagase, D. R. Townsend, and R. G. Warnock, *Prog. Water Technol.*, **10**, 329 (1978).
185. D. R. Miller and H. Akagi, *Ecotoxicol. Environ. Saf.*, **3**, 36 (1979).
186. L. Landner and P. O. Larsson, *IVL Report BIIS Swedish Inst. Water Air Poll. Res.*, Stockholm, 1972.
187. T. A. Jackson, *Appl. Organomet. Chem.*, **3**, 1 (1989).
188. P. J. Craig, in *Organometallic Compounds in the Environment* (Ed. P. J. Craig), Longman, London, 1986, p. 92.
189. J. O. Nriagu (Ed.) *The Biogeochemistry of Mercury in the Environment*, Elsevier North-Holland, Amsterdam, 1979.
190. J. L. Wardell, in *Comprehensive Organometallic Chemistry* (Eds. E. W. Abel, F. G. A. Stone, and G. Wilkinson), Vol. 2, Pergamon Press, Oxford, 1982, p. 863.
191. G. E. Coates, M. L. H. Green, and K. Wade, *Organometallic Compounds*, Methuen, London, 1967, p. 147.
192. C. A. McAuliffe (Ed.), *The Chemistry of Mercury*, Mcmillan, London, 1977.
193. *Mercury and the Environment*, OECD, Paris, 1974.
194. Mercury Contamination, in *Man and His Environment*, IAEA, Vienna, 1972.
195. *Environmental Health Criteria, 1, Mercury*, WHO, Geneva, 1976.
196. O. Lindquist, A. Jermilov, K. Johansson, and H. Rodhe, *Report of the Swedish Environmental Protection Board*, No. SNV PM 1816, 1984.
197. T. W. Clarkson, R. Hamada, and L. Amin-Zaki, in *Changing Metal Cycles and Human Health* (Ed. J. O. Nnagu), Life Sci. Res. Rept. No. 28, Dahlem Knof, Springer, Berlin, 1984.
198. Department of the Environment, *Chemical Compounds Used as Pesticides*, H. M. Stationary Office, London, 1982.
199. *The Agrichemicals Handbook*, Royal Society of Chemistry, London, 1983.
200. B. H. Belliveau and J. T. Trevors, *Appl. Organomet. Chem.*, **3**, 283 (1989).
201. B. L. Lewis, M. O. Andreae, and P. N. Froelich, in *The Biological Alkylation of Heavy Metals* (Eds. P. J. Craig and F. Glockling), Royal Society of Chemistry, London, 1988, p. 77.
202. M. O. Andreae and P. N. Froelich, *Anal. Chem.*, **53**, 287 (1981).
203. G. A. Hambrick, P. N. Froelich, M. O. Andreae, and B. L. Lewis, *Anal. Chem.*, **56**, 421 (1984).
204. B. L. Lewis, P. N. Froelich, and M. O. Andreae, *Nature (London)*, **313**, 303 (1985).
205. M. O. Andreae, J.-F. Asmode, P. Foster, and L. Van't Dack, *Anal. Chem.*, **53**, 1766 (1981).
206. M. O. Andreae and P. N. Froelich, *Tellus*, **36b**, 101 (1984).
207. M. O. Andreae, in *Trace Metals in Seawater* (Eds. C. S. Wong, E. Boule, K. W. Bruland, J. L. Burton, and E. D. Goldberg), Plenum Press, New York, London, 1983.
208. P. Barnard, *PhD Thesis*, University of Leeds (1947).

209. F. Huber and H. Kirchmann, *Inorg. Chim. Acta*, **29**, L249 (1978).
210. F. Huber, U. Schmidt, and H. Kirchmann, *ACS Symp. Ser.*, **82**, 65 (1978).
211. D. Dolphin (Ed.), B_{12}, Vols. 1 and 2, Wiley–Interscience, New York, 1982.
212. Y. K. Chau and P. T. S. Wong, in *Organometallic Compounds in the Environment* (Ed. P. J. Craig), Longmans, London, 1986, p. 254.
213. J. S. Thayer, *Appl. Organomet. Chem.*, **3**, 203 (1989).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

CHAPTER 11

Bioorganotin compounds

KIERAN C. MOLLOY

School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

I. INTRODUCTION AND SCOPE

Although organotin compounds represent only about 5% of the tin currently in world use, the tonnage output of these chemicals has increased at least six-fold over the last 25 years, to a current level in excess of 30 000 tonnes per annum[1]. Non-toxic applications of mono- and di-organotin compounds (PVC stabilizers, flame retardants, oxide layer precursors)[2,3] account for about two-thirds of this output, whereas tetraorganotins have few commercial outlets, save in the preparation of less alkylated or arylated systems. The remaining 8000 tonnes of annual production represent the biocidal applications of primarily triorganotin compounds, and although still of relatively minor economic importance, this area of activity has been expanding rapidly and is certainly the most diverse of all the organotin markets. The aim of this chapter is to review the state of knowledge of this latter area under the broad umbrella of 'bioorganotin compounds'. Clearly the content of such a review is subjective and will of necessity focus more on the metal centre than the Sn—C bond, since with few exceptions this entity plays a passive role in the biocidal chemistry of organotin compounds. Synthetic aspects are only briefly noted and slanted in favour of industrial routes to organotin compounds, since excellent reviews of laboratory syntheses exist, both elsewhere[1] and in other parts of this series. Toxicity and its manifestations are covered on an empirical basis and, where possible, an attempt has been made to correlate and rationalize the link between toxicity and the composition and structure of the organotin toxin. The interactions of organotin compounds with biologically important receptors are treated from both the chemically feasible (model compounds) and the biochemically relevant (*in vivo* studies) viewpoints in a manner which is hoped will link the results and ideas from these generally disparate areas. Finally, the industrial applications of biocidally active organotin compounds, much of the driving force behind the current extensive research activity in organotin chemistry, are reviewed and collated.

For the newcomer to this field, background to the chemistry of organotin compounds can be found in existing texts[1,4-6], annual surveys[7], and reviews on structure[8,9] and specialist spectroscopic techniques[10,11].

II. HISTORICAL PERSPECTIVE

The toxic nature of organometallic compounds has been known for several centuries, and in the case of organotins the pioneering work of Buckton (1858) first reported the irritating effect of alkyltins on the mucous membrane[12]. Toxicity is, of course, a two-edged sword, posing a threat to human life as well as affording opportunities, when properly targeted, to control malevolent organisms, and it is remarkable in the hindsight of history what compatible bed-fellows these two conflicting properties make. The simultaneous development of organoarsenicals as chemotherapeutic drugs and as poison gases in the early part of this century provides a striking example of this phenomenon. After several decades of widespread use, organo-mercury and -arsenic compounds began to be phased out in the early post-1945 era, in part owing to the mammalian toxicity of both the organometallics and their inorganic degradation products. Sociological factors, for example the Minamata tragedy[13] in the case of mercury, have hastened legislation against exploitation of these organometallic biocides, and similar events now surely signal the end for organolead additives in petrol.

Against this perspective, the 'bioorganotin cycle' is probably at or slightly past its zenith.

Its beginnings were less than auspicious, when in 1954 capsules intended for the treatment of staphylococcal infections were marketed in France under the trade-name Stalinon, and resulted in 102 deaths[14]. The active ingredient, Et_2SnI_2, and a co-formulated impurity, Et_3SnI, have since been found to be potent neurotoxins[15]. Paradoxically, nitrogen-donor adducts of Et_2SnI_2 have now been shown to exhibit promising anti-tumour activity[16]. Despite these events, systematic evaluation of the fungicidal and bactericidal properties of organotin compounds by van der Kerk and Luijten[17] in the 1950s paved the way for their commercial exploitation as agrochemicals, which began in the early 1960s when Ph_3SnOAc was marketed as a fungicide (Brestan®; Hoechst). The pace at which further developments ensued was no doubt aided by the low toxicity of inorganic tin compounds formed by biodegradation of the organometallics, in contrast to the case for mercury, arsenic, and lead. The past two decades have seen the growth of organotin biocides in many diverse and expanding fields (see Section VI), but tempered in recent years by concern as to the long-term environmental impact of these compounds. The effects of organotin anti-fouling paints on marine and estuarine life, notably oysters[18], has led to legislation controlling the use of these paints and, if the examples of mercury and arsenic tell anything, it is that this is probably only the first of series of stringent appraisals of these chemicals.

III. SYNTHESIS

Considerable attention has been paid to the synthetic routes by which Sn—C bonds may be formed. Many of these methods are predominantly of relevance to the synthesis of laboratory- rather than industrial-scale amounts, and are reviewed elsewhere[1]. For the synthesis of the commercially important tri- and di-organotin compounds, relatively few viable large-scale routes exist. The most common of these is the formation of a tetraorganotin from tin(IV) halides and another organometallic reagent, usually RMgX or R_3Al, followed by disproportionation of R_4Sn with the required stoichiometric amount of SnX_4 (equations 1–4).

$$SnX_4 + 4RMgX \longrightarrow R_4Sn + 4MgX_2 \quad (1)$$

$$4R_3Al + 3SnCl_4 + 4R'_2O \longrightarrow 3R_4Sn + 4AlCl_3{\cdot}R'_2O \quad (2)$$

$$R_4Sn + SnCl_4 \longrightarrow 2R_2SnCl_2 \quad (3)$$

$$3R_4Sn + SnCl_4 \longrightarrow 4R_3SnCl \quad (4)$$

Complex formation between Et_2O and tin(IV) halides inhibits total alkylation, a problem which is best overcome on an industrial scale by using toluene with a minimum amount of Grignard-solvating ether as reaction solvent[19], rather than the laboratory method of employing excess of Grignard reagent. Where organoaluminium compounds are the alkylating agents of choice, the presence of complexing agents such as ethers, amines or sodium chloride aids the separation of R_4Sn from the final mixture, by coordinating the $AlCl_3$ produced during the course of the reaction[20].

Direct synthesis of organotin compounds from tin metal has, until recently, been limited to the production of diorganotin compounds (equation 5).

$$2RX + Sn \longrightarrow R_2SnX_2 \quad (5)$$

This reaction follows the reactivity sequences X = I > Br > Cl and R = Me > Et > Pr, and generally, but not always[21], requires a catalyst (R_4MX, R_3M; M = N, P, Sb).

More recent work has extended this method to the production of triorganotin compounds (equation 6).

$$3RX + R^1_4MX + 2Sn \longrightarrow R_3SnX + [R^1_4M]^+[SnCl_3]^- \quad (6)$$

The reaction is carried out at 120–140 °C, thereby utilizing Group V halide salts as both reagent and solvent, and yields of > 95% have been reported for the synthesis of Bu_3SnBr. This method also incorporates electrolytic recovery of reagents (equation 7)[22].

$$2NaOH + [R^1_2M]^+[SnX_3]^- \xrightarrow{2\ Faradays} 2NaX + R^1_4MX + Sn + \tfrac{1}{2}O_2 + H_2O \quad (7)$$

The organotin halides described above are the starting reagents for other functionally substituted organotin compounds, and their utilization in this respect has been reviewed[1]. Only where appropriate will specific syntheses be addressed in this review.

IV. TOXICITY

Several reports on the toxicology of organotin compounds are now available[23–29], and those features, of both composition and structure, which manifest themselves in active compounds are clearly discernible. It is the aim of this section merely to delineate these structure–activity relationships, based on empirical observation rather than chemical evaluation of the *modus operandi*. This latter topic is addressed more fully in Section V.

Several reviews of the biochemical and biological manifestations of organotin toxicity are also available, covering anti-tumour activity, cytotoxicity and immunotoxicity[30–33], neurotoxicity and related effects[34–37], and behavioural toxicity[38–40].

A. The Influence of R Groups

The number and nature of the R groups in R_nSnX_{4-n} is the most significant influence on both the extent and species specificity of biocidal activity. Inorganic tin compounds, i.e. with $n = 0$, have no notable toxicity, and since SnO_2 is the ultimate environmental degradation product of all organotin compounds these species have an obvious advantage over analogous organo-mercurials and -arsenicals. However, dealkylation of tin may well occur (in part) by trans-methylation of other inorganic metals in the environment[41–43], thereby generating volatile, toxic organometallic compounds of other elements. Furthermore, environmental methylation of inorganic tin to highly mammalian toxic methyltin compounds is feasible and, on a laboratory scale, demonstratable[41,44–46]. Hence a cycle in which commercial organotins of low toxicity are converted via SnO_2 or possibly SnS to more toxic Me_3SnX species cannot be ignored. These latter issues are currently the subject of some debate, but what is now clear is that in environmental terms, the fate of organotin compounds cannot be viewed in isolation.

Triorganotin compounds are significantly more biocidally active than other classes with either more or fewer hydrocarbon groups bonded to tin. For example, far higher concentrations of R_2SnX_2 are required to inhibit *Mycobacterium phlei* than the corresponding R_3SnX species (Figure 1)[47]. Any biological activity associated with R_4Sn compounds arises from their rapid *in vivo*[48] or *in vitro*[49] dealkylation to triorganotins, whereas monoorganotin compounds have no notable activity[50].

Within the R_3SnX unit, the nature of the R groups determines the species specificity of the biocide. Figure 1 shows that against *Mycobacterium phlei* tributyltin compounds are the most potent, with decreasing activity for derivatives in which the R groups have both more or fewer carbon atoms. Trioctyl- and higher triorgano-tins are essentially inactive. Similar activity–composition plots are available for other target organisms, and these are depicted in Figure 2 and summarized in Table 1. The highest mammalian toxicity occurs in Me_3SnX and Et_3SnX compounds, while the former are also active insecticides. The commercial applications of Bu_3SnX compounds in anti-fouling paints, Ph_3SnX as fugicides and $(c\text{-}Hex)_3SnX$ and $(NeO)_3SnX$ as miticides are clearly reflected in the activity patterns of Table 1.

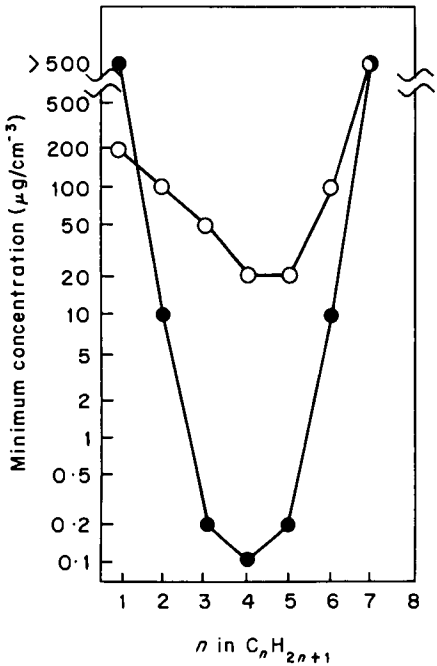


FIGURE 1. Influence of chain length of di- and tri-substituted organotin compounds on minimum concentration inhibitory to *Mycobacterium phlei*: ●, R_3SnX; ○, R_2SnX_2. Reproduced by permission of the American Chemical Society from H. Gitlitz, in *Organotin Compounds: New Chemistry and Applications (Ed. J. J. Zuckerman), Adv. Chem. Ser.*, No. 157, 170 (1976). Copyright (1976) American Chemical Society

The basis of the relationship between hydrocarbon chain length and activity in R_3Sn systems is not fully resolved[51], but several workers have noted that in a variety of toxicity assessments it is those organotins which have *n*-octanol–water partition coefficients >1 (Pr_3SnCl, Bu_3SnCl, Ph_3SnCl) which show greater toxicity than more water-soluble

TABLE 1. Activity–composition maxima for triorganotin compounds, R_3SnX

Target species	R for maximum activity
Mammals	Et
Insects	Me
Gram-negative bacteria	Pr
Gram-positive bacteria	Bu
Fish, fungi, molluscs	Bu, Ph
Mites	c-Hex, Neo

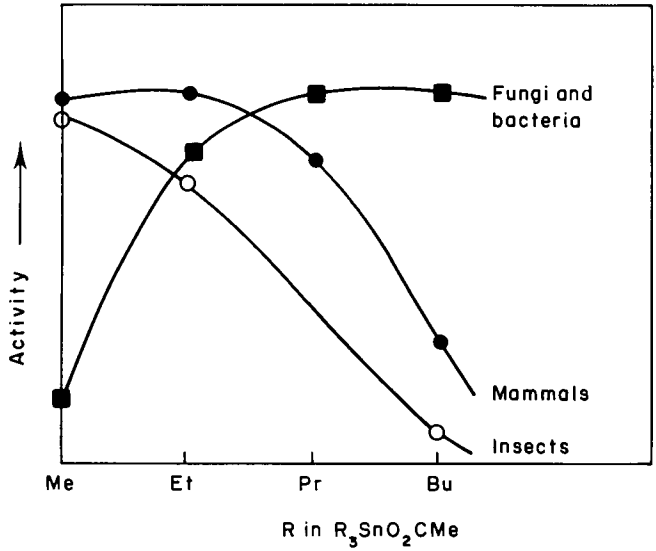


FIGURE 2. Dependence of the biological activity of triorganotin acetates on the nature of the hydrocarbon group for different species. Reproduced by permission of the International Tin Research Institute from P. J. Smith, International Tin Research Institute Publication 621

compounds (Me_3SnCl)[52–56]. Such behaviour may well be related to chemical effects at or near the cell wall–water interface. The activity maximum for triorganotin compounds with a total of ca 12 carbons could be a result of optimum lipid–water partioning, or that longer alkyl chain derivatives have much of their reactivity mitigated by steric bulk and/or lower Lewis acidity at tin.

B. The Influence of Anionic Ligands

Anionic ligands (X) play a secondary role in determining the degree of activity of R_3SnX compounds. This is amply demonstrated by the data in Table 2, showing the acute toxicity of various Bu_3SnX to rats[24]. LD_{50} values for a range of anionic X groups fall in the narrow range 0.27–0.49 mmol kg^{-1}, which is a statistically insignificant variation given the nature of the tests. However, although the X groups in Table 1 and those generally found in the commercially exploited organotin compounds are biocidally passive, they do play a role in determining molecular structure, and common structural features among all the active triorganotin compounds exist. The known structural variations for R_3SnX compounds are four-coordinate, tetrahedral, incorporating a unidentate ligand X (**1**), and five-coordinate, *trans*-R_3SnXY (**2**) or *cis*-R_3SnXY (**3**) trigonal bipyramidal, both of the latter

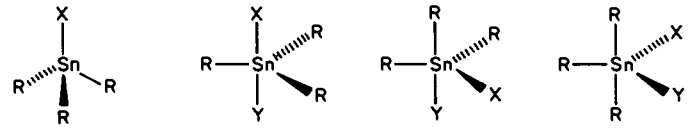
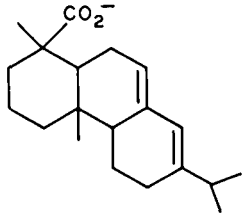


TABLE 2. Acute toxicity of tributyltin compounds (Bu_3SnX) to rats

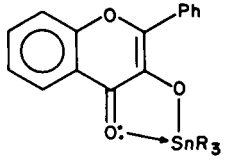
X	LD_{50} (mmol kg^{-1})
F^-	0.30
Cl^-	0.38
O^{2-}	0.42
$PhCO_2^-$	0.49
$Me(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2^{-}$ [a]	0.34
 [b]	0.27
$C_{10}H_7CO_2^-$ [c]	0.37

[a]Linoleate.
[b]Abietate.
[c]Naphthenate.

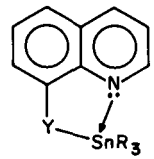
structures usually occurring with bidentate ligation from the anion (XY). The *mer*-R_3SnXY isomer (**4**) is yet to be authenticated crystallographically for an organotin compound[8,9].

Representative examples taken from compounds of known activity adopt structures **1** and **2** but not **3**. $(Bu_3Sn)_2O$ and $[(Neo)_3Sn]_2O$ are both four-coordinate at tin[57], whereas Ph_3SnOAc, Ph_3SnOH and Cy_3Sn(1,2,4-triazol-1-yl) all form coordination polymers which incorporate the five-coordinate *trans*-R_3SnXY moiety. Ph_3SnOAc (Figure 3)[58] has planar $[Ph_3Sn]$ units linked by bidentate, bridging carboxylate groups and a similar arrangement is found in Ph_3SnOH (Figure 4)[59] and Cy_3Sn(1,2,4-triazol-1-yl)[60] (Figure 5) employing bridging hydroxy or heterocyclic groups, respectively. Cy_3SnOH has a polymeric structure analogous to Ph_3SnOH, based on spectroscopic evidence[61].

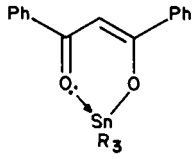
Compounds which adopt structural type **3** inevitably occur where chelating ligands are present in the molecule. The two five-coordinate arrangements **2** and **3** therefore differ not only in the stereochemical arrangement of ligands about the metal, but also because **2** arises as part of a polymer chain whereas **3** exists as discrete molecular entities. Structural type **3** often leads to diminished biocidal activity. Triphenyl- and tricyclohexyl-tin derivatives of 3-hydroxyflavone (**5**), quinolin-8-ol (**6**; Y = O), quinolin-8-thiol (**6**; Y = S), and 1,3-diphenylpropane-1,3-dione (**7**) show lower activity than Ph_3SnOAc and Cy_3SnOH[62,63]. Tzschach *et al.*[64] have shown that (**8**; R = H, Ph) are both less active than $(Bu_3Sn)_2O$.



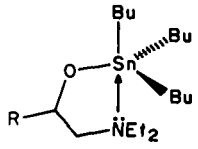
(5)



(6)



(7)



(8)

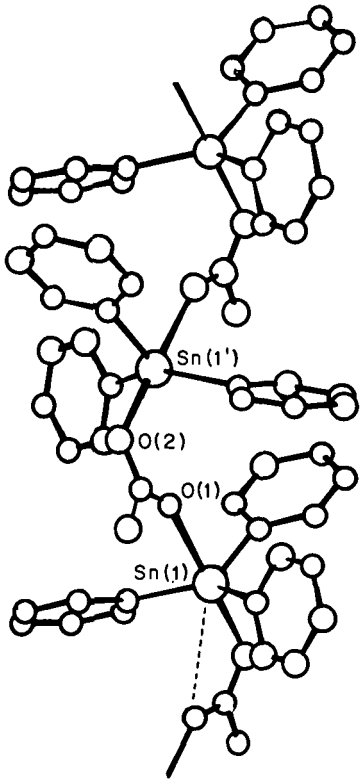


FIGURE 3. Structure of triphenyltin acetate. Reproduced by permission of Elsevier Sequoia from Reference 58

Structures **1** and **2** are linked by that fact that in solution both forms generate the tetrahedral structure **1**, the polymeric arrangement by intermolecular fragmentation. On the other hand, the chelated monomers **3** retain their five-coordinate structure even in solution. Triorganotin compounds have a strong tendency to increase their coordination number to more that 4 by interaction with, for example, O, S, or N donor molecules[1]. Compounds which are four-coordinate in solution will undergo such interactions, but five-coordinate species can be considered 'coordinatively saturated' and will not. It is this structural feature which most obviously distinguishes active from inactive organotins. The inter-relationship between activity and solution-state coordination number at tin has been further endorsed by Ascher and Nemny[65], who showed that concentrated solutions of Ph_3SnOAc, which contain a higher content of five-coordinate polymer, are less active than dilute solutions.

Since the extent of activity is independent of X in active compounds (Table 1), it seems almost certain that the anionic ligand is displaced from tin when the organometallic unit is bound to the active site of a biological macromolecule. The chronology of nucleophilic displacement of X^- from tin is still uncertain. X may remain bonded to tin until it reaches its active receptor site, where it is displaced by a suitable donor atom, for example

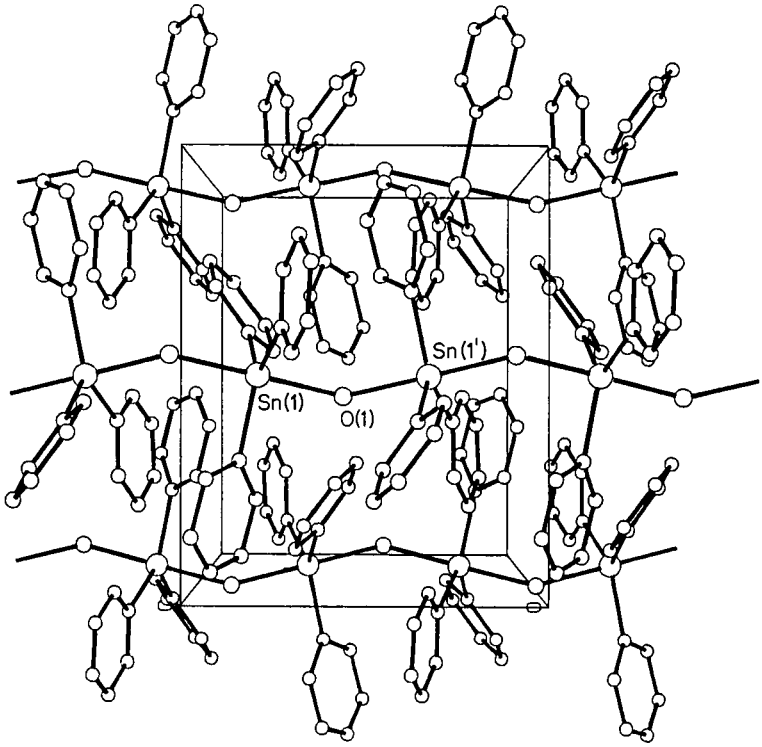


FIGURE 4. Structure of triphenyltin hydroxide. Reproduced by permission of the International Union of Crystallography from Reference 59

proteinaceous nitrogen (equation 8; **9**, or **11**). Under such circumstances, X may well influence the ease with which the R_3SnX molecule is transported to the active site, e.g. passage across membranes. Alternatively, in aqueous environments the Sn—X bond may be readily hydrolysed to the hydrated cation **10**. Such species have long been postulated in the aqueous equilibria of organotin compounds[66], but only recently has this structural

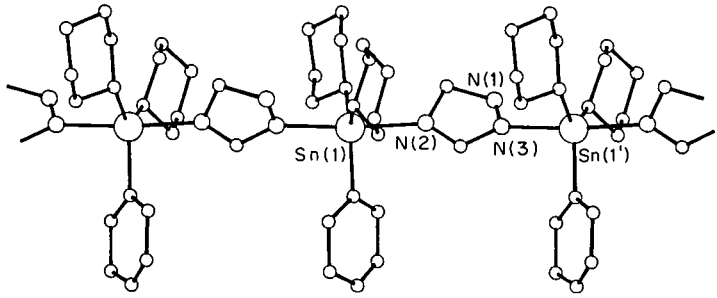


FIGURE 5. Structure of tricyclohexyl(1,2,4-triazol-1-yl)tin. Reproduced by permission of Bayer from Reference 60

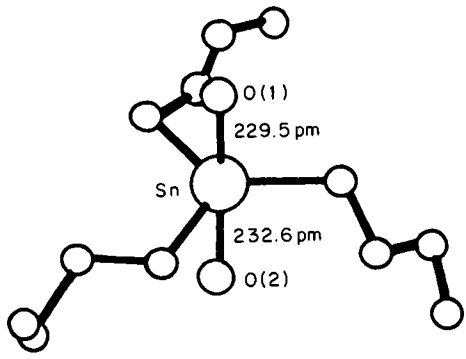
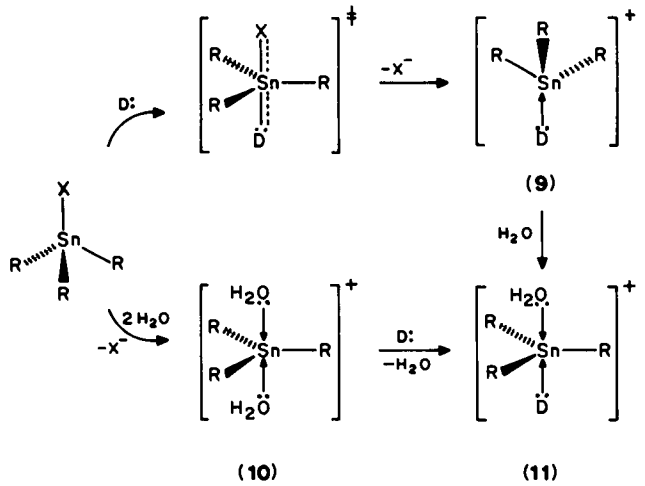
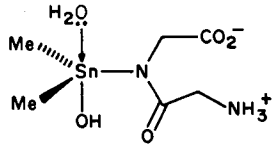


FIGURE 6. Structure of the hydrated ri butyltin cation. The counter ion (not shown) is $[C_5(CO_2Me)_5]^-$. Reproduced by permission of the Royal Society of Chemistry from Reference 67



(8)

unit been confirmed in the solid state with the X-ray analysis of $Bu_3Sn(H_2O)_2^+$ (Figure 6)[67]. The weakly bound solvent molecules are then displaced by donor group(s) to yield **9** or **11**, which may or may not undergo further complexation with other donor atoms. In this reaction sequence X^- determines the ease of formation of the aquated cation, but plays no long-term role in the *in vivo* chemistry of the organotin. Studies

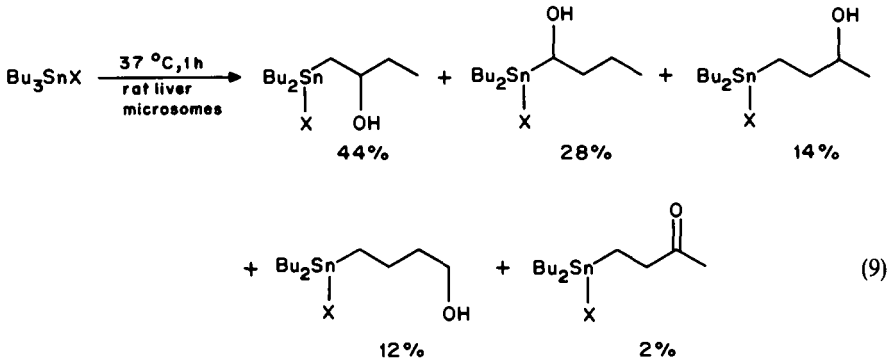


(12)

relating to the aqueous chemistry of $Me_2SnGlyGly$ (GlyGly = anion of glycylglycinate) suggests that the formation of the hydrated cation $Me_2Sn(H_2O)_4^{2+}$ takes place via a partially solvated intermediate (**12**)[68].

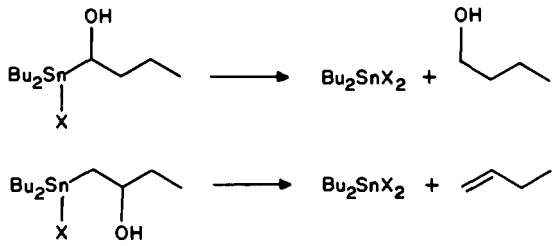
C. Metabolism

It has now been established that the primary metabolic reaction of organotins is hydroxylation of the hydrocarbon group. Using rat liver microsomes and [1-^{14}C]-tributyltin acetate, Fish *et al.*[69] have shown (a) that a cytochrome P-450 monooxygenase enzyme system is responsible for the oxidation rather than a lipid peroxidase and (b) the distribution of metabolic products is as shown in equation 9. Similar reactions have been shown to occur *in vivo* with mice[49].



(9)

The mechanism for the insertion of oxygen into the C—H bond is believed to be a radical process[70], and ESR studies have shown that carbon atoms α- or β- to an organotin centre are particularly susceptible to radical attack[71]. The α- and β-hydroxy metabolites are unstable and rapidly undergo destannylation reactions (equation 10). The net result of this sequence of reactions is a detoxification of the organometallic compound by dealkylation. Indeed, many of the earliest studies in this area[48,72,73] only note the progressive metabolic dealkylation of the organotin. Microorganisms have also been shown to dealkylate bis(tributyltin) oxide[74].



(10)

In vivo metabolism of (*c*-Hex)$_3$SnOH also follows a sequential dealkylation process (equation 11)[75] but, as with the tributyltin case discussed above, evidence also points to the formation of 2-, 3- and 4-hydroxycyclohexyltin species[70]. Ph_3SnOAc and Ph_3SnCl are metabolized in rats to Ph_2SnX_2 and $PhSnX_3$ species[49,76], but as yet compelling evidence for the formation of hydroxylated metabolites is lacking[70].

$$(c\text{-Hex})_3SnOH \longrightarrow (c\text{-Hex})_2SnO \longrightarrow (c\text{-Hex})SnO_2H \longrightarrow Sn^{4+} \qquad (11)$$

The half-life of Et_3SnBr in rats has been estimated at 8 days[77], whereas other reports indicate that 99% of $(c\text{-Hex})_3SnOH$ is excreted from rats in *ca* 9 days[78]. The half-life of $(Bu_3Sn)_2O$ in mice has been measured at 29 days, but even at this residence time it was concluded there had been no long-term accumulation of tin in the animal[79]. Data showing the bio-distribution of tin in the organs of rats, rabbits, mice, etc., are available, but depending on the assay method may only give total tin content rather than being species-specific for the varying compositions of organotin[80–83].

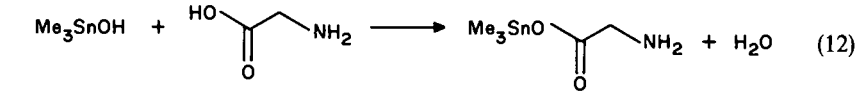
V. INTERACTIONS WITH BIOCHEMICAL SPECIES

A. Amino Acids

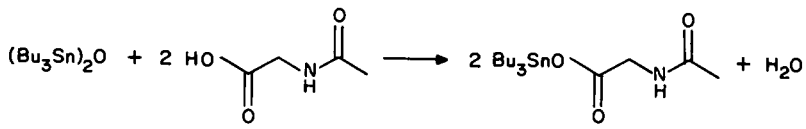
The most widely studied interactions between biochemically important substrates and organotins relate to the amino acids and their analogues, although data on several of the 20 most common naturally occurring acids are still outstanding.

1. Glycine

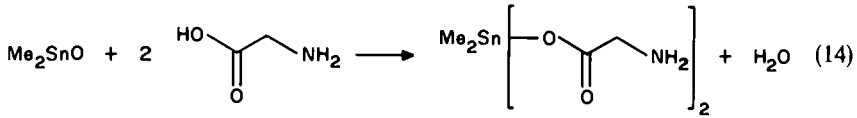
Known organotin glycinates and their *N*-protected analogues are listed in Table 3. These compounds, as with all the amino acid derivatives discussed below, are formed from the reaction between the free amino acid and an organotin oxide or hydroxide[84,90], e.g. equations 12–14. Dmf is occasionally added to catalyse these reactions[84–86], which are all carried out in normal organic solvents. In aqueous solutions at pH 7, there is little evidence of complex formation between $[Me_3Sn(H_2O)_2]^+$ and glycine[91,92].



(12)



(13)



(14)

Infrared and Mössbauer data indicate that organotin derivatives of glycine are *N*-bridged polymers[85,86]. This structure has been confirmed crystallographically (Figure 7) and extensively evaluated by Mössbauer spectroscopy[93]. The N:→Sn interaction apparently occurs in glycine derivatives because the carbonyl oxygen is involved in hydrogen bonding C=O···H—N. In *N*-protected glycine derivatives, polymeric structures arise either from bidentate carboxylate groups [**13**; $R^1 = H$; $R^2 = COPh$[87], $C_6H_3(NO_2)_2$-2,4[89]] or by bridging through the amide oxygen (**14**; $R^1 = H$; $R^2 = H$, Me[87,88]). Tri- and di-methyltin derivatives of *N*-benzoylglycine have been found to be active in anti-tumour tests against leukaemia P-388 cells[94]. Tin(II) glycinate has also been synthesized[86].

TABLE 3. Organotin glycinates[a]

Compound	M.p.(°C)	Infrared $\nu_a(CO_2)$ (cm^{-1})	Infrared ν(CO)amide (cm^{-1})	Mössbauer qs[b] ($mm\,s^{-1}$)	Ref.
$L = O_2CCH_2NH_2$:					
Me_3SnL	163–164	1630		3.14	85
Bu_3SnL	127–128	1625		3.21	85
$(c\text{-Hex})_3SnL$	122–123	1620		3.14	85
Me_2SnL_2	>200(d)	1629		3.73	86
$L = O_2CCH_2NHC(O)H$:					
Me_3SnL	184	1628	1653	3.48	88
Ph_3SnL	174	1633	1655		88
$L = O_2CCH_2NHC(O)Me$:					
Me_3SnL	138	1654	1627	3.49	90
Et_3SnL	110				84
Bu_3SnL	122	1629	1637	3.55	84,90
Ph_3SnL	160(d)	1613	1626	3.31	90
$L = O_2CCH_2NHC(O)Ph$:					
Me_3SnL	131.5	1587	1648	3.68	88
Et_3SnL	60				84
Ph_3SnL	154	1557	1659		88
Me_2SnL_2	227–228				94
$L = O_2CCH_2NHC_6H_3(NO_2)$-2,4:					
Me_3SnL	193	1582		3.78	89
Ph_3SnL	172	1583		3.54	89
$L = O_2CCH_2NHC(O)OCH_2Ph$:					
Et_3SnL	60				84
Bu_3SnL	78				84

[a]Data refer to the solid state.
[b]Mössbauer quadrupole splitting.

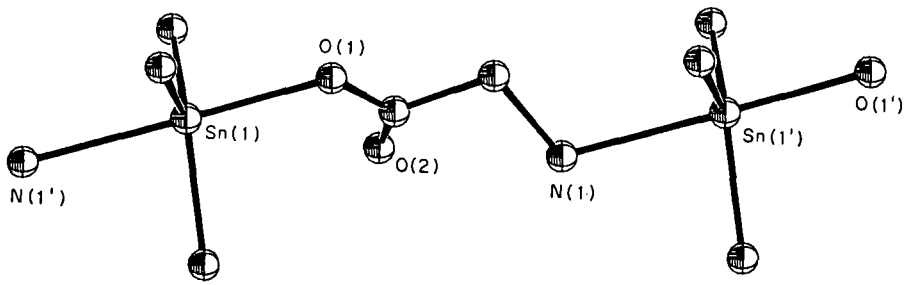
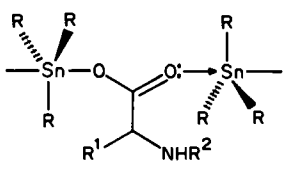
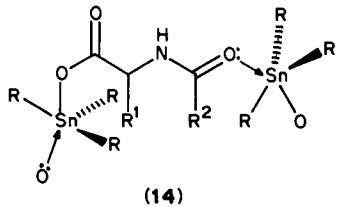


FIGURE 7. Structure of trimethyltin glycinate. Reproduced by permission of Elsevier Sequoia from Reference 93



(13)



(14)

2. *Leucine, isoleucine, and valine*

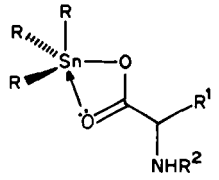
Known tri- and di-organotin leucinates and isoleucinates are listed in Table 4[84,85]. The optical activity of the amino acid appears to be retained during organostannyl esterification[84]. The three trimethyltin derivatives adopt an *N*-bridged polymeric structure analogous to $Me_3SnO_2CH_2NH_2$ (Figure 7), but this arrangement is inhibited on steric grounds for the corresponding tricyclohexyltin compounds which instead form

TABLE 4. Organotin L-leucinates, L-isoleucinates and valinates[a]

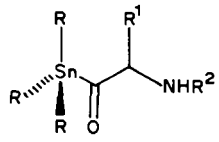
Compound	M.p.(°C)	Infrared $\nu_a(CO)_2$ (cm^{-1})	Infrared ν(CO)amide (cm^{-1})	Mössbauer qs[b] ($mm\,s^{-1}$)	Ref.
$L = O_2CCH(Bu^i)NH_2$:					
$MeSnL$	147–148(d)	1638		3.28	85
Bu_3SnL	93–95				84
$(c\text{-}Hex)_3SnL$	118–121(d)	1590		2.75	85
$L = O_2CCH(Bu^i)NHC(O)Me$:					
Et_3SnL	35				84
Me_2SnL_2	160	1580	1650	3.63	95
Et_2SnL_2	171	1580	1640	3.35	95
Bu_2SnL_2	185	1590	1665	3.46	95
Oct_2SnL_2	115–120			3.39	95
$L = O_2CCH(Bu^i)N(CO)_2C_6H_4$:					
$Me_2SnL_2{\cdot}H_2O$	170–175			3.44	96
$Et_2SnL_2{\cdot}3H_2O$	265–266			4.09	96
Bu_2SnL_2	200–206			3.40	96
$Oct_2SnL_2{\cdot}3H_2O$	106–108			3.43	96
$L = O_2CCH(Bu^s)NH_2$:					
Me_3SnL	161–162(d)	1635		3.23	85
$(c\text{-}Hex)_3SnL$	54–57(d)	1585		3.20	85
$L = O_2CCH(Pr^i)NH_2$:					
Me_3SnL	152–153(d)	1647		3.24	85
Bu_3SnL	60				84
$(c\text{-}Hex)_3SnL$	131–133(d)	1652		2.78	85
$L = O_2CCH(Pr^i)NHC(O)Me$:					
Et_3SnL	157				84
Bu_3SnL	121				84

[a]Data refer to the solid state.
[b]Mössbauer quadrupole splitting.

either five-coordinated monomers with chelating carboxylate groups (**15**; R^1 = *i*-Bu, *s*-Bu; R^2 = H) or a simple tetrahedral structure (**16**; R^1 = *i*-Pr; R^2 = H)[85].

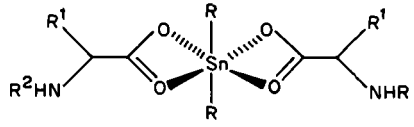


(**15**)



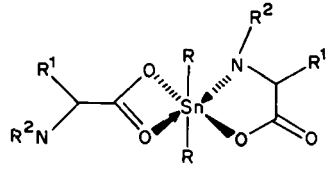
(**16**)

Several diorganotin derivatives of *N*-acylated leucine have also been synthesized[95,96]. Based on spectroscopic data, these *N*-acylated leucine derivatives adopt distorted, *trans*-R_2SnO_4 octahedral structures (**17**; R^1 = *i*-Bu; R^2 = COMe) with ⟨C—Sn—C in the range 138–148°, and which in some instances (R = Et, Oct) dimerize through pairs of CO···HN hydrogen bonds[95].

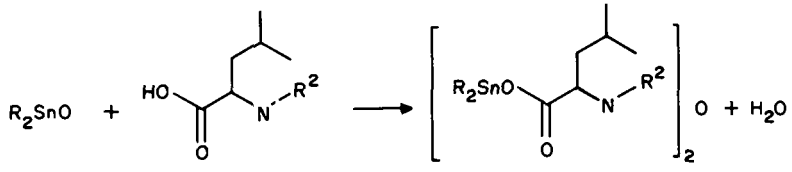


(**17**)

The structures assigned to the corresponding *N*-phthaloyl analogues are essentially similar, but the octahedral coordination about tin is now made up of a chelating carboxylate in conjunction with *O,N*-chelation from a second ligand (**18**; R^1 = *i*-Bu; R^2 = $C_6H_4(CO)_2$-1,2)[96]. Several diorgannostannoxane derivatives of leucine have also been synthesized (equation 15)[95,96]:



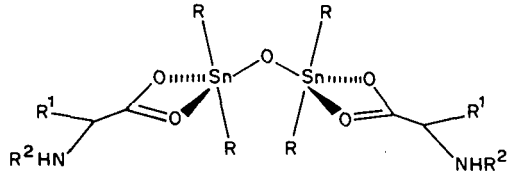
(**18**)



R^2 = MeCO, $C_6H_4(CO)_2$-1,2 (15)

Tentative structures based on collective spectroscopic data suggest a five-coordinate trigonal bipyramidal arrangement at tin (**19**; R^1 = *i*-Bu; R^2 = COMe) with some tendency for dimer formation through hydrogen bonds, as above[95]. Stannoxy-*N*-phthaloyl leucinates are potentially more complex, with *O,O,N*-tridentate ligands in either

monomeric or polymeric formulations[94], but in the absence of confirmatory crystallographic evidence such assignments must be taken as speculative.



(19)

3. Alanine

Several organotin derivatives of both α- and β-alanine and of *N*-protected α-alanine are known (Table 5) and have been prepared by conventional routes (equations 12–14)[84–86,90,96,97]. Trimethyltin α- and β-alanates are *N*-bridged polymers (cf. Figure 7),

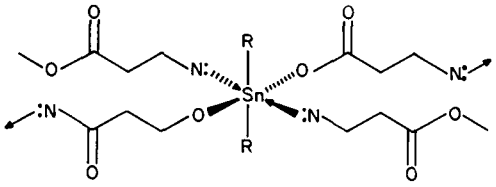
TABLE 5. Organotin derivatives of α- and β-alanine and related *N*-acyl derivatives[a]

Compound	M.p.(°C)	Infrared $\nu_a(CO_2)$ (cm^{-1})	Infrared ν(CO)amide (cm^{-1})	Mössbauer qs[b] ($mm\,s^{-1}$)	Ref.
$L = O_2CCH(Me)NH_2$:					
Me_3SnL	141–142(d)	1635		3.21	85
Bu_3SnL	130–132				84
$(c\text{-Hex})_3SnL$	142–143(d)	1600		2.09	85
$L = O_2CCH_2CH_2NH_2$:					
Me_3SnL	126–127	1636		3.08	85
$(c\text{-Hex})_3SnL$	140–141	1640		3.21	85
Me_2SnL_2	>200(d)	1629		3.77	86
$L = O_2CCH(Me)NHC(O)Me$:					
Me_3SnL	178(d)	1595	1630	3.45	90
Bu_3SnL	89	1620	1620	3.54	90
Ph_3SnL	169(d)	1602	1645	3.65	90
$L = O_2CCH(Me)NHC(O)Ph$:					
Me_3SnL	95–105	1647	1606		97
Pr_3SnL[c]	50–70	1655	1655		97
Bu_3SnL[c]	65–70	1640	1640		97
$(c\text{-Hex})_3SnL$	124–128	1635	1600		97
Ph_3SnL	195	1646	1612		97
$L = O_2CCH(Me)N(CO)_2C_6H_4$:					
Me_2SnL_2	190–195			3.41	96
Et_2SnL_2	210			3.91	96
$Bu_2SnL_2{\cdot}3H_2O$	170–173			3.52	96
Oct_2SnL_2	95–98			3.63	96

[a]Data refer to the solid state unless indicated otherwise.
[b]Mössbauer quadrupole splitting.
[c]Solution state.

but the structures of the corresponding tricyclohexyltin derivatives are a function of the competing steric demands of the cyclohexyl- and α-carbon substituents of the amino acid. For α-alanine, the steric demands of c-Hex and Me, respectively, inhibit polymer formation and a carboxylate-chelated architecture (**15**; R^1 = Me; R^2 = H) results, whereas β-alanine, being more 'pointed' in character, allows the *N*-bridged system to construct[85].

Dimethyltin β-alaninate is an amorphous, insoluble powder which hydrolyses rapidly in moist air and which, from its physical and spectroscopic properties, adopts a doubly *N*-bridged sheet structure with local *trans*-$R_2SnN_2O_2$ stereochemistry at tin (**20**; R = Me) in a manner similar to the corresponding glycinate[86].

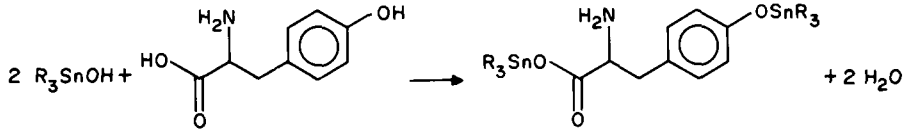


(**20**)

The structural pattern among the *N*-acetyl[90], *N*-benzoyl[97], and *N*-phthaloyl α-alaninates[96] follows **14** (R^1 = Me; R^2 = Me), **14** (R^1 = Me; R^2 = Ph) and **18** [R^1 = Me; $R^2 = C_6H_4(CO)_2$-1,2], respectively, paralleling the corresponding glycinates and leucinates described previously. Similarly, a range of diorganostannoxy alaninates, $[R_2Sn(N\text{-PhthaloylAla})]_2O{\cdot}nH_2O$ (R = Me, R = Et, Bu, Oct, $n = 0$) are structurally isomorphic with the analogous leucinates and contain tridentate *O,O,N*-bonded ligands[96].

4. Phenylalanine and tyrosine

Very little work has been carried out on triorganotin derivatives or these two aromatic-substituted amino acids. No derivatives of free phenylalanine have been reported, although two *N*-benzoyl compounds [$R_3SnO_2CCH(CH_2Ph)NHC(O)Ph$; R = Et, Bu] have been prepared but not structurally characterized[84]. The same report states that tyrosine requires 2 equivalents of organotin hydroxide for complete reaction, although no further comment is made on the reaction product. Presumably, both hydroxy and carboxylate functionalities take part in reaction (equation 16).

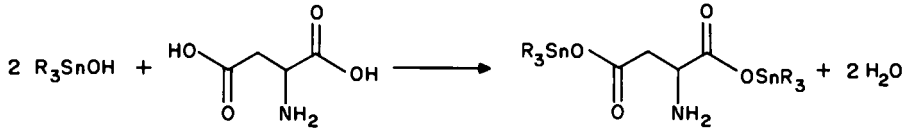


(16)

Diorganotin derivatives of both *N*-acetyl-[95] and *N*-phthaloyl-phenylalanine[96] and the corresponding distannoxane compounds[95,96] are more numerous, and parallel the derivatives of leucine and alanine described previously.

5. Aspartic acid

Aspartic acid is reported as binding two triorganotin moieties (presumably following equation 17) when reaction is carried out in aromatic solvents[84], but little or no interaction appears to take place in aqueous media[92].

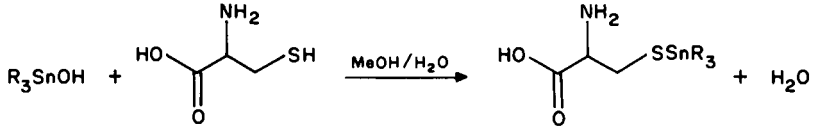


(17)

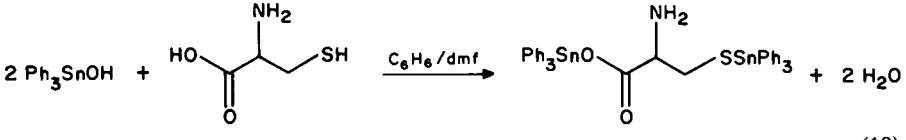
6. *Cysteine, methionine, and their analogues*

Considerable attention has been paid to the interactions between organotins and sulphur-containing amino acids in the light of the binding of these organometallics by proteins *via* cysteine residues (see Section V.D.1).

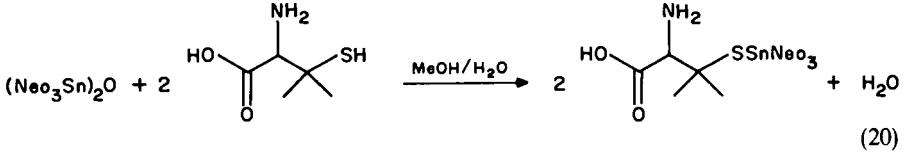
Cysteine bonds to triorganotins preferentially *via* sulphur[98,99], but at the appropriate reaction stoichiometries will also bind a second organotin *via* the carboxylate residue[100] (equations 18 and 19). A similar series of syntheses is known for the cysteine analogue penicillamine[98–100], e.g. equation 20.



(18)



(19)

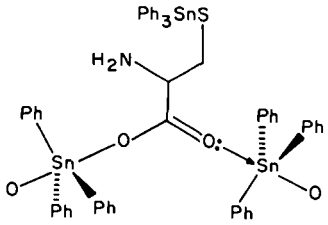


(20)

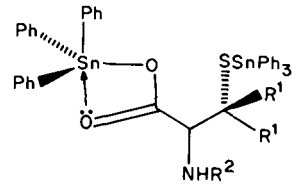
Compounds of formula $R_3SnSCR^1_2CH(NH_2)CO_2H$ (R^1 = H, R = Me, c-Hex, Neo[98], Ph[98,99]; R^1 = Me, R = Ph[99]) are characterized by ν(Sn—S) in the range 327–338 cm^{-1}, a unidentate carboxylate with $\nu_{asym}(CO_2) \approx 1630\,cm^{-1}$, and a Mössbauer qs value in the range 1.34–1.79 $mm\,s^{-1}$[98], all of which indicate a tetrahedral coordination sphere about tin. Compounds where R = Me, Et and R^1 = H, Me are unstable[98].

Of the compounds with a 2:1 tin-to-ligand ratio, bis(triphenyltin)Cyst and the corresponding penicillamine derivative are the most thoroughly studied. Both compounds contain tin in two distinct environments based on pairs of doublets in their respective Mössbauer spectra: cysteine, qs = 1.36, 3.12 $mm\,s^{-1}$[100]; penicillamine, qs = 1.31, 2.07[100] (1.20, 2.58[101]) $mm\,s^{-1}$. The smaller splitting has been assigned to the Ph_3SnS residue in a tetrahedral environment, the larger to a five-coordinated R_3SnO_2 unit, both by comparison with model organotin sulphides and acetates. From the temperature dependance of the Mössbauer spectral area, the sulphur-bound tin ($a = -10^2 d\ln A/dT =$

1.97 and 2.01 K^{-1} for cysteine and penicillamine, respectively) is less tightly bound in the solid lattice than the oxygen-bound tin ($a = 1.26$ and 1.59 K^{-1}, respectively); however, for the cysteinate this latter environment is embraced within a polymeric arrangement (**21**), while steric hindrance in the penicillaminate enforces a chelated system (**22**; $R^1 = Me$; $R^2 = H$)[100]. The role of steric effects in the structures of organotin carboxylates has been independently assessed[102,103]. Both compounds exist as discrete monomers in solution[99].

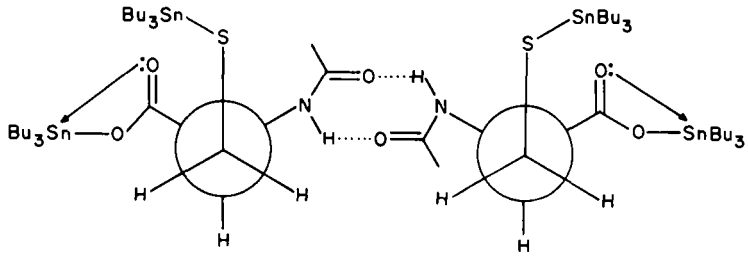


(21)



(22)

Few derivatives of *N*- or *O*-protected cysteine or penicillamine have been reported. $(R_3Sn)_2$(*N*-acetCyst) (R = Me, Bu) are stable compounds[104], but only the latter has been fully characterized[105]. The *S*- and *O*-bonded tin sites are clearly discernible in its Mössbauer spectrum (qs = 1.62 and 3.59 mm s^{-1})[106]. I.r. and collective n.m.r. data indicate a structure similar to $(Ph_3Sn)_2$Pen (**22**; $R^1 = H$; $R^2 = COMe$) (cf. comparative steric crowding about the carboxylate group), but in concentrated solutions and/or the solid-state hydrogen-bonded dimers predominate. The preferred rotamer, based on n.m.r. data, is shown in **23**. *S*-(Bu_3Sn)-*O*-ethylCyst is an unstable, hydrogen-bonded oil, which contains a four-coordinate tin[105].

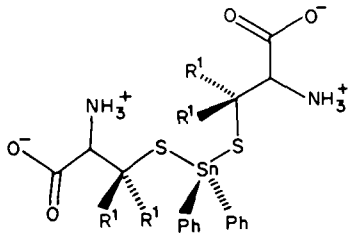


(23)

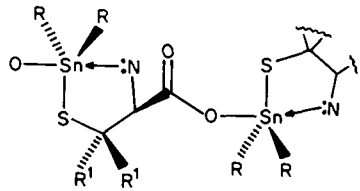
Diorganotin compounds of stoichiometry R_2SnL_2 and R_2SnL (L = cysteine, penicillamine) have been synthesized[99]. The former series bind preferentially through sulphur and are tetrahedral at tin (R = Ph, qs = 2.32 and 2.36 mm s^{-1} for L = HCyst and HPen, respectively)[101]. A zwitterionic structure (**24**; $R^1 = H$, Me) has been proposed[99].

Compounds of 1:1 stoichiometry are *O*-, *S*-bonded to tin[99]. Analysis of Mössbauer qs for dimethyl- and diphenyl-tin penicillaminates based on a point-charge model suggests a five-coordinated tin with *trans*-, axial *O*-, *N*-donors (**25**). Intermolecular coordination *via* the carboxylate group has been inferred from the temperature dependence of the Mössbauer spectral area [$a = 1.335\ K^{-1}$; cf. $(Ph_3Sn)_2$Cyst above)][107].

A unique series of chlorodialkyltin amino acid derivatives has been synthesized according to equation 21. In the cysteine series ($R^1 = H$), the amine hydrochloride is used directly. For penicillamine ($R^1 = Me$), dilute acid is added to maintain the pH of the reaction at 3.6–3.8[108]. Known compounds and selected spectral data are given in

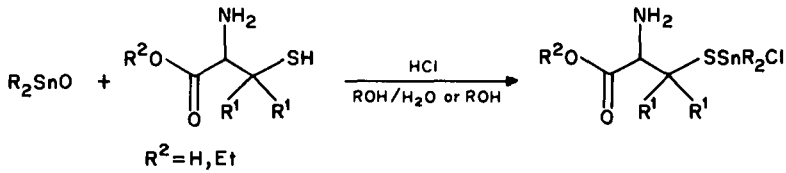


(24)

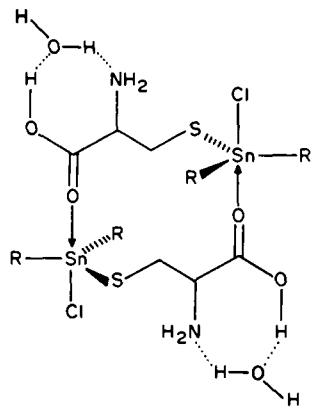


(25)

Table 6. On the basis of these data, compounds containing free carboxylic acid groups are either zweitterions, $ClR_2SnSCH_2CH(NH_3^+)CO_2^-$, or, on the basis of ditin fragments in the relevant mass spectra, dimers (**26**), both structures containing five-coordinated tin[106,108]. A similar structural ambiguity arises from the spectral data for the ethylcysteinate derivatives, between *S*-,*N*-chelated monomers and *S*-,*N*-bridged dimers, the latter again based on mass spectral data[108]. The former structure has been confirmed crystallographically for $ClMe_2SnSCH_2CH(NH_2)CO_2Et$ (Figure 8)[109], thus calling into question the interpretations of all the mass spectral data.



R^2=H,Et (21)



(26)

The chemistry of organotin cysteinates and penicillaminates in water is complex. Both cysteine and penicillamine displace one water molecule from the hydrated trimethyltin cation, and formation constants for the products measured as log $k = 4.67$ and 3.64, respectively[91,92].

Steric factors have been suggested as lowering the stability of the penicillamine compound[92]. The nature of the reaction product in equation 22 is pH dependent, and

TABLE 6. Chlorodialkyltin cysteinates and penicillaminates[a]

Compound	M.p. (°C)	ν(Sn—S) (cm^{-1})	$^2J(^{119}Sn, ^1H)$ (Hz)	$^1J(^{119}Sn, ^{13}C)$ (Hz)	qs[b] (mms^{-1})
L = $SCH_2CH(NH_2)COOH$:					
$ClMe_2SnL \cdot H_2O$	>156(s)	390	80.1		3.26[c]
$ClBu_2SnL \cdot H_2O$	90–92				3.15[c]
L = $SCH_2CH(NH_2)COOEt$:					
$ClMe_2SnL$	93–96	392	72.0	581.1	2.84[c]
$ClBu_2SnL$				539.6	
L = $SC(Me)CH(NH_2)COOH$:					
$ClMe_2SnL$	140(d)	412	79.1	600.6	3.16[c]
$ClBu_2SnL \cdot H_2O$	Oil	410			

[a]Data taken from Ref. 108 unless indicated otherwise.
[b]Mössbauer quadrupole splitting.
[c]From Ref. 106.

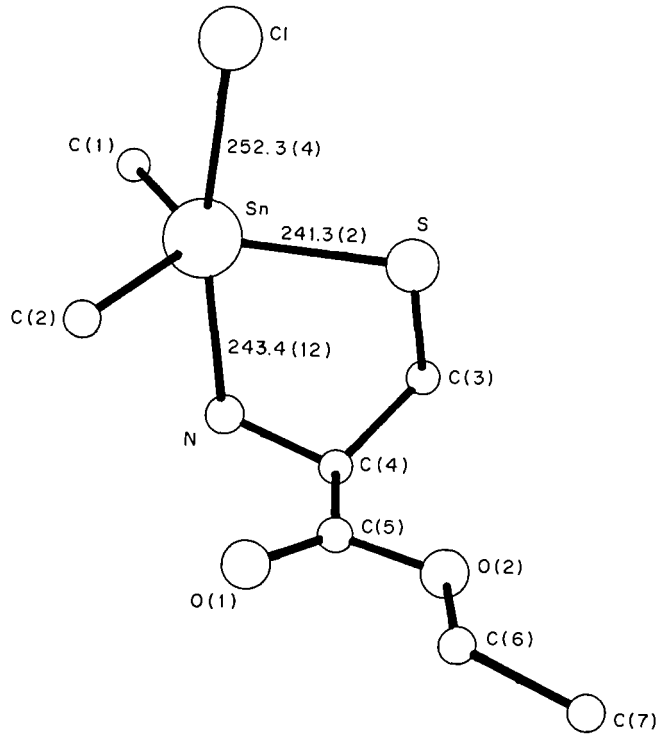
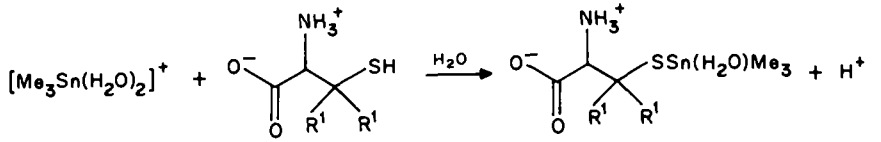


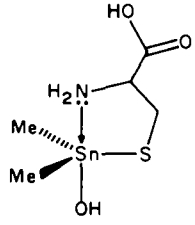
FIGURE 8. Structure of ethyl-L-cysteinato-*S*,*N*-(chlorodimethyl)-stannate(IV). Adapted by permission of Elsevier Sequoia from G. Domazetis *et al.*, *Inorg. Chim. Acta*, **34**, L247 (1978)

a species distribution diagram for trimethyltin in the presence of cysteine is shown in Figure 9. At increasing pH, complex formation between the metal and cysteine competes well with tin hydrolysis[92].



(22)

Barbieri[110] has studied the aqueous chemistry of dimethyltin cysteinate by analysing the Mössbauer spectra of frozen solutions. The environment about tin in water is similar to that in the solid state (**25**; $R^1 = H$) and is suggested to be as shown in **27**. At pH 7.4, this species, together with $Me_2Sn(OH)GlyGly$ and $Me_2Sn(OH)_2$·hepes (hepes = *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulphonic acid, an *N*-donor buffer), all react with cysteine to yield $Me_2Sn(Cyst)_2$[110].



(27)

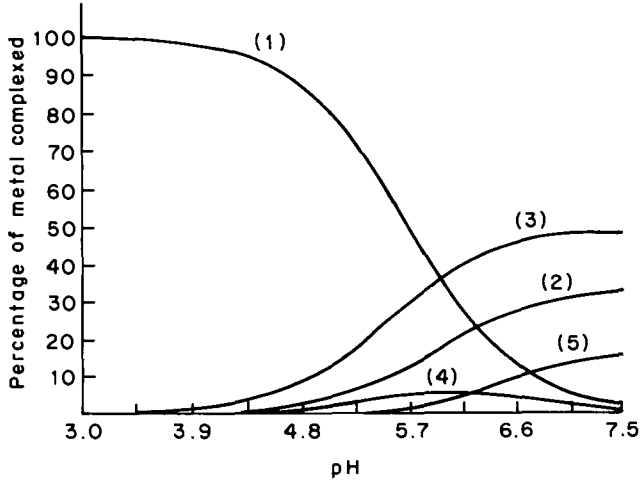
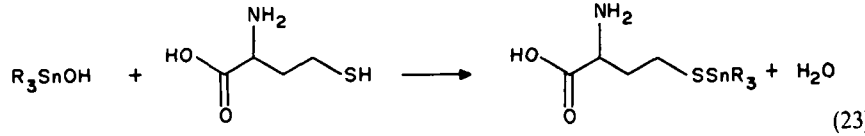


FIGURE 9. Computer-simulated distribution of species present in aqueous solutions of $[Me_3Sn(H_2O)_2]^+$(M) and both cysteine (H_2Cyst) and histidine (HHist), with pH. (1) M; (2) [M(OH)]; (3) [M(HCyst)]; (4) $[M(HHist)]^+$; (5) [M(Hist)]. Reproduced by permission of the Royal Society of Chemistry from Reference 92

Several inorganic tin compounds containing *S*-amino acids are known[111], and the structure of $Cl_2Sn[SCH_2CH(NH_2)CO_2Me]_2$ has been determined by diffraction methods[112].

Four triorganotin derivatives of homocysteine (R = Bu, c-Hex, Neo, Ph) have been prepared. The products precipitate from aqueous, alcoholic mixtures of organotin hydroxide or oxide and the acid (equation 23) and are spectroscopically and structurally similar to the analogous cysteine derivatives (see above)[98].



(23)

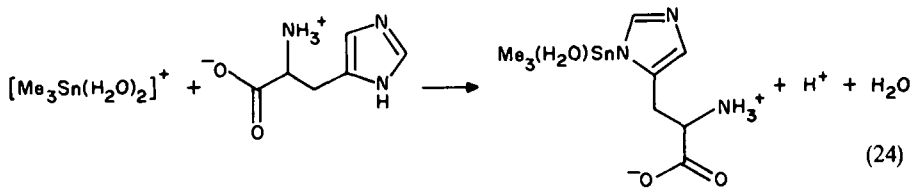
In organotin derivatives of methionine, the preferred Sn—S linkage is precluded and the organometal moiety bonds *via* the carboxylate group. The product formulated as Ph_3SnMet has been analysed by Mössbauer spectroscopy and found to exist primarily as monomers (**16**; $R^1 = CH_2CH_2SMe$; $R^2 = H$; $qs = 1.35\,mm\,s^{-1}$, $a = 2.20\,K^{-1}$) with minor amounts of a polymeric material ($qs = 2.84\,mm\,s^{-1}$, $a = 1.90\,K^{-1}$) which may have either *N*-(cf. Figure 7) or *O*-bridged structures (**13**; $R^1 = CH_2CH_2SMe$; $R^2 = H$)[100]. When Ph_3SnMet is prepared in the presence of excess methionine, $Ph_3SnMet{\cdot}HMet$ results. This is structurally similar to the major, monomeric form of Ph_3SnMet ($qs = 1.59\,mm\,s^{-1}$, $a = 2.20\,K^{-1}$), with an additional molecule of methionine hydrogen bonded within the lattice[100].

Organotin derivatives of *N*-acetylmethionine are known (R = Me[90], Bu[84], Ph[90]) and adopt an amide-bridged structure (**14**; $R^1 = CH_2CH_2SMe$; $R^2 = Me$)[90].

7. *Histidine and tryptophan*

Surprisingly little work has been carried out on organotin derivatives of amino acids containing *N*-heterocycles bonded to the α-carbon, particularly in view of the role of proteinaceous histidine in binding triorganotins (see Section V.D.1). Attempts to prepare histidine derivatives by the conventional routes (e.g. equations 12–14) in organic solvents have not been reported, although such reactions are mentioned for tryptophan[84]. Physical data for and characterization of these latter compounds are still lacking.

In aqueous solution, the hydrated trimethyltin cation binds histidine through the secondary amino nitrogen with the exocyclic NH_2 group remaining protonated (equation 24). The resulting complex is weaker (log $k = 1.76$) than the corresponding cysteine complex, which dominates in aqueous solutions of trimethyltin and these amino acids[91,92] (Figure 9). Tin(II) histidine has been prepared and is a weakly associated solid[100].



(24)

8. *Aminobutyric acid*

Three organotin esters of α-aminobutyric acid are known (Table 7), all of which have

TABLE 7. Triorganotin α-aminobutyrates[a]

	M.p. (°C)	$\nu_a(CO_2)$ (cm^{-1})	qs ($mm\,s^{-1}$)[b]	Ref.
$L = O_2CCH(NH_2)Et$:				
Me_3SnL	105–108	1631	3.17	85
Bu_3SnL	110			84
$(c\text{-Hex})_3SnL$	131–133	1657	2.41	85

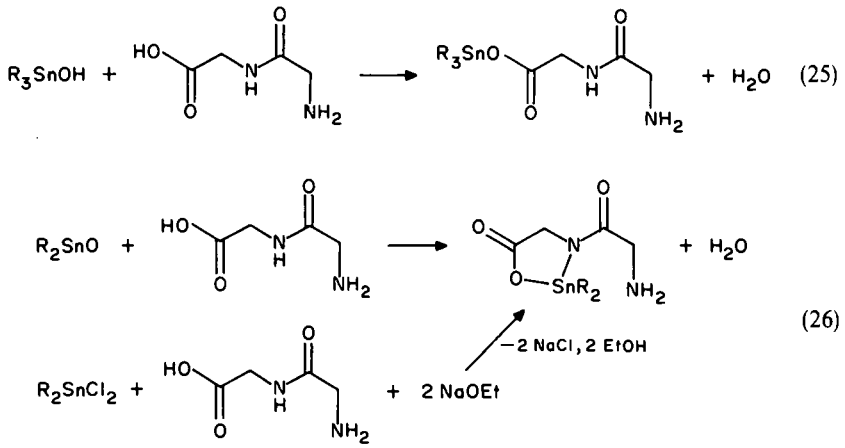
[a]All data refer to the solid state.
[b]Mössbauer quadrupole splitting.

been prepared by the method of equation 12[84,85]. Trimethyltin α-aminobutyrate is an amino-bridged polymer (cf. Figure 7), while steric factors enforce a tetrahedral, monomeric structure (**16**; $R^1 = Et$; $R^2 = H$) on the tricyclohexyltin analogue[85].

Trimethyltin compounds are known to inhibit the uptake of γ-aminobutyric acid, an effect antagonized to some extent by thiol groups, although this is probably *via* Na^+,K^+-ATPase inhibition rather than direct metal–acid interactions[113].

B. Peptides

The most thoroughly investigated of a limited range of di- and tri-peptides is glycylglycine ($H_2GlyGly$), and compounds incorporating this ligand with mono-, di-, and tri-organotins have been studied. Covalent compounds in which the dipeptide deprotonates on complexation are prepared *via* an organotin oxide, hydroxide, or halide (equations 25 and 26)[85,114,115].



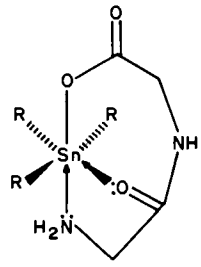
Of the two known triorganotin derivatives (Table 8), $Me_3Sn(HGlyGly)$ adopts an *N*-bridged polymeric structure akin to Me_3SnGly, although which of the two amino nitrogen atoms completes to coordination sphere about tin has not been specified[85]. $(c\text{-Hex})_3Sn(HGlyGly)$ does not appear to be polymeric, based on the tentative evidence of no observable room-temperature Mössbauer effect and a lack of Gol'danskii–Karyagin line asymmetry in the 78 K Mössbauer spectrum, both of which are normally (although not always) present for polymeric materials, e.g. $Me_3Sn(HGlyGly)$. In addition, when binding $(c\text{-Hex})_3Sn$ the dipeptide behaves as an *O*-,*O*-,*N*-tridentate ligand on the basis

TABLE 8. Organotin glycylglycinates[a]

Compound	M.p. (°C)	Infrared			Mössbauer	Ref.
		ν(N – H) (cm^{-1})	$\nu_a(CO_2)$ (cm^{-1})	ν(CO)amide (cm^{-1})	qs[b] ($mm\,s^{-1}$)	
$Me_3Sn(HGlyGly)$	171–172(d)	3280, 3180 3090	1635	1683	3.26	85
$(c\text{-Hex})_3Sn(HGlyGly)$	126–127(d)	3370sh, 3320	1639	1658	3.45	85
$Me_2SnGlyGly$	273(d)				3.29	114
$Bu_2SnGlyGly$	196–197				3.19	114
$Oct_2SnGlyGly$	135–137				3.43	114
$Ph_2SnGlyGly$	289				−2.253	115, 117
$Me_2SnCl_2{\cdot}H_2GlyGly$		3275, 3165	1745	1678	3.58	118
$Bu_2SnCl_2{\cdot}H_2GlyGly$	39	3340, 3230	1740	1678	3.71	118
$Oct_2SnCl_2{\cdot}H_2GlyGly$	91	3335, 3210	1720	1678	3.82	118
$Ph_2SnCl_2{\cdot}H_2GlyGly$		3340, 3230	1740	1678	1.80	118
$BuSnCl_3{\cdot}H_2GlyGly$		3340, 3200	1738	1678	2.06	118
$OctSnCl_3{\cdot}H_2GlyGly$		3320, 3180	1732	1678	2.18	118
$PhSnCl_3{\cdot}H_2GlyGly$		3360, 3180	1730	1678	2.18	118

[a]Data refer to the solid state.
[b]Mössbauer quadrupole splitting.

of i.r. data. A six-coordinated *mer*-R_3SnO_2N stereochemistry (**28**; R = c-Hex) about tin has therefore been proposed for $(c\text{-Hex})_3Sn(HGlyGly)$ ($qs = 3.45\,mm\,s^{-1}$)[85], and although six-coordinate triorganotin compounds are rare[58,116] similar dipeptide chelation is now known to occur in $R_2SnGlyGly$ systems (see below)[115].



(28)

$Ph_2SnGlyGly$ is trigonal bipyramidal in structure (Figure 10) with tridentate *O,O*-,*N*-chelation of two axial and one equatorial sites by the dipeptide[115]. The structure has been analysed in detail by point-charge simulations of Mössbauer qs data and, by comparison of Mössbauer data, the same structure has been assigned to other $R_2SnGlyGly$ species (R = Me, Bu, Oct)[117].

Simple Lewis acid–base adducts are formed when equimolar amounts of mono- or di-organotin chlorides are mixed with $H_2GlyGly$ in methanol (equation 27).

$$R_nSnCl_{4-n} + H_2GlyGly \longrightarrow R_nSnCl_{4-n}{\cdot}H_2GlyGly \quad (27)$$
$$(n = 1,2)$$

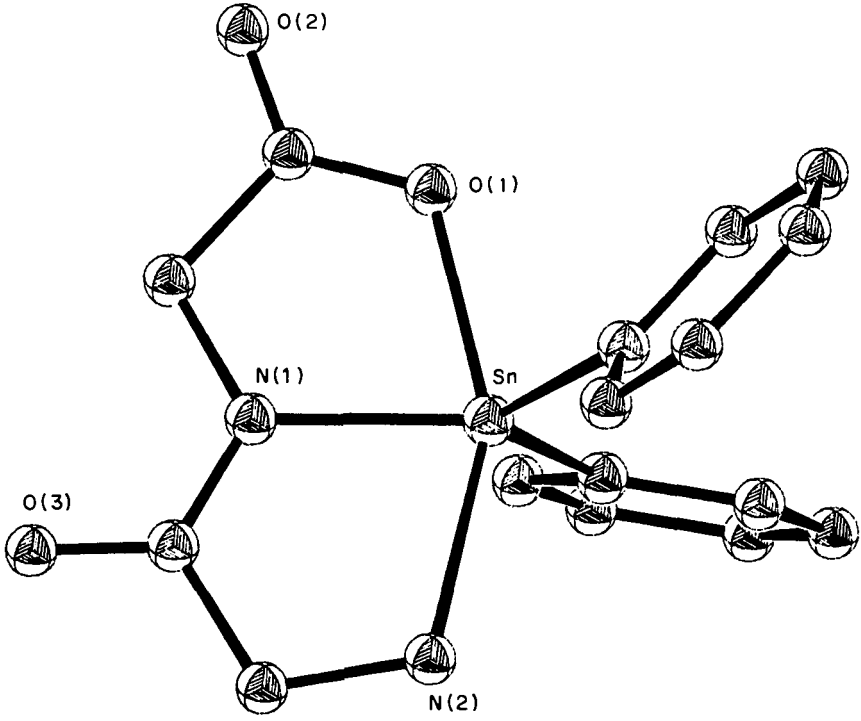


FIGURE 10. Structure of diphenyltin glycylglycinate. Adapted by permission of VEB J. A. Barth Verlag from Reference 115

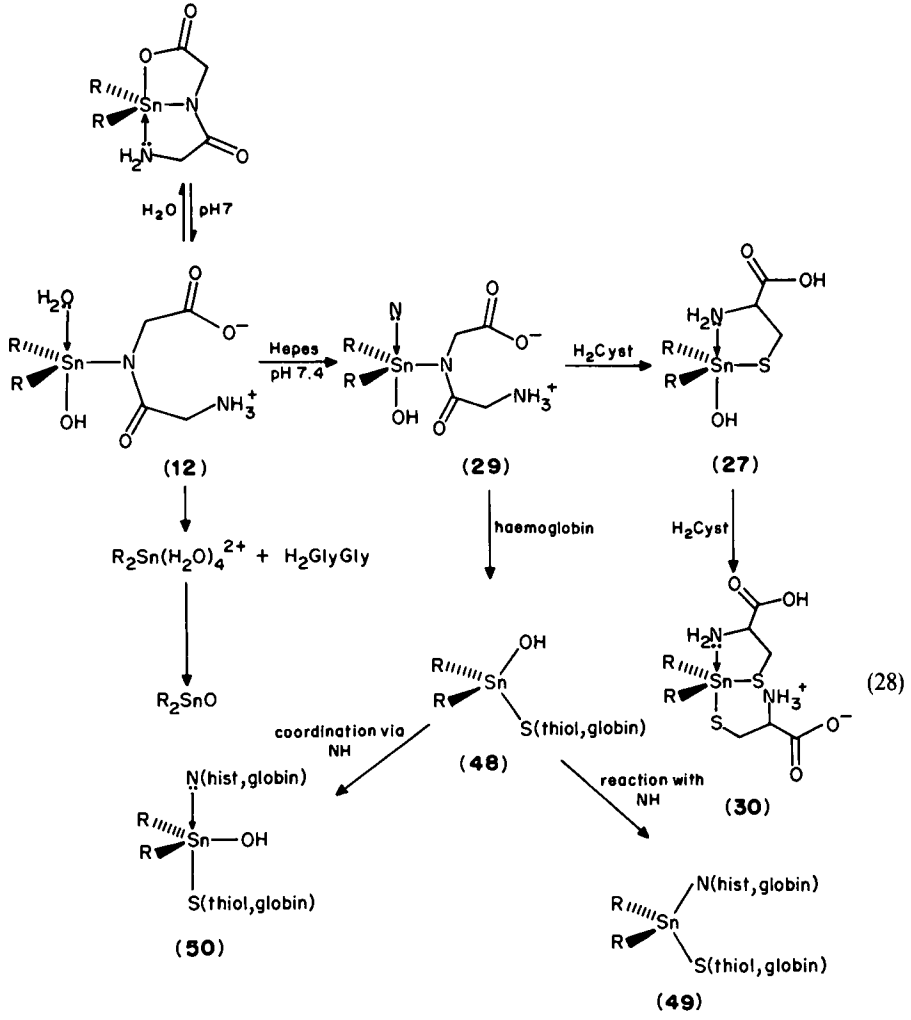
In the solid state, all of these compounds are assigned a five-coordinated tin, with the dipeptide acting as a monodentate ligand through the amino nitrogen. The carboxylic acid is un-ionized and hydrogen bonded to the amine groups leading to a lattice strengthening ($a = 1.41\,K^{-1}$). The thermal decomposition of this series of compounds has been studied, but no discernible trends could be found for the $R_2SnCl_2{\cdot}H_2GlyGly$ series, while the decomposition of $RSnCl_3{\cdot}H_2GlyGly$ is complex and multi-stage[118]. Tin(II) derivatives of glycylglycine are known[119].

Aqueous solutions of $Me_3SnGlyGly$ have been extensively studied by NMR (^1H, ^{13}C, ^{119}Sn), Mössbauer and i.r. spectroscopy and conductivity measurements. All point to an equilibrium of the solute with a partially hydrolysed product, in which the dipeptide remains bonded to the tin *via* the peptide nitrogen (**12**, equation 28; R = Me). $(Me_2SnO)_n$ slowly precipitates from these solutions, presumably by way of the hydrated cation $[Me_2Sn(H_2O)_4^{2+}]$[68]. Mössbauer studies of frozen, aqueous solutions of $Me_2SnGlyGly$ under different conditions are given in Table 9, and their interpretations, based on a point-charge analysis of qs data, are shown in equation 28. The partially hydrolysed species **12** will lose its weakly held water of solvation to stronger *N*-donors, e.g. hepes buffer (**29**). This in turn will react with cysteine, as a model for proteinaceous cysteine, to yield either 1:1 (**27**) or 1:2 (**30**) complexes of trigonal bipyramidal structure, although within the limits of the point-charge approach it is difficult to distinguish closely related species, e.g. *N*-donation from cysteine or hepes[110].

TABLE 9. Mössbauer data for aqueous solutions of $Me_2SnGlyGly$[a]

Solute	Conditions/reagent	Product	is[b] ($mm\,s^{-1}$)	qs[b] ($mm\,s^{-1}$)	Ref.
$Me_2SnGlyGly$	Solid	—	1.26	3.29	114
$Me_2SnGlyGly$	H_2O, Klucel[c]	**12**	1.26	3.38	110
	H_2O, hepes[d], pH ≈ 7	$Me_2Sn(OH)GlyGly$·hepes	1.16	3.02	110
	H_2O, H_2Cyst, pH ≈ 7	$Me_2Sn(OH)Cyst$	1.23	2.91	110
	H_2O, excess H_2Cyst, pH ≈ 7	$Me_2Sn(Cyst)_2$	1.27	2.27	110

[a]Frozen solutions (78 K) unless indicated otherwise.
[b]Mössbauer: is = isomer shift; qs = quadrupole splitting.
[c]2-Hydroxypropylcellulose.
[d]*N*-2-Hydroxyethylpiperazine-*N'*-2-ethanesulphonic acid.



(28)

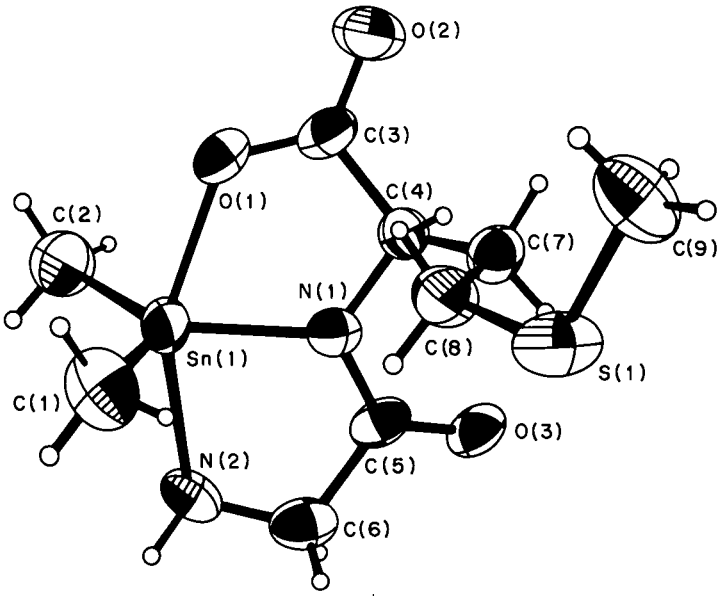


FIGURE 11. Structure of dimethyltin glycylmethionate. Reproduced by permission of the International Union of Crystallography from Reference 120

Aqueous solutions of $Me_2SnCl_2 \cdot H_2GlyGly$ are stable, and are less acidic (0.2 M solution, pH 4.08) than a simple mixture of Me_2SnCl_2 and $H_2GlyGly$ (pH 2.87). ^1H n.m.r. data suggest that the adduct is in equilibrium with its dissociated components[118].

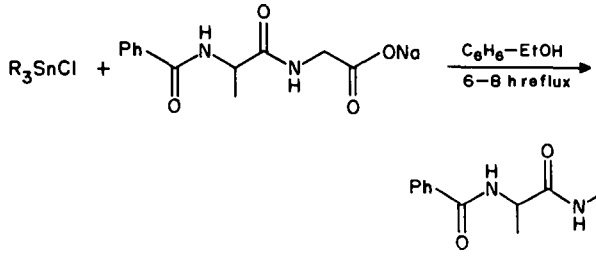
The structure of dimethyltin glycylmethionate has been determined by X-ray crystallography (Figure 11)[20] and is isostructural with $Ph_2SnGlyGly$[115]. Within a *cis*-R_2SnONN coordination sphere about tin, the < O(1)—Sn—N(2) in both compounds is identical (Table 10). In $Me_2SnGlyMet$, the $Sn—N(1)_{peptide}$ bond is very strong, and is the shortest Sn—N bond (207.1 pm) yet recorded. It is noteworty that it is the analogous bond in $Me_2SnGlyGly$ which resists hydrolytic cleavage under conditions where the axial Sn—O, $Sn—N_{amine}$ bonds are broken (see above[68,110]).

Triorganotin derivatives of *N*-benzoylalanylglycine have been synthesized (equation 29).

TABLE 10. Comparative crystallographic data (pm, °) for organotin amino acids and peptides

Compound	Sn—O	Sn—N(pep)	$Sn—NH_2$	< O—Sn—NH_2	N(2)···O(2)[a]	N(2)···O(3)[a]	Ref.
$Me_2SnGlyMet$	216.1(4)	207.1(4)	224.9(4)	153.0(2)	288.1(6)	286.3(6)	120
$Ph_2SnGlyGly$	215.7(8)	208.2(8)	227.3(9)	153.2(3)	275(1)	281(1)	115
Me_3SnGly	221(1)		246(2)[b]	169.2(6)	286(2)		91
$ClMe_2Sn$(ethylCyst)	241.3(3)[c]		243(1)	270[d]			109

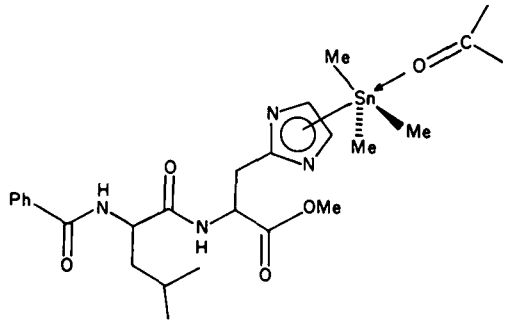
[a]Intermolecular hydrogen bonds; numbering scheme as in Figures 10 and 11.
[b]Intermolecular bridging interaction.
[c]Sn—S bond.
[d]Intramolecular hydrogen bond.



(29)

Spectroscopic evidence (Table 11) specify a four-coordinated, tetrahedral geometry in non-coordinating solvents [**16**; R = Me, Pr, Bu, c-Hex, Ph; R^1 = H; R^2 = COCH(Me)NHCOPh] while in the solid state, weak bridging *via* the amide oxygen produces a polymeric structure with a distorted *trans*-R_3SnO_2 stereochemistry at tin [e.g. **14**; R^1 = H; R^2 = CH(Me)NHC(O)Ph], although which of the two available amide oxygens is utilized remains unspecified[97].

The closest approach to modelling organotin–protein interactions using representative peptide fragments has been made by and Sharpe[121], who investigated the trimethyltin derivatives of methyl *N*-benzoyl-*l*-leucyl-*l*-histidine (**31**) and methyl *N*-benzoyl-*l*-histidyl-



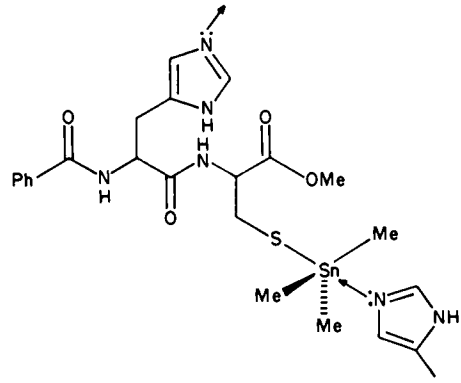
(**31**)

TABLE 11. Spectroscopic data for triorganotin *N*-benzoyl-DL-alanylglycines[97]

R[a]	ν(N—H) (cm^{-1})	$\nu_a(CO_2)$ (cm^{-1})	ν(CO)amide (cm^{-1})	$\delta^{119}Sn$ (ppm)[b]	$^1J(^{119}Sn, ^{13}C)$ (Hz)
Me	3419, 3288 (3430)[c]	1647 (1646)[c]	1639, 1616 (1646)[c]	147.4	401.5
Pr	3360	1651	1610–1640	127.4	351.6
Bu	3300	1655	1610–1640	129.0	349.4
c-Hex	3300	1655	1620–1650		
Ph	3300 (3430)[c]	1659 (1649)[c]	1650, 1606 (1649)[c]	−58.6[d]	832.4

[a]See equation 29.
[b]ppm with respect to Me_4Sn.
[c]Solution state ($CHCl_3$) values in parentheses.
[d]In hmpa; a solvent molecule coordinates the tin, increasing its coordination number to five.

l-cysteinate (**32**) as models for the high- (histidine only) and low-affinity (histidine and cysteine) sites of proteins (see Section V.D.1), in which terminal blocking at both ends of the dipeptide mimics the continuing protein chain.



(32)

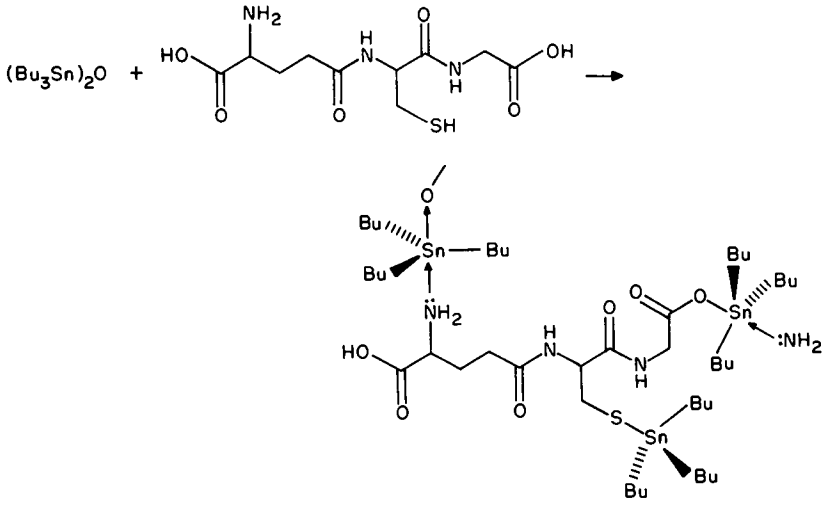
In the solid state **31** is a weakly polymeric material ($qs = 3.16\,mm\,s^{-1}$, $a = 1.91\,K^{-1}$) with bridging from the oxygen of a terminal amide group [cf. R_3Sn(*N*-benzoylAlaGly) above], and which incorporates a distorted *trans*-R_3SnNO trigonal bipyramidal arrangement of ligands about tin. In methanol-d_4, the polymer chain is disrupted, but solvent coordination maintains a coordination number of five at tin [$^1J(^{119}Sn, ^{13}C) = 493.1$ Hz]. Both *cis* and *trans* isomers arise from restricted rotation about the amide and/or peptide bonds, and the tin is bonded to N(1) of the imidazole ring. In CH_2Cl_2 solutions, only the *trans* conformer is observed, and a five-coordinated tin [$^1J(^{119}Sn, ^{13}C = 475$ Hz; $^2J(^{119}Sn, ^1H) = 63.9$ Hz] is now maintained by a 'head-to-tail' dimerization, in which the triorganotin is bonded to the amide carbonyl and one of the imidazole nitrogens.

Compound **32** is also five coordinate at tin in the solid state, but the trigonal bipyramid is more regular than in **31**, with a planar C_3Sn unit ($qs = 3.35\,mm\,s^{-1}$) and in a more rigid polymeric array ($a = 1.69\,K^{-1}$). Mass spectral fragments imply that the S (cysteine) and N (imidazole) are *trans*-axially bonded to tin[121].

The only organotin–tripeptide system studied centres on glutathione (γ-L-glutamy-L-cysteinylglycine; H_2Glut), an intracellular peptide present in most, if not all, cells. $(Bu_3Sn)_2O$ and glutathione react to produce $(Bu_3Sn)_2Glut$ (equation 30) in which the two tin atoms occupy clearly distinguishable sites. One site is *S*-bonded and of tetrahedral geometry ($qs = 1.76\,mm\,s^{-1}$), the other is a five-coordinate glycinate ester ($qs = 3.43\,mm\,s^{-1}$) in which the additional coordination site is occupied by an intermolecular bridge from the glutamic acid amine group of an adjacent molecule[105,106]. The corresponding $(Ph_3Sn)_2Glut$ separates as a monohydrate, again with two metal atoms per tripeptide ($qs = 2.20, 2.29\,mm\,s^{-1}$). These have been assigned to a hydrated, *S*-bound tin and a *cis*-*S*,*N*-glycinate ester[106]. Impure $(Me_3Sn)_2Glut$ has also been reported[104]. The formation constant for $Me_3Sn(HGlut)$ in aqueous solution has been measured as $\log k = 4.39$[92].

C. Nucleotides, Nucleosides, and Their Components

Interest in the interactions between organotins and nucleic acids stems largely from the anti-tumour activity of diorganotin compounds (see Section VI.D) and their relationship, in both structural and chemical terms, to active square-planar platinum complexes. In

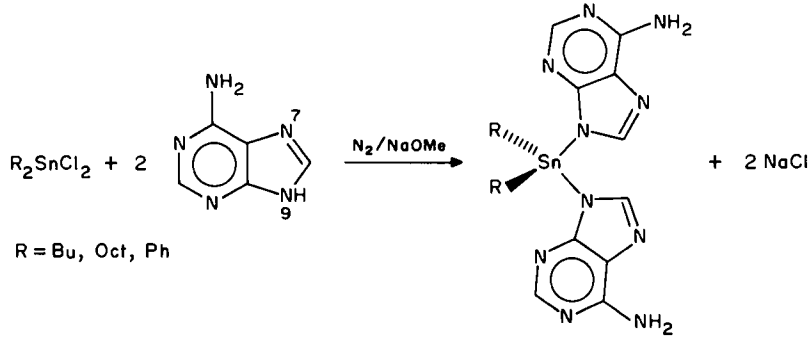


(30)

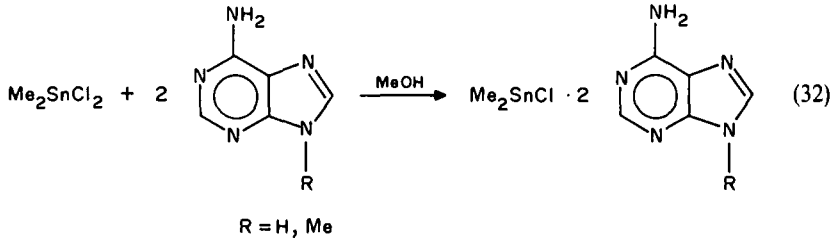
addition to model compounds in which tin is bonded to a nucleotide or nucleoside, several groups have synthesized organotin derivatives of the individual nucleotide components—purine and pyrimidine bases, carbohydrates (particularly pentoses), and phosphoric acids. These latter two areas cover significantly large tracts of organotin chemistry in their own right, and will only be superficially addressed here. These brief overviews should, however, provide the interested reader with an entré into each area. The chemistry of organotin carbohydrates has been particularly active in recent years owing to the synthetic utility of diorganotins as protecting groups for ring substituents, but is also of considerable relevance to bio-organotin chemistry, not only in terms of anti-tumour activity but also from the organotin–cellulose chemistry central to the applications of organotin wood preservatives (see Section VI.B).

1. Purine and pyrimidine bases

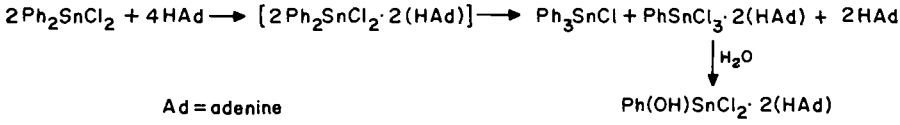
Diorganotin bis(adenine) derivatives have been synthesized using the adeninato nucleophile (equation 31). Analysis of Mössbauer qs data (1.91–2.21 mm s^{-1}) is consistent with a tetrahedral geometry at tin, although a *cis*-R_2SnN_4 configuration cannot be excluded[122]. When adenine and 9-methyladenine are refluxed in methanol with



(31)



(32)



(33)

Me_2SnCl_2, simple adducts result (equation 32). A similar reaction sequence involving Ph_2SnCl_2 leads, *via* disproportionation and aerial hydrolysis, to a monoorganotin adduct (equation 33).

Under similar conditions, R_2SnCl_2 does not react with guanine, cytosine, thymine, uracil, or theopylline[123]. The products of reactions 31 and 33 have been formulated as octahedral complexes, with the bases coordinating in a monodentate fashion through N(9) (adenine) or N(7) (9-methyladenine). Crystallization of acetone solutions of Me_2SnCl_2 and purine leads to a product in which hydrated Me_2SnCl_2 is coordinated to four purine molecules *via* a network of hydrogen bonds (Figure 12)[124].

Reactions between organotins and 6-thiopurine (6-TPH_2), an anti-cancer antimetabolite, are more complex and temperature dependent. At 0 °C, Me_3SnOH or Bu_3SnOMe and 6-thiopurine yield an analytically pure product which Mössbauer spectroscopy shows to be a structural mix of polymeric *N,S*- (**33**) or *N,N*-bound tin (**34**), corresponding to thiol and thione ligand tautomers, respectively.

At >0 °C, only the *N,N*-bonded product is observed. Similar reactions involving Ph_3SnOH yield only one product, which has been formulated as $(Ph_3Sn)_3$(6-TP)(6-TPH) and which contains both *N,N*- and *N,S*-linked tin in the same structure. Apparently, the triphenyltin complex is more resistant to thermal *S*-destannylation than the corresponding trialkyltin compounds[125,126]. Dibutyltin forms a six-coordinate complex with 6-TPH_2 in which the *S*-stannyl tautomer is stabilized by *N,S*-chelation (**35**)[125]. Tin(II) derivatives of adenine are also known[127].

2. *Carbohydrates*

Di- and tri-organotin derivatives of carbohydrates have been widely employed in recent years because of the regioselective directing power of the metal towards further reactivity of the sugar substrate. Extended reference to such applications, which are too numerous to cover here, can be found in the papers cited below and several recent reviews[128–130] and books[131]. With regard to bio-organotin chemistry, that is interactions with nucleotides and cellulose, the following questions need to be addressed: under what conditions do organotins react with sugars and at what positions on the carbohydrate, what are the stabilities of the resulting species, and can this be related to their structural chemistry? These topics are briefly considered below.

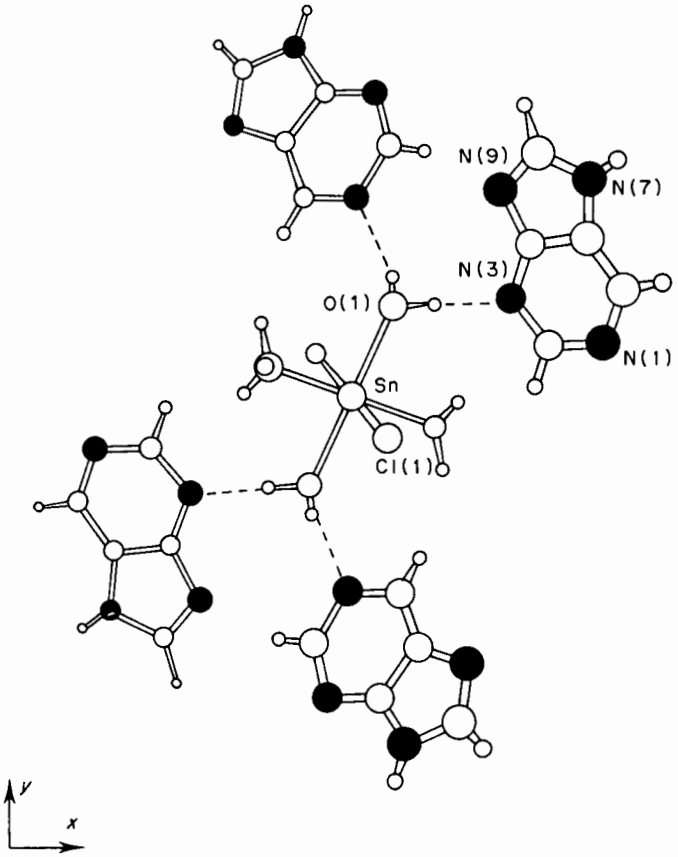
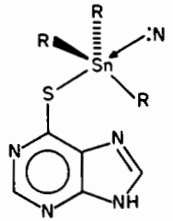
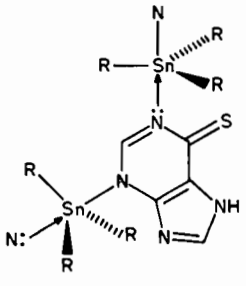


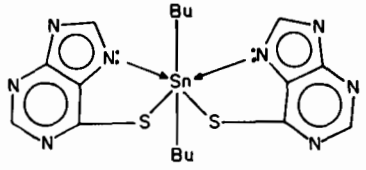
FIGURE 12. Structure of $Me_2SnCl_2 \cdot 2H_2O \cdot 4C_5H_4N_4$. Reproduced by permission of the Royal Society of Chemistry from Reference 124



(33)

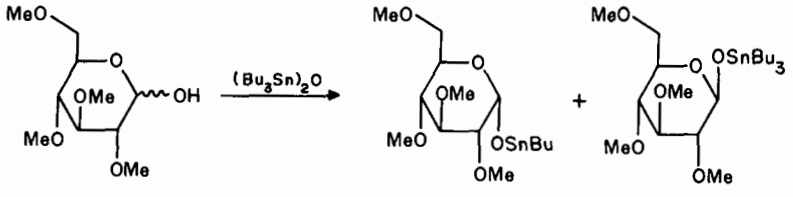


(34)

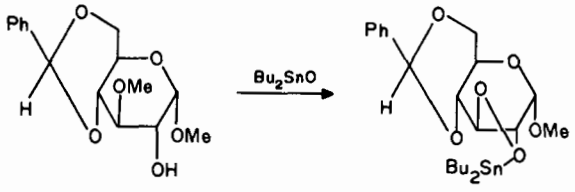


(35)

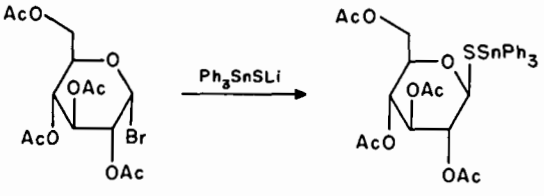
Organotin carbohydrates are simply synthesized by refluxing an organotin oxide or hydroxide with the appropriate sugar in toluene, e.g.[130] equations 34 and 35. Stable compounds containing Sn—S[132] or Sn—C[133,134] linkages between tin and the sugar are also known (equations 36 and 37).



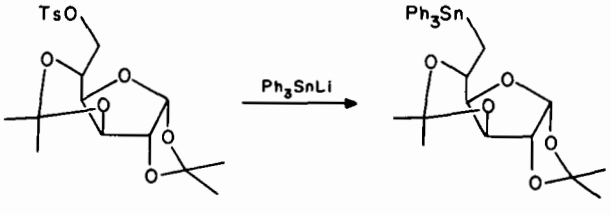
(34)



(35)



(36)

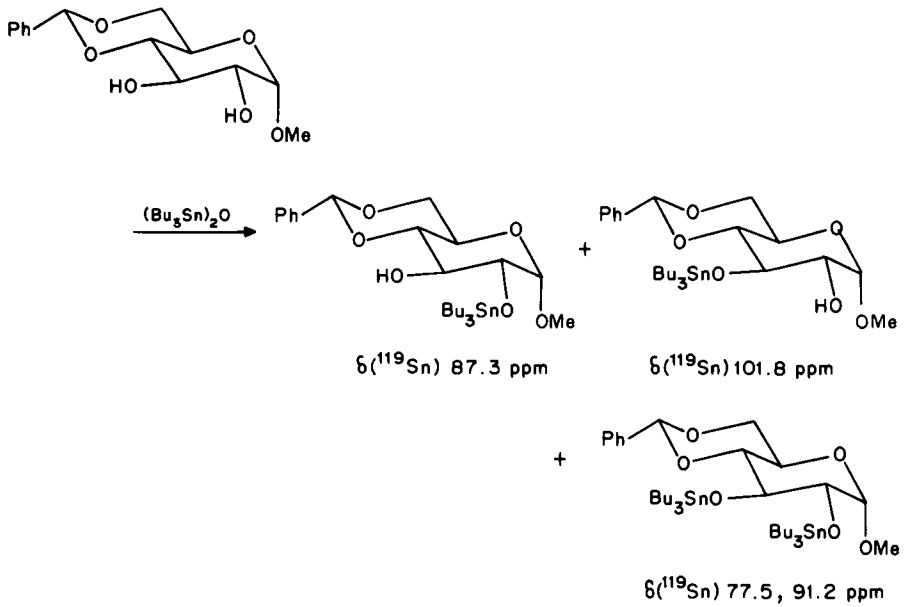


(37)

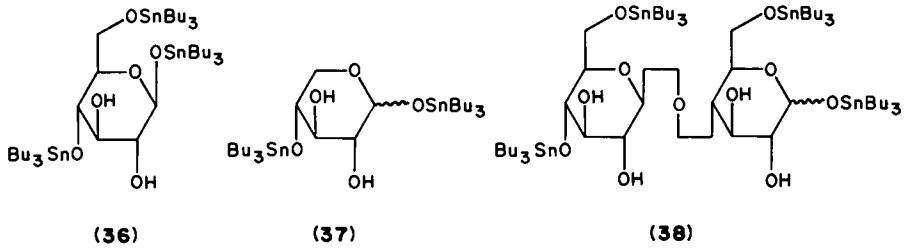
Where more than one unprotected hydroxy group is available for reaction, both partly or fully stannylated products are possible[135–138]. ^{13}C and ^{119}Sn n.m.r. have been used to compare the site selectivity of *O*-trialkylstannylation of polyhydroxy sugars. For example,

methyl-4,6-*O*-benzylidene-α-D-glucopyranoside reacts with $(Bu_3Sn)_2O$ in toluene over a 24 h period to yield O(2)-, O(3)-, and O(2,3)-substituted products (equation 38). However, whereas substitution at O(3) is facile, very little substitution takes place primarily at O(2). The reactivity at O(2) does increase significantly after stannylation at O(3), and the O(2,3)-disubstituted product is as easily formed as the monosubstituted O(3) precursor[136].

Similarly, glucose, xylose, and cellobiose react with $(Bu_3Sn)_2O$ to yield tri- (**36**), di- (**37**) and tetra-substituted (**38**) products, respectively, although spectroscopic confirmation of product integrity is still awaited[139].

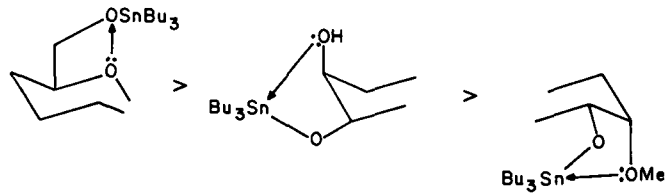


(38)



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

Recent work has defined the regioselectivity of tributylstannylation of sugars and has been related to the ease with which tin can coordinate a neighbouring oxygen atom. Thus, the C(6) position is most reactive, followed by secondary hydroxy groups, all of which are capable of coordinating tin by a second, *cis*-oxygen[140] (**39–41**). Triorganotin carbohydrates are distillable oils, which are rapidly hydrolysed on exposure to air, although the aerobic stability increases if free hydroxy groups are retained in the product[139].



(39) (40) (41)

The regioselectivity of hydroxy group reactivity towards diorganotin compounds is also dictated by the ability of the system to allow formation of additional O: → Sn bonds. Thus, two vicinal, secondary hydroxy groups in a *cis*-(axial, equatorial) relationship are most reactive, and another favourable combination is a secondary hydroxy group in conjunction with a *cis*-(axial) alkoxy moiety for further coordination. Least favoured are a pair of *trans*-(equatorial, equatorial) hydroxy groups[140], although the overall order of reactivity is partly dependent on the reaction conditions.

Diorganotin sugars are stable, crystalline solids. Structural analysis of R_2SnL (R = Me, Bu, Oct; L = erythrose, arabinose, ribose, fructose, sorbose, galactose, glucose, or rhamose) by Mössbauer spectroscopy (qs = 2.78–3.07 mm s^{-1}) has been interpreted in terms of a *cis*-R_2SnO_3 structure within a polymeric framework[141]. This arrangement has been confirmed crystallographically in the model compound $Bu_2Sn\overline{OCH_2CH_2O}$ (**42**; butyl groups above and below the plane of the molecule have been omitted for clarity)[142], but the glucose derivative (methyl-4,6-*O*-benzylidene-α-D-glucopyranoside; **43**) is only a dimer (Figure 13)[143] while the mannose analogue (methyl-4,6-*O*-benzylidene-α-D-mannopyranoside; **44**) is a pentamer in which the interior three tin atoms are octahedrally

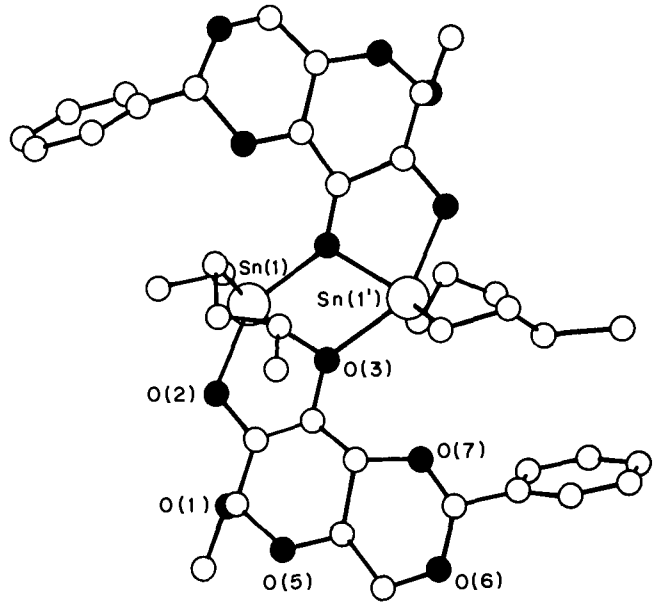
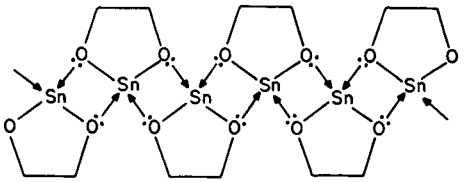
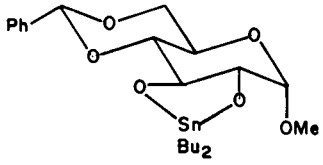


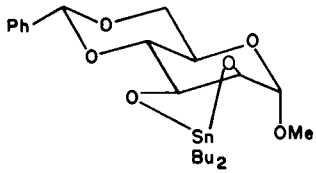
FIGURE 13. Structure of dimeric methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside. Reproduced by permission of Ganthier-Villars CNRS from Reference 143



(42)



(43)



(44)

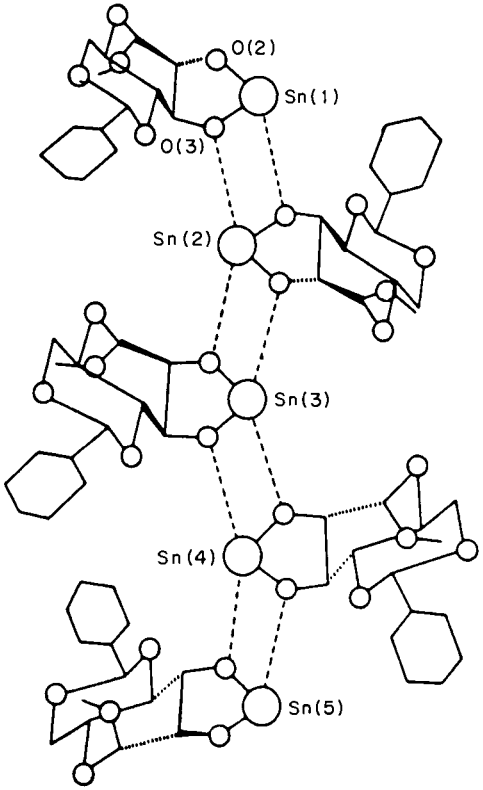
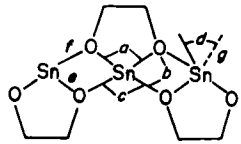


FIGURE 14. Diagramatic representation of the structure of pentameric methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside. Reproduced by permission of the South African Chemical Institute from Reference 144

TABLE 12. Crystallographic data for dibutyltin carbohydrates and related species



Bond length (Å) or angle (°)	Coordination of tin	43	44	42
Intramonomer	5	77(4), 82(4)	79.1(5), 80.0(7)	
O—Sn—O (*a*)	6		77.6(5)–78.3(5)	79.0(5)
Intermonomer	5–5	67(2), 70(2)		
O—Sn—O (*b*)	5–6		69.6(?), 70.6(?)	
	6–6		65.5(?)–69.2(?)	65.2(6), 66.8(6)
Intermonomer	6		142.0(?)–150.5(?)	149.0(6)
O—Sn—O (*c*)				
Exocyclic	5	126(2), 139(2)	124.2(8), 127.4(13)	
C—Sn—C (*d*)	6		134.7(9)–142.7(8)	138.6(6)
Intramonomer	5	2.13(8), 2.09(8)	2.02(4)–2.07(5)	
Sn—O (*e*)	6		2.06(5)–2.13(5)	1.98(1), 2.10(1)
Intermonomer	5	2.29(7), 2.17(7)	2.23(?)–2.27(?)	
Sn—O (*f*)	6		2.43(?)–2.60(?)	2.50(2), 2.52(1)
Exocyclic	5	2.23(4), 2.26(4)	2.04(3)–2.25(3)	2.13(2), 2.14(2)
Sn—C (*g*)	6		2.14(4)–2.20(7)	

coordinated and the two terminal metal atoms trigonal bipyramidal in coordination (Figure 14)[144]. Collected structural data are given in Table 12.

Thermal decomposition pathways for several diorganotin carbohydrates have been reported[141].

3. *Organotin phosphates*

Organotin esters of numerous phosphoric acids have been synthesized, including derivatives of the anions PO_4^{3-}[145,146], HPO_3^{2-}, FPO_3^{2-}, $H_2PO_2^{2-}$[145], $F_2PO_2^{2-}$[147], $PhPO_3^{2-}$[148,149], $PH(PhO)PO_2^{-}$[150], $(PhO)PO_3^{2-}$[151], $(PhO)_2PO_2^{-}$[151–153], $(R_2N)_2PO_2^{-}$[154], and $R_2PO_2^{-}$[155]. The unifying structural feature emerging from this collective is that the phosphorus acid behaves as a bridging ligand to produce polymeric organotin esters. This has been confirmed crystallographically for $(Me_2Sn)_3(PO_4)_2 \cdot 8H_2O$ (Figure 15)[146], $Me_3SnO_2P(Ph)(OH)$ (Figure 16)[149], and hexameric $Ph_3SnO_2P(OPh)_2$ (Figure 17)[156].

4. *Nucleotides and nucleosides*

A wide range of organotin nucleosides have been prepared (Table 13) from the reaction of the appropriate diorganotin oxide and nucleoside, usually in methanol (equation 39)[157–160]. In each case, the organotin binds *via* the 2′,3′-hydroxy groups and no interactions with the bases are evident from i.r. and n.m.r. spectroscopic data. Dimethyltin compounds are usually insoluble whereas other organotin nucleosides are soluble in polar, organic solvents. Structurally the compounds parallel simple diorganotin

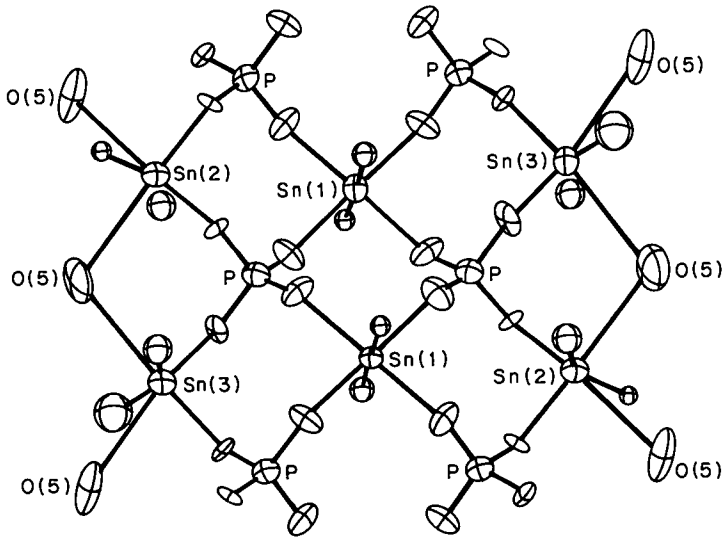


FIGURE 15. Structure of $(Me_2Sn)_3(PO_4)_2 \cdot 8H_2O$. Four of the water molecules of solvation are involved in hydrogen bonding to the phosphate groups and have been omitted for clarity. The remaining water molecules bond as two pairs to Sn(2) and Sn(3) and are indicated as O(5). Reproduced by permission of the American Chemical Society from Reference 146. Copyright (1977) American Chemical Society

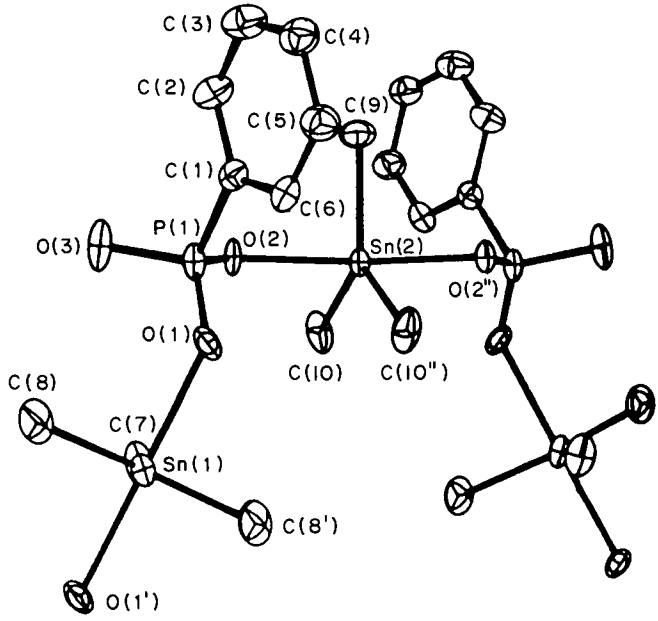


FIGURE 16. Asymmetric unit of α-(phenylphosphonato)trimethyltin. Primed and doubly primed atoms are related to unprimed atoms by the two-fold axes along Sn(1)—C(7) and Sn(2)—C(9), respectively. Reproduced by permission of the American Chemical Society from Reference 149. Copyright (1981) American Chemical Society

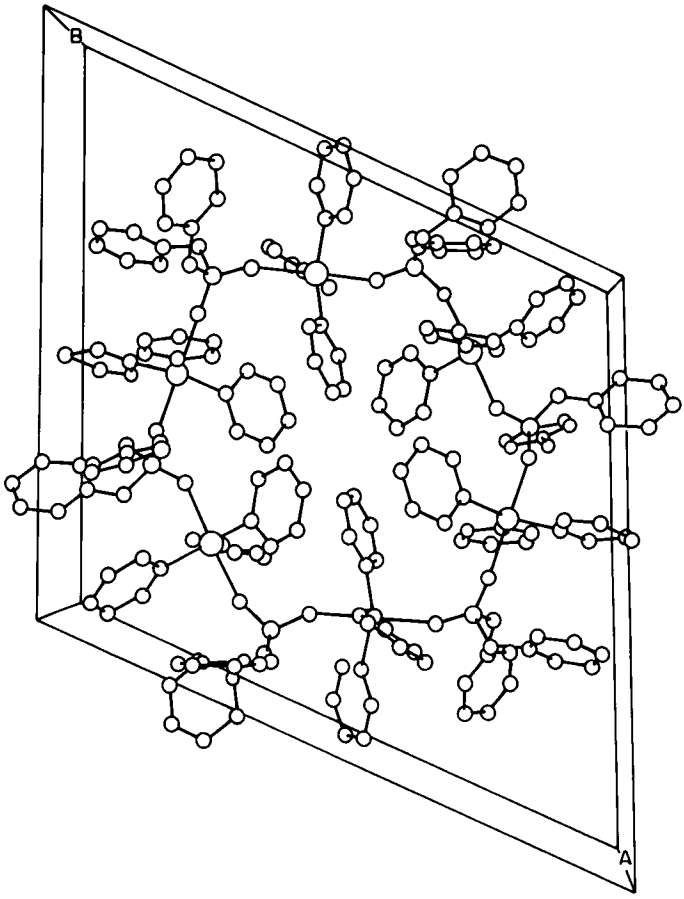
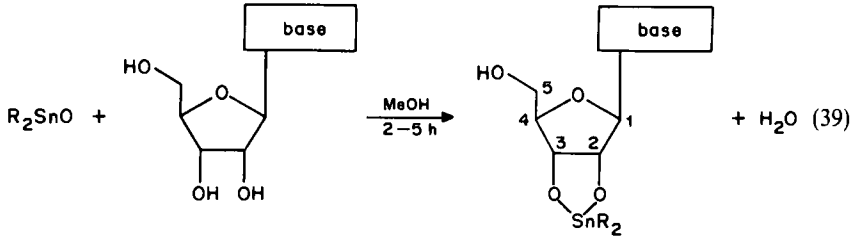
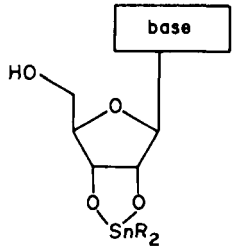


FIGURE 17. Unit call of hexameric (diphenylphosphato)triphenyltin. Reproduced by permission of the American Chemical Society from Reference 156. Copyright (1982) American Chemical Society



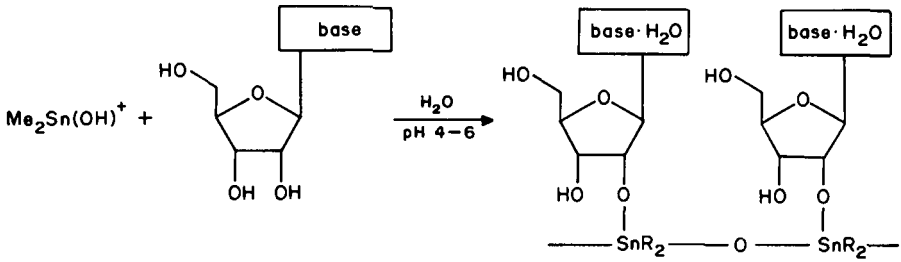
carbohydrates in having a *cis*-R_2SnO_3 coordination sphere about tin (qs = 2.97–3.24 mm s^{-1})[159] arising from intermolecular coordination of either the 2′ and 3′ oxygen to an adjacent tin centre (cf. Figures 13 and 14).

TABLE 13. Diorganotin nucleosides



Base	R	M.p. (°C)	is[a] (mm s^{-1})	qs[b] (mm s^{-1})	Ref.
Adenine	Me	268	1.15	3.12	158
	Bu	154–156	1.28	3.06	157, 159
	Oct	203–205	1.29	3.08	159
Guanine	Me	208(d)	1.15	3.09	159
	Bu	235(d)	1.27	3.12	159
	Oct	244–247	1.33	3.24	159
Hypoxanthine	Me	290(d)	1.14	3.06	159
	Bu	202–204	1.29	3.08	159
Cytosine[c]	Me	250(d)	1.17	3.05	159
	Bu	217–218			159
	Oct	220	1.26	2.97	159
Uracil	Me	275(d)	1.16	3.10	159
	Bu	233	1.29	3.02	157, 159
	Oct	226	1.29	3.08	159

[a]Mössbauer isomer shift.
[b]Mössbauer quadrupole splitting.
[c]An ethylphenylstannylene derivative has also been reported[160].

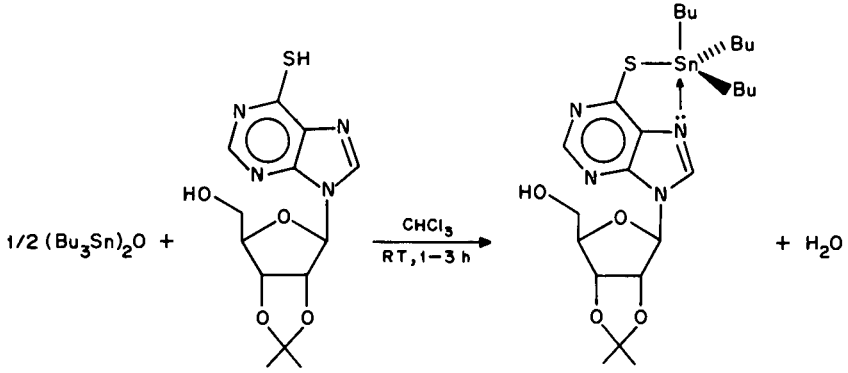


(40)

In aqueous solutions at pH 4–5, the reaction between Me_2SnCl_2 and either adenosine, guanosine, or inosine can be represented by equation 40. A polymeric structure is indicated by the low solubility of the compounds, and monodenate binding between tin and the ribose has been inferred from the disappearance of O(2′)—H but not O(3′)—H signals in the ^{1}H n.m.r. spectrum[161]. This study highlights the feasibility of organotin binding to RNA through the free ribose 2′-OH group, although in the case of DNA, which includes a deoxyribose moiety and in which the O(3′)- and O(5′)-hydroxy groups have condensed with phosphates, such a linkage is precluded.

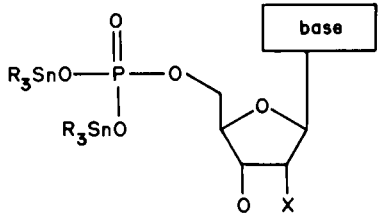
Adenosine forms neutral adducts of composition $Me_2SnCl_2 \cdot 2L$ and $PhSnCl_3 \cdot 2L$ (L = adenosine) in a parallel manner to adenine (equation 33), although the steric bulk of adenosine in comparison with its parent base inhibits hydrolysis of the $PhSnCl_3$ to which it is coordinated. Under similar conditions, no adducts are formed between organotin halides and either cytidine, thymidine, or uridine[123]. Only one triorganotin nucleoside is known (equation 41). The site of reaction is SH rather than OH (cf. cysteine, Section V.A.6) and the low-temperature preparation preserves the thiol over the thione tautomer (cf. reactions of 6-thiopurine, Section V.C.1)[162]. Tin(II) chloride adducts, $SnCl_2 \cdot L \cdot MeOH$ (L = adenosine, cytidine, and inosine) have been reported[127].

Known tri- and di-organotin nucleotide derivatives are listed in Tables 14 and 15,



(41)

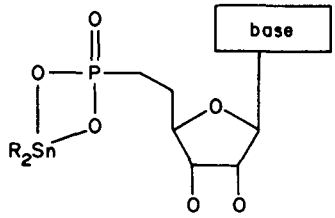
TABLE 14. Bis(triorganotin) nucleotides



Base	R	X	M.p. (°C)	is[a] (mm s^{-1})	qs[b] (mm s^{-1})	Ref.
Adenine	Me	OH		1.24	3.50	163
	Bu	OH	197–198			157
	Ph[c]	OH		1.17	2.89	163
Guanine	Me	OH		1.31	3.50	163
	Ph[d]	OH		1.23	3.08	163
Cytosine	Me	OH	>300(d)			157
	Bu	OH	163–166			157
	Bu	H	190–191			157

[a]Mössbauer isomer shift.
[b]Mössbauer quadrupole splitting.
[c]A complex of composition $(Ph_3Sn)_4AMP$, is = 1.16, qs = 2.85 mm s^{-1}, has also been reported[163].
[d]A complex of formula $(Ph_3Sn)_4GMP$, is = 1.20, qs = 2.87 mm s^{-1} has also been reported[163].

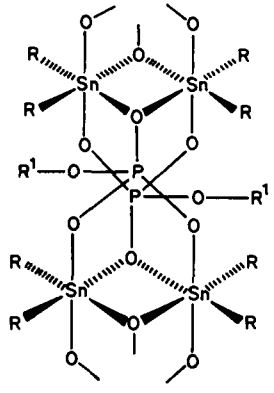
TABLE 15. Diorganotin nucleotides



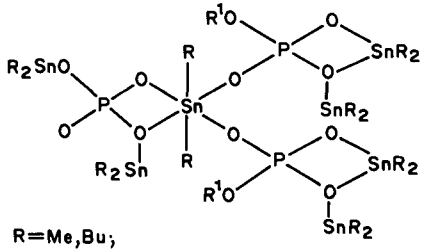
Base	R	is[a] ($mm\,s^{-1}$)	qs[b] ($mm\,s^{-1}$)	10^2a (K^{-1})	Ref.
Adenine	Me[c]	1.228	3.803	0.95	151
	Bu[c]	1.274	3.355	1.28	151
Guanine	Me	1.25	3.87		163
Uracil	Me	1.20	3.60		163
Hypoxanthine	Me	1.25	3.78		163
	Pr	1.24	3.33		163
	Bu	1.24	3.28		163
	Ph	1.00	2.90		163

[a]Mössbauer isomer shift.
[b]Mössbauer quadrupole splitting.
[c]Contain two molecules of H_2O as solvate.

respectively[151,157,163]. The diorganotin series involve phosphate-only bonded tin, and both the physical properties of the compounds (insolubility, etc.) and variable-temperature Mössbauer spectral data[151] indicate a polymeric system. Mössbauer qs data (2.90–3.80 $mm\,s^{-1}$) are significantly smaller than for the model systems $R_2Sn[O_2P(OPh)_2]_2$ (ca. 4.7 $mm\,s^{-1}$)[151,152] which are believed to be of *trans*-R_2SnO_4 stereochemistry. Data for the diorganotin nucleotides have thus been interpreted as resulting from a bending of the ⟨C—Sn—C away from 180° in a similar *trans*-R_2SnO_4 configuration, and both two (**45**) and three-dimensional (**46**) arrays have been postulated, both of which have precedents in related transition metal systems[151].



(45)



(46)

The phosphate residue is also the primary site for binding triorganotins[157,163], although the interactions between $[Me_3Sn(H_2O)_2]^+$ and either adenosine or inosine 5′-monophosphate in water are weak (log $k = 1.59$ and 2.52, respectively)[92]. The structure of the bis(triorganotin) nucleotides is postulated as *trans*-R_3SnL_2 on the basis of Mössbauer qs data, the unspecified ligands being O or heterocyclic N[163]. Similarly, nucleotides binding four triorganotin residues have been mentioned (Table 14), but the binding sites in addition to phosphate, presumably O(2′,3′) of the ribose unit, await clarification[163].

D. Macroscopic Assemblies

An understanding of the biochemical *modus operandi* of organotin compounds can only finally be achieved by studies of their interactions with relevant, macromolecular receptor substrates. The synthesis and structural characterization of model compounds are an integral part of this understanding, but can ultimately only be used as an indicator of the validity of a biochemical hypothesis. The interactions of organotins with cells and their components are complex, and no effort is made here to describe the biochemical methodology used to arrive at our current level of understanding. What are emphasized are the molecular interactions responsible for the biochemical activity of organotins—at least as far as our present knowledge permits—and a correlation of these with the model, purely chemical investigations already described. The gross biochemical effects of these interactions, in this instance, are of secondary importance and will only be alluded to where they provide a particular insight into bio-organotin chemistry at the molecular level. Any advances in our unravelling of these chemical interactions will undoubtedly benefit from a closer cooperation between chemists and biochemists, and this analysis is intended as a stimulus to bringing these disciplines together.

Surprisingly, organotins are known to bind to relatively few biochemical macromolecules, despite the fact that these species provide a large reaction surface abounding with a variety of functional groups. Some of the macromolecules which do not bind organotins are given in Table 16[164,165]. This in itself implies a high specificity for binding and as such suggests that only a relatively few binding sites need to be characterized. However, the situation is complicated by the fact that binding is not only a function of substrate, but also of the particular organotin, medium and conditions (reagent concentration, pH, complementary anions, etc.). Under judicious experimental conditions[166] one of the effects can be maximized at the expense of others, and these effects can be classified into two broad areas:

(i) In the absence of chloride ions, triorganotins inhibit oxidative phosphorylation in a specific rather than general manner, and in this respect are similar in behaviour to certain other ATP inhibitors such as the antibiotic oligomycin. Studies in this area have focused on identifying the binding site(s) on various proteins, from well

TABLE 16. Macromolecules which do not bind triethyltin

Guinea pig haemoglobin	Phosvitin
Horse haemoglobin	Clupeine
Rabbit haemoglobin	Salmine
Human haemoglobin	Cytochrome-c
Horse myoglobin	Bovine plasma albumin
Chymotrypsin	DNA
Bovine pancreatic ribonuclease	RNA
Glycogen	Dextran

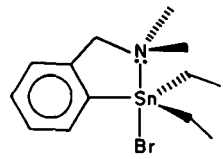
characterized systems such as cat and rat haemoglobin[110,166–175] to less well defined enzymes such as mitochondrial ATPase[176–180], glycolytic hexokinases[181–183], or one of the proteins of rat brain myelin[184,185] or guinea-pig liver supernatant[186].

(ii) When chloride anions are present, triorganotins mediate the exchange of this anion (and, indeed, others) with hydroxide ions across biological membranes[187–193]. Related to this process is the swelling of mitochondria in the presence of organotins[52,191] and identification of the positioning of the organotin transporter with respect to the membrane and its inner/outer aqueous environments[191,194].

Each of these two areas is considered in turn.

1. Proteins

Well characterized proteins such as rat and cat haemoglobins bind two moles of R_3Sn per mole of haemoglobin tetramer[166], and have been extensively studied as models for less well defined proteins, e.g. ATPase. Only *ca* 5% of the total membrane protein is responsible for binding *ca* 70% of the triorganotin, suggesting that the binding site is specific[186]. This binding site or sites has an affinity constant of $3.5 \times 10^4 - 2 \times 10^6\ mol^{-1}$, depending on the protein[167,168,186]. Evidence for the five-coordinate nature of tin at this site came initially from the fact that binding of Et_3Sn to cat haemoglobin is influenced by the presence of $PhEt_2SnBr$ but not the intramolecularly coordinated analogue **47**[170].



(47)

Originally, the coordination sphere about tin was postulated as R_3SnN_2, the two donor ligands being imidazole nitrogens from a pair of histidine residues[168,169], but this has now been superseded by evidence implicating both cysteine and histidine residues bonding to tin[170,171]. The strong affinity for cysteine SH groups and the relatively strong coordination of Me_3Sn to both cysteine and histidine in aqueous media has already been described (Section V.A.6,7). In both cat and rat haemoglobin, the two α-subchains of the protein tetramer have more SH binding sites than the β subchain pair, and in particular, both α chains have cysteine residues at 13α in the amino acid sequence which are absent in other animal haemoglobins that do not bind triorganotins[172]. Although a histidine at 20α, which is part of the neighbouring B helix, was suggested as being suitably proximate to partner cysteine 13α of the A helix[172], recent molecular dynamics using human haemoglobins (which have 81–85% sequence homology with cat haemoglobin) imply that this group is separated from cysteine 13α by the A helix. However, histidine 113α, which is part of the G helix, is 600 ppm from cysteine 13α, and this is the only sulphur–imidazole pair of this closeness. This separation is ideally placed to bind Me_3Sn and, indeed, any simple triorganotin group, since the binding site is at the protein surface (Figure 18)[173]. The finding by Harrison and Sharpe[121] that Me_3Sn is linked by the N and S atoms of two different methyl *N*-benzoyl-*l*-histidyl-*l*-cysteine units (**32**) rather than chelation from one dipeptide goes some way to modelling this phenomenon.

The molecular mechanics have also rationalized the preference for organotin binding by oxygenated (R-state) rather than de-oxygenated (T-state) haemoglobin[174]. In the T-state, while the basic structure and tin coordination are maintained relative to the R-state, the A

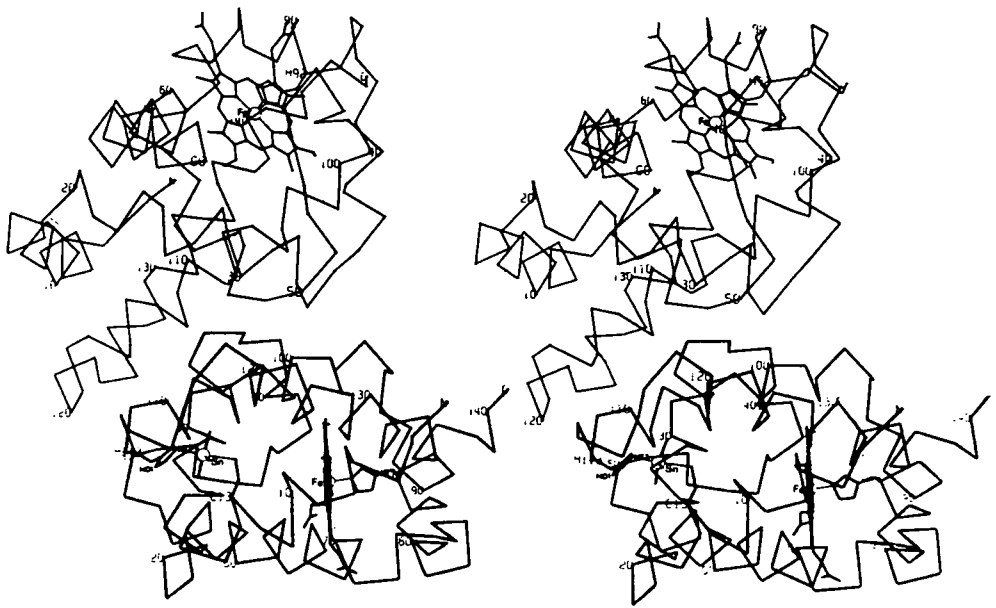


FIGURE 18. Stereo-drawing of the α- (lower) and β-subunits (upper) of R-state cat haemoglobin A. N and C terminii, and every tenth carbon of each subunit, have been labelled. The binding site for trialkyltin compounds lies on the surface of the α-subunit between the A and G helices. The side-chains of the two primary protein ligands, Cyst-13 and Hist-113, are also labelled along with the bound trimethyltin complex. Reproduced by permission of the authors of Reference 173

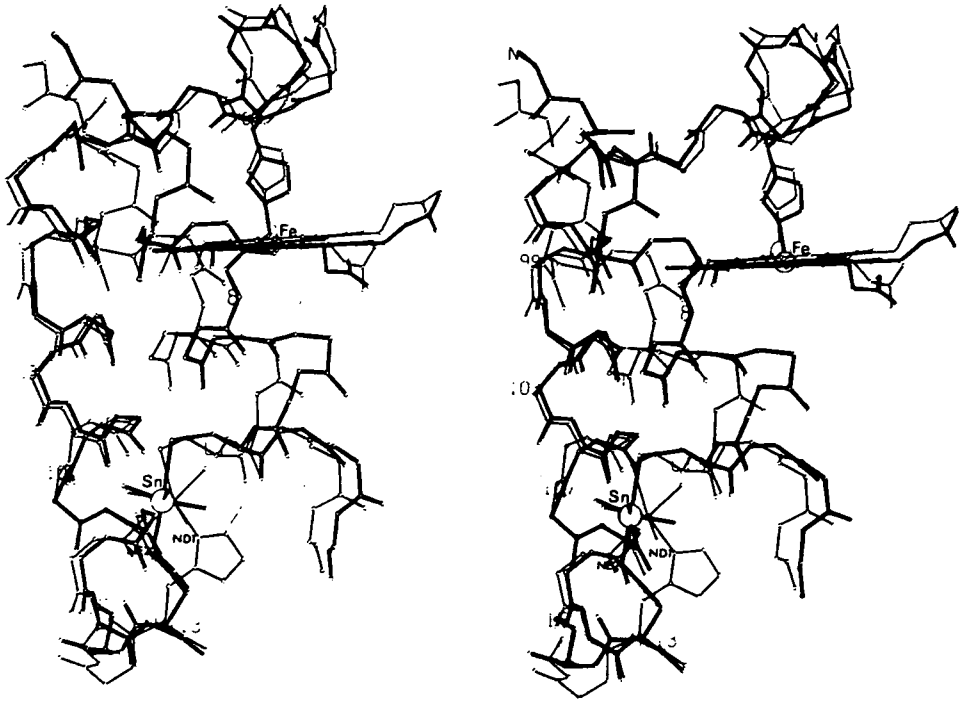


FIGURE 19. Comparison of the polypeptide chain conformations of the A and G helices in the R- (thick bonds) and T-states (thin bonds) about the trialkyltin binding site of cat haemoglobin. In the R-state, tin complexation occurs through N(3) of the histidine whereas in the T-state binding switches to histidine N(1). Reproduced by permission of the authors of Reference 173

and G helices rotate with respect to each other and although the N···S separation is still 600 pm, it is the sterically less favourable N(1) rather than N(3) which now bonds to the metal (Figure 19)[173].

Despite the coherence of the triorganotin–protein binding picture which has now emerged, some confusion still exists concerning the interpretation of Mössbauer qs data for these systems (Table 17). The original Mössbauer measurements by Elliot *et al.*[171] were interpreted in terms of a *cis*-R_3SnNS arrangement, on the basis of the widely quoted systematics which indicate that such a configuration has a smaller qs (**3**; 1.70–2.40 mm s^{-1}) than the corresponding *trans*-R_3SnNS isomer (**2**; 3.00–4.00 mm s^{-1})[195]. Barbieri[196] has shown that from a point-charge approach, surprisingly, the predicted qs for a *trans*-R_3SnNS system is only *ca* 2.13 mm s^{-1}, thereby implying that it is this isomer which is incorporated into the protein structure. This argument has also been used to identify the same architecture in one isomer of trialkyltin 6-thiopurines[128] (Section V.C.1), and it is this isomer which emerges from the dynamical modelling of Chu *et al.*[173]. However, the model compound trimethyltin(methyl *N*-benzoyl-*l*-histidyl-*l*-cysteinate) prepared by Harrison and Sharpe[121], which has also been designated a *trans*-R_3SnNS structure (**32**), has a qs of 3.35 mm s^{-1}.

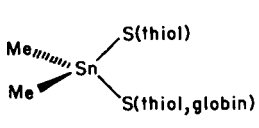
Investigation of the interactions of various diorganotin compounds with rat haemo-

TABLE 17. Mössbauer data for triorganotin–Protein interactions

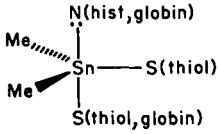
Organotin	Substrate	Tin: substrate ratio	is[a] (mm s^{-1})	qs[a] (mm s^{-1})	Ref.
Et_3Sn	Cat haemoglobin	2.00	1.48	1.74	171
Me_3Sn	Rat haemoglobin	1.88	1.32	1.50	175
		0.71	1.24	1.52	175
Et_3Sn	Rat haemoglobin	2.00	1.40	1.79	175
		1.83	1.43	−1.76	175
		2.20	1.38	1.61	175
Bu_3Sn	Rat haemoglobin	0.89	1.49	2.07	175
		1.58	1.56	1.61	175
$Me_2Sn(OH)_2$·hepes	Rat haemoglobin	1.81	1.19	2.23	110
		1.18	1.24	2.30	110
$Me_2Sn(OH)GlyGly$·hepes	Rat haemoglobin	1.76	1.29	2.23	110
		1.40	1.28	2.10	110
$Me_2Sn(OH)Cyst$	Rat haemoglobin	1.83	1.16	2.19	110
		1.44	1.33	2.39	110
Et_3Sn	Rat liver mitochondria		1.56[b]	3.44	
			1.49[c]	2.78	179
			1.22[d,e]	1.67	
Et_3Sn[f,g]	Rat liver mitochondria		1.25[d]	1.67	
			1.12[d,h]	1.41	180
			1.25[d,i]	1.57	

[a]Mössbauer data: is = isomer shift and qs = quadrupole splitting.
[b]Membrane partitioned organotin.
[c]Low-affinity site.
[d]High-affinity site.
[e]Incorrectly quoted as is = 1.59, qs = 2.22 mm s^{-1} in ref. 179. Data given are taken from ref. 180.
[f]Using ^{119}Sn-enriched organotin.
[g]Two additional doublets of unspecified parameters arising from soya bean lipid partitioning of the organotin are also observed.
[h]Proteolipid–organotin complex isolated from mitochondria and stabilized in soya bean liposomes prior to data collection.
[i]Proteolipid isolated from mitochondria before organotin binding and subsequent liposome stabilization.

globin has been made by Mössbauer spectroscopy (Table 17). $Me_2Sn(OH)_2$·hepes (i.e. Me_2SnCl_2 in an aqueous hepes buffer) and $Me_2Sn(OH)GlyGly$·hepes (i.e. $Me_2SnGlyGly$ in aqueous hepes buffer) yield either four- (**48**, **49**) or five-coordinate structures (**50**) (equation 28), although no distinction could be made between these possibilities on the basis of a point-charge analysis of qs data. Similarly, **51** and **52** represent possible alternative products for the reaction of $Me_2Sn(OH)Cyst$ (aqueous $Me_2SnCyst$) with rat haemoglobin. From this study of diorganotin binding to haemoglobin, no distinction could be made between cysteine-only or cysteine and histidine coordination to tin[110].



(51)



(52)

Triorganotins interact with rat liver mitochondria, yeast mitochondria or rat brain myelin in a similar manner, although in each case the situation is different, and more complex, than with cat and rat haemoglobins. The effects produced are specific and oligomycin-like, and are pH dependent, possibly related to the formation and stability of a hydrophilic organotin phosphate complex[177]. In general, three different organotin environments occur in these systems, one of which can be classed as a partitioning of the organotin within the lipid bilayer[179,180]. The other two sites have been classified as 'high affinity, low concentration' and 'low affinity, high concentration', respectively, with approximately an order of magnitude difference in both concentrations and affinities[176,178,184]. The active binding site with respect to oxidative phosphorylation inhibition is associated with a proteolipid[180], but at least with respect to rat brain myelin no particular protein is affected[185]. The local binding site on the protein is also different to that for dicyclohexylcarbodiimide, even though the effects produced are similar in the two cases[180].

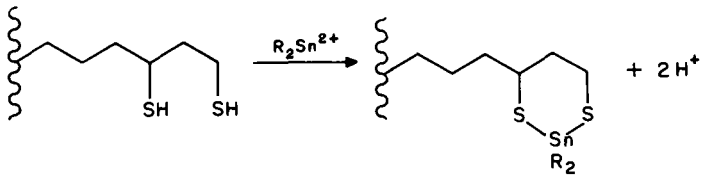
Two Mössbauer spectroscopic studies have probed the coordination sphere of tin in the two binding sites (Table 17)[179,180]. The high-affinity site is postulated to involve histidine associated with a four-coordinated tin. This assertion has been supported primarily by the similarity in activity of both Et_3SnBr and various intramolecularly five-coordinate organotin bromides, the latter having only one potential coordination site (the displaced halide) for protein binding[179,197,198]. However, this assertion must, at present, be treated with caution. Firstly, the high affinity for the low-concentration site is unusual for a molecule linked to the protein by a single bond, which thus requires that the environment of the metal is either hydrophobic or at least displays resticted access to hydroxide ions[198]. Secondly, the Mössbauer qs data fit a number of models and, for example, show similarity to the single site in cat or rat haemoglobin binding. Finally, Harrison and Sharpe[121] have shown that in trimethyltin(methyl *N*-benzoyl-*l*-leucyl-*l*-histidinate), tin bound to a single imidazole is still strongly Lewis acidic, and shows a tendency to bind an additional group in a *trans*-five-coordinate trigonal bipyramidal manner (**31**).

The low-affinity, high-concentration binding site has been ascribed to combined cysteine, histidine coordination similar to the cat and rat haemoglobins, but the Mössbauer data are by no means identical (Table 17)[179], even allowing for the scatter inherent in all such spectra due to the low concentrations of Mössbauer-active nucleii present in the samples.

Triphenyl- and tributyl-tin compounds also interfere with the enzymatic behaviour of rabbit white blood cells (polymorphonuclear leukocytes) which are low in mitochondrial

content. The origin of toxicity here is unlikely to be inhibition of ATP production *via* the mitochondrial mechanism, and inhibition of glycolysis, the main source of energy in these blood cells, has been suggested as an alternative[183]. Sulphydryl groups on the inner plasma membrane may be the active site here[183] or, since organotins promote dimer →monomer dissociation of hexokinase B, the first enzyme in the glycolytic pathway, interactions with the lysine linkages between dimer components are also plausible[199,200].

The toxicity of diorganotin compounds results from binding of enzymatic thiol groups, which causes an inhibition of the oxidative decarboxylation of α-keto acids (equation 42)[168]. The most probable binding site is the sulphur atoms of lipoic acid or its related enzymes[201,202].



(42)

Many organotin–sulphur compounds have been synthesized which may serve as models for enzyme binding[203–205].

2. *Membranes*

In addition to an oligomycin-like inhibition, organotins also inhibit mitochondrial and photosynthetic phosphorylation by uncoupling the electron transport reactions associated with the conversion of ADP to ATP[187–192]. The organotins act as ionophores which promote the exchange of Cl^-, Br^-, SCN^-, I^-, and F^- ions (but not NO_3^-, SO_4^{2-}, or $HOCH_2CH_2SO_3^-$) with OH^- ions across phospholipid membranes and, in particular, Cl^-/OH^- exchange in chloride-containing media results in a clamping of transmembrane pH differences and concommitant shifts in the pH optima of enzymes, uncoupling of electron transport phosphorylation, and the enhanced movement of a variety of ions. In the case of triorganotins, the organometallic species is believed to reside in the lipid bilayer and form R_3SnOH and R_3SnA (A = anion) which have both aqueous and lipid solubility. A simplified diagramatic representation of this process is shown in Figure 20. The efficiency of this process is maximized by a balanced lipid–water partitioning, and long-chain triorganotins, which have high lipid:water solubilities, are relatively poor ionophores[191].

Visual confirmation of these ideas comes from studies of the swelling and rupture (haemolysis) of human erythrocyte membranes (red blood cells, RCB)[194,206]. Tributyltin-treated RBCs show, by scanning electron microscopy, the presence of organotin aggregates of mean diameter 71.5 ± 18.2 nm associated with the cell membrane and occasionally linking two cells together (Figure 21). These structures are unique, and no other xenobiotic material is known to produce such aggregates in biological membranes. Freeze-fracture of the lipid bilayer shows both relief on one face and depressed relief on the other (Figure 22), indicating that the aggregate is partitioned within the lipid bilayer, not just embedded in the membrane from the outside surface. The self-aggregation of tributyltin units protects the hydrophobic alkyl groups from the hydrophilic medium and encourages lipid intercalation. From the shape deformations of the cells prior to haemolysis, it appears that the membrane intercalate is 'electrically silent', i.e. complexed to an (unspecified) anion[194]. The scheme proposed by Selwyn[191] for Cl^-–OH^- exchange (Figure 20) should then be modified to incorporate a triorganotin aggregate that straddles

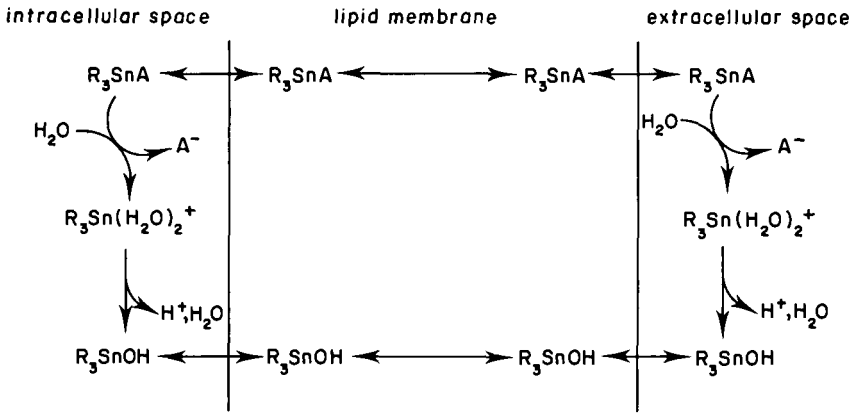


FIGURE 20. Proposed mechanism for the trans-membrane anion–hydroxide exchange mediated by triorganotins. Reproduced by permission of the American Chemical Society from Reference 191. Copyright (1976) American Chemical Society

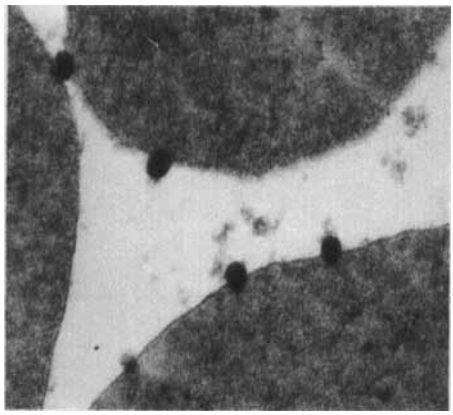
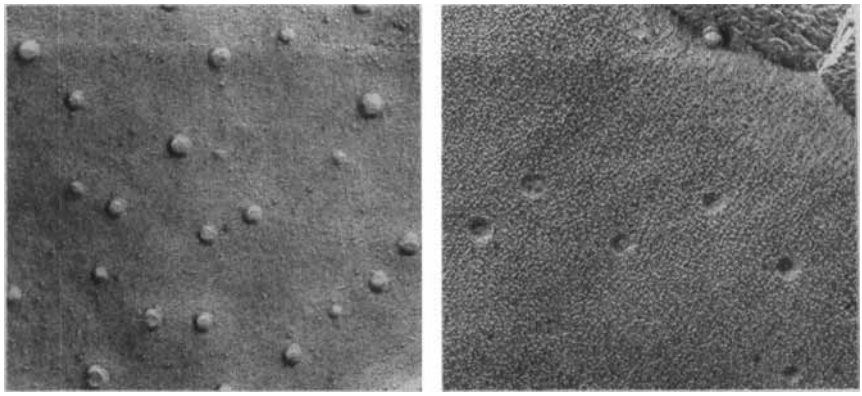


FIGURE 21. Transmission electron micrographs of tributyltin-treated red blood cells 30 min after treatment. Electron-dense spheres (tributyltin aggregates) are visible penetrating the plasma membranes and fusing adjacent cells. Reproduced by permission of the US and Canadian Academy of Pathology from Reference 194, Copyright (1986)

the water–lipid–water interfaces, and anion transport then possibly occurs by 'hopping' between adjacent tin sites within the aggregate. The fact that many triorganotin systems incorporate Sn—Cl:→Sn[8,207] or Sn—O(H):···Sn bridges (Figure 4)[8,59] would not invalidate this proposition.

In addition to oligomycin-like inhibition and Cl^-–OH^- exchange, higher molecular weight (more lipophilic) trialkyltins also promote gross swelling of cells, as indicated above. This may be associated with binding to the low-affinity site of lipoproteins[52] and/or



(a) (b)

FIGURE 22. Freeze-fracture electron micrograph of tributyltin-treated red blood cells showing (a) electron-dense relief on the membrane E-face and (b) corresponding depressed relief on the P-face. Reproduced by permission of the US and Canadian Academy of Pathology from Reference 194, copyright (1986)

TABLE 18. Concentrations of triorganotins (R_3Sn) causing different effects on mitochondria[a]

R	pI_{50}[b]		
	Cl^- dependent[c]	Cl^- independent[d]	Gross swelling
Me	5.7	3.2[e]	2.1[e]
Et	7.0	5.25	3.7
n-Pr	6.7[e]	6.0[e]	4.6
n-Bu	6.3[e]	5.9[e]	5.15
Ph	5.8[e]	5.6[e]	5.4[e]

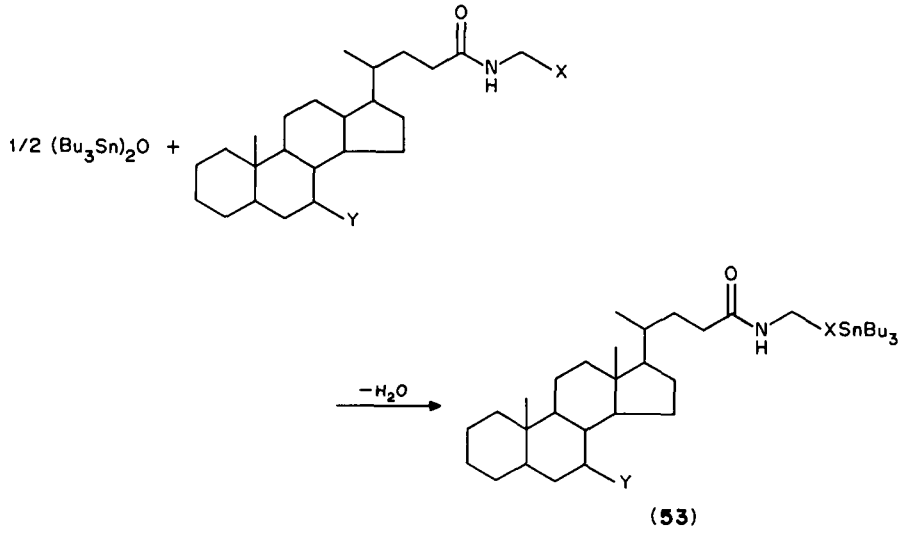
[a]Data taken from ref. 168.
[b]pI_{50} = − log molar concentration for 50% inhibition.
[c]e.g. Cl^-–OH^- exchange.
[d]E.g. specific, oligomycin-like inhibition.
[e]The effective ranges overlap.

enhanced lipid partition of aggregates as described above for tributyltin in RBCs. Different systematics (concentrations) of triorganotin are required for each of the three effects (Table 18)[168], and it is clear that Cl^-–OH^- exchange and cross swelling are favoured by different organotins, even though it is likely that all partition into the lipid bilayer. Two scenarios could explain the differing effects of the same phenomenon. Firstly, more lipophilic (long-chain) triorganotins would have a smaller tendency to straddle the water–lipid interface, and so complexation with aqueous anions would be diminished. Alternatively, long-chain trialkyltins are less associated by Lewis acid bridges (e.g. Cl^-, OH^-) than shorter chain analogues, so any anion hopping mechanism would become less viable. Such speculations await both investigation and elucidation.

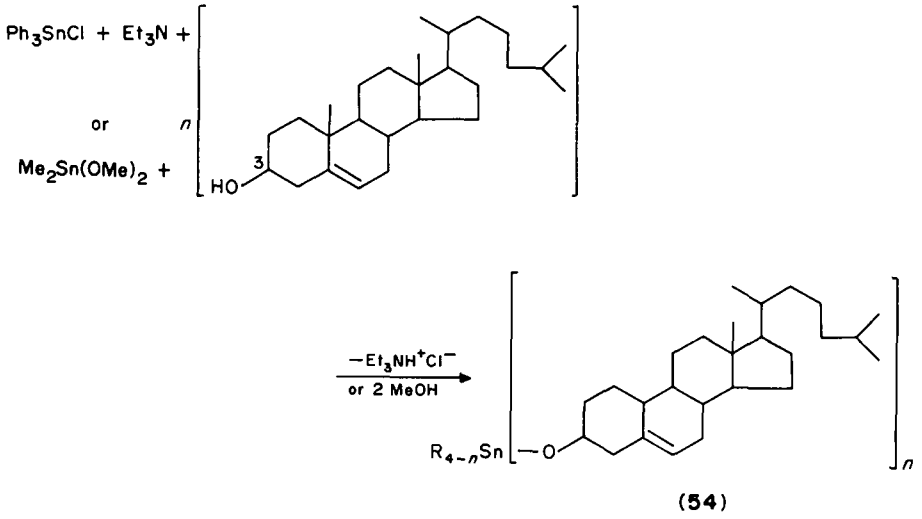
E. Steroids

Recent interest in organotin steroids has arisen from the hypothesis that the anti-tumour activity of simple organotins derives from the formation of such species in

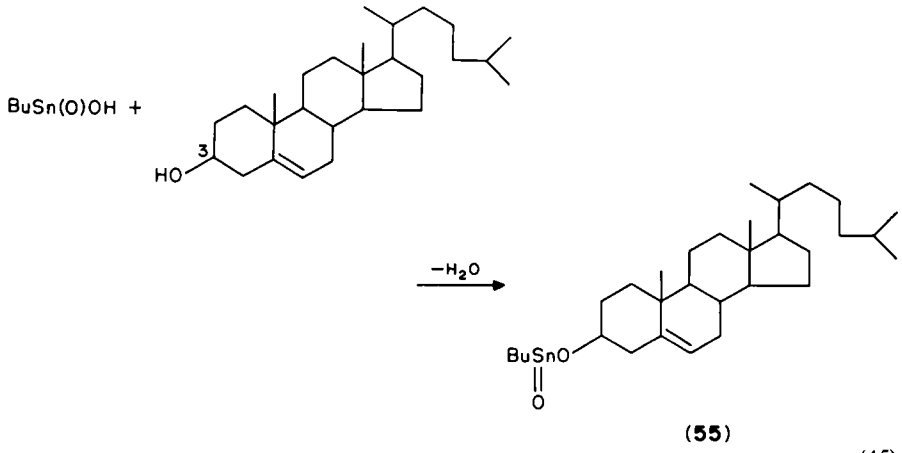
the thymus. The steroidal head of these complexes, it has been suggested, aids the penetration of the phospholipid–protein membrane, followed by subsequent attack by the organometallic moiety on the tumour cell. Tri- and di-organotin derivatives of cholic acid[208], the bile acids, taurocholic, taurodeoxycholic, and glycocholic acid[209], cholesterol, and deoxycholic acid[210], and a compendium of other patented yet ill-defined analogues[208] have been prepared by methods typified by the following. Physical data for these compounds are given in Table 19.



(43)

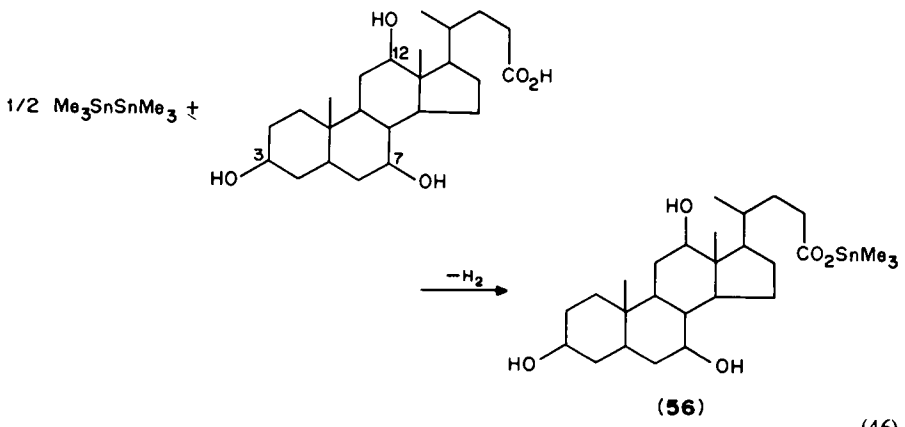


(44)



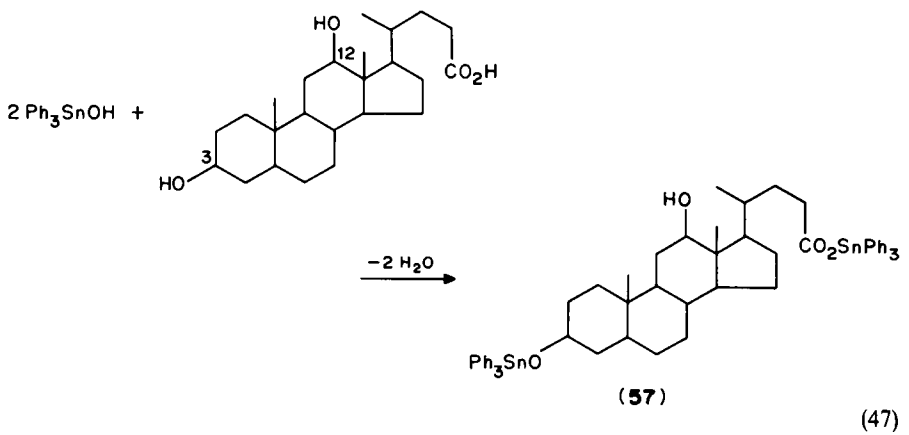
(55)

(45)



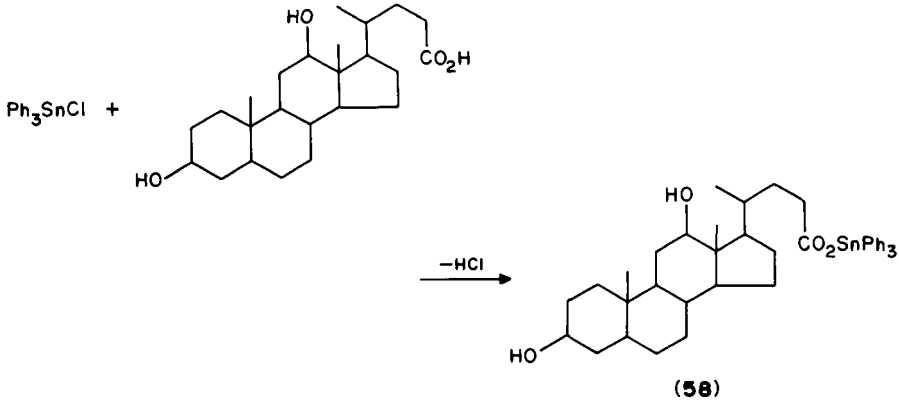
(56)

(46)



(57)

(47)



(58)

(48)

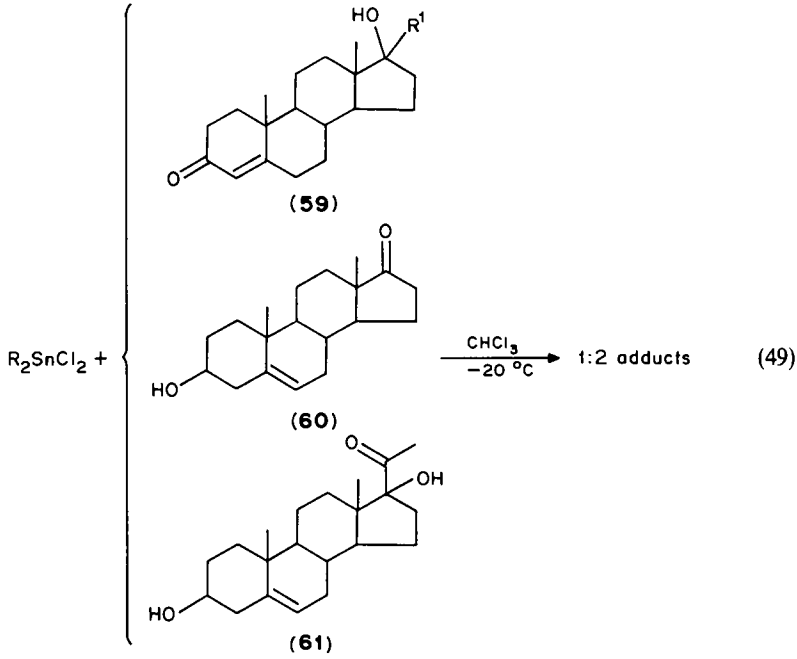
TABLE 19. Organotin steroids

Structure	R_nSn	M.p. (°C)	$\nu_a(CO_2)$ (cm^{-1})	qs[a] ($mm\,s^{-1}$)	$\delta^{119}Sn$ (ppm)	Ref.
53	Bu_3Sn[b]	113	1540		69.93	209
	Bu_3Sn[c]	140[d]			701.2(?)[e]	209
	Bu_3Sn[f]	140[d]			699.1(?)[g]	209
54	Me_3Sn	119		3.373	121.2	210
	Bu_3Sn	83–85				208
	Ph_3Sn	180		1.606	−84.23	210
	Me_2Sn	>220		2.658	128.75	210
	Ph_2Sn	123		1.889	−45.02	210
55	BuSn(O)	135–141				208
56	Me_3Sn	90–92				208
	Ph_3Sn	123–127				208
57	Ph_3Sn	67	1590, 1528		−109.76[h], −118.12[i]	210
58	Ph_3Sn				−116.57[i]	210
	Bu_3Sn	100–104				208
59[j]	Et_2Sn	62	1661		7.27[k]	211
	Bu_2Sn	42	1658			211
	Oct_2Sn	32	1655			211
	Ph_2Sn	40	1655		−188.20[k]	211
59[l]	Me_2Sn	134	1660		2.64[k]	211
	Ph_2Sn	114	1665		−123.22[k]	211
60	Me_2Sn	117	1725		6.11[k]	211
	Ph_2Sn	62	1730		−169.06[k]	211
61	Me_2Sn	230(d)	1685			211
	Ph_2Sn	228	1685			211

[a]Mössbauer quadrupole splitting.
[b]X = CO_2, Y = OH.
[c]X = CH_2SO_3, Y = OH.
[d]For monohydrate.
[e]Misprint in original for 70.1?
[f]Y = H, X = CH_2SO_3.
[g]Misprint in original for 69.9?
[h]Ether-bonded tin.
[i]Ester-bonded tin.
[j]R^1 = H.
[k]Measured at 223 K.
[l]R^1 = Me.

Tributyltin glycocholate has been proposed as a covalent, four-coordinate tin assembly, although the low stretching frequency for $\nu_{asym}(CO_2)$ suggests some intermolecular interaction[209]. The carboxylate-bound tin in $(Ph_3Sn)_2$(deoxycholate) is five-coordinate, so steric factors do not appear to inhibit solid-state association[210]. Conductance measurements indicate that the tributyltin esters of the two sulphonated bile acids both undergo some ionization into steroid anion/organometallic cation in dmf[209]. Studies involving hydroxy steroids (cholesterol, cholic acid, deoxycholic acid) show that whereas organostannylation of 3-OH is possible, no reaction at 7-OH and 12-OH has yet been observed[208–210]. Both trimethyl- and diorgano-tin derivatives of cholesterol are polymeric in the solid state through bridging hydroxy groups (cf. Figure 4), enforcing five and six coordination, respectively, on tin in the two cases. On the other hand, *O*-triphenylstannyl cholesterol is a four-coordinate monomer[210].

Diorganotin dihalides also form very weak 1:2 adducts with certain steroids, exclusively by coordination between the metal and ketonic oxygen (equation 49, Table 19). The products are weakly six-coordinate *trans*-$R_2SnCl_2O_2$ structures, in which the C—Sn—C moiety is distinctly non-linear[211]. Although no organotin steroid has been authenticated crystallographically, cell parameters for tributyltin deoxycholate have been reported[208]. The acute toxicity of tributyltin taurocholate towards rats has been examined, and found to be similar to that observed with other trialkyltin compounds[212].



(49)

VI. APPLICATIONS

One of the features of organotin chemistry is the diversity of applications which exist for its constituent compounds. There are now more organometallic compounds of tin in commercial use than for any other element, covering a spectrum of fields of which the

biologically related applications represent only a part. Indeed, non-biological applications—primarily, in tonnage terms, PVC stabilizers, but also catalysts in polymer chemistry and precursors for forming SnO_2 films on glass—consume the majority of the yearly output of organotin chemicals. This brief survey will attempt only to highlight those areas which, over the last decade or so, have fuelled the research activity already described in previous sections of this work. Reviews of the industrial applications of tin compounds are available to the interested reader[213–215], including a recent book from workers at the International Tin Research Institute[216].

A. Agrochemicals

Six triorganotin compounds are currently marketed as agrochemicals, and although these compounds have broad-spectrum activity, in practice their usage is restricted to a more limited arena. Historically, the first application of organotins in agriculture was as fungicides and bactericides with Ph_3SnOAc (Brestan®, Hoechst), Ph_3SnOH (Duter®, Philips Duphar) and to a lesser extent Ph_3SnCl (Brestanol®, Hoechst), all commercially available. Unfortunately, the high phytotoxicity[217] of these compounds towards many plants has restricted their potential use, which is limited principally to control of *Phytophthora infestans* (late blight) in potatoes (the disease central to the Irish potato famine in the mid-19th century), *Cercospora beticola* (leaf spot) in sugar beet, and *Septoria apii* (leaf spot) in celery.

The second generation of organotin agrochemicals, arriving on the market in the late 1960s, were a group of three compounds used to control mites, many of which feed off plants (phytophagous) and are the scurge of nurserymen, citrus farmer, and household gardener alike. Acaricidal activity is shown by $(c\text{-Hex})_3SnOH$ (Plictran, Dow Chemicals), $[(Neo)_3Sn]_2O$ (Vendex®, Torque®, Shell Chemicals) and $(c\text{-Hex})_3Sn$-1,2,4-triazole (Peropal®, Bayer)[60] and are used to control a number of harmful arachnids, including *Tetranychus urticae* (two-spotted mite), *Panonychus ulmi* (European red mite), *Eotranychus carpini* (yellow spider mite), and *Panonychus citri* (citrus red mite).

Organotins are also powerful insecticides, but since the most effective class of compounds are the mammalian-toxic trimethyltins[218], this property is yet to be commercially harnessed.

Concern in recent years about the widespread use of heavy metal-based chemicals in the environment has led to investigations of biocidal activity which occur at much lower concentration levels than those described above. These are essentially indirect methods of pest control, for example by cessation of the feeding stimulus to the pest by the host plant (anti-feedants)[219–221], or control of the pest population by sterilisation (chemosterilants)[220,222]. Both triphenyl- and tricyclohexyl-tins show promise in these two areas and, legislation permitting, will most likely be the basis for any new generation of organotin agrochemicals.

A full listing of reports on the evaluation of organotin chemicals in agriculture can be found in a two-part review by Crowe[223,224].

B. Wood Preservation

Tributyltin compounds in general have good fungicidal properties and low mammalian toxicities, and their potential use as wood preservatives has been appreciated since the early 1950s[17]. Consequently, $(Bu_3Sn)_2O$ (commonly referred to by the acronym tbto) has been a component of wood anti-fungal formulations for over 20 years, and is used as an organic solvent-based fungicide in at least 60 formulations in the UK alone, with many more world wide. Tbto-treated wood is effectively preserved for up to 25 years, although there is some concern as to the long-term stability of the organotin with respect to

dealkylation to less effective diorganotin compounds[295]. Some fungi which colonize wood, for example, are capable of causing this dealkylation process[225,226].

Despite the fact that other tributyltin compounds have been tested for their anti-fungal activity, tbto still dominates the tin-based wood preservation market, although both $(Bu_3Sn)_3PO_4$ and tributyltin naphthenate have been introduced into use in The Netherlands and Scandinavia[227–230]. A water-based tbto wood preservative has been developed by combination with quaternary ammonium salts[231], or more fundamentally by the synthesis of water-soluble tributyltin compounds, e.g. Bu_3SnOSO_2Et, which has 3–10% aqueous solubility[232]. This compound is currently undergoing field trials in Canada[216], while the former formulation has also found use in the restoration of moss, algae, and lichen-covered stonework[233].

The fundamental question as to the precise nature of the tributyltin compound *within the cellulose matrix* is not fully resolved, although some general concensus of opinion has now been reached. Early suggestions that the tributyltin group condenses with the terminal hydroxy groups of wood cellulose[234] (see Section V.C.2) have been put into question by later electron microscopy studies[235]. Mössbauer spectra of tbto-impregnated pine strongly suggest the presence of $(Bu_3Sn)_2CO_3$, formed by reaction with atmospheric (equation 50) CO_2[236].

$$(Bu_3Sn)_2O + CO_2 \longrightarrow (Bu_3Sn)_2CO_3 \qquad (50)$$

The addition of a polar Sn—O bond to an unsaturated substrate is well known in organotin chemistry[237]. Similar Mössbauer studies relating to Bu_3SnOSO_2Et and $(Bu_3Sn)_3PO_4$ indicate that these materials are unchanged on impregnation into wood (Table 20)[238,239]. It should be noted that $(Bu_3Sn)_2CO_3$ and $(Bu_3Sn)_3PO_4$ adopt structures which contain both four- and five-coordinate tin, and this is indicated by the appearance of two Lorentzian doublets in their Mössbauer spectra[240,241].

Mössbauer spectra, however, because of their relatively broad lines, may hide a more complex situation which involves several tin sites of similar, yet different, coordination. N.m.r. studies of organotin binding to carbohydrates (see Section V.C.2) certainly indicate that a more complex pattern is possible. Moreover, the nature of the interaction between $(Bu_3Sn)_2CO_3$ and wood cellulose has yet to be confirmed, although hydrogen bonding has been suggested as a possibility[236].

TABLE 20. Mössbauer data for tributyltin wood preservatives[a]

Compound	is[b] (mm s^{-1})	qs[b] (mm s^{-1})	Γ[c] (mm s^{-1})
$(Bu_3Sn)_2O$	1.17	1.46	0.89, 0.93
$(Bu_3Sn)_2O$ in wood	1.39	2.84	1.19, 1.19
	1.46	3.59	0.86, 0.86
$(Bu_3Sn)_2CO_3$	1.38	2.70	1.07, 1.05
	1.43	3.79	0.94, 1.02
$(Bu_3Sn)_2CO_3$ in wood	1.39	2.64	0.89, 0.89
	1.44	3.66	0.91, 0.91
Bu_3SnOSO_2Et	1.58	4.36	1.16, 1.15
Bu_3SnOSO_2Et in wood	1.57	4.23	1.22, 1.01
$(Bu_3Sn)_3PO_4$	1.36	2.57	1.10, 1.10
	1.37	3.74	0.88, 0.92
$(Bu_3Sn)_3PO_4$ in wood	1.36	2.56	1.04, 0.98
	1.38	3.69	0.86, 0.86

[a]Data taken from Ref. 238.
[b]Mössbauer data: is = isomer shift, qs = quadrupole splitting.
[c]Full width at half-height.

Detailed reviews of organotin wood preservatives are available for the interested reader[216,227,242,243].

C. Anti-fouling Paints

Marine fouling is the attatchment of marine species (animals, plants, etc.) to the surfaces of immersed structures, commonly ships hulls, buoys, or sonar equipment, or sea-water conduits, e.g. cooling pipes. In the case of ships, this fouling can lead to inefficient travel through the water because of drag, with dramatic increases in fuel consumption. In other situations, fouling can impair the performance of sonar equipment, reduce the visibility of buoys which sit lower in the water, or lead to blockage of pipes carrying sea water. The fungicidal and bactericidal effectiveness of triphenyl- and tributyl-tin compounds, already discussed in relation to plant protection and wood preservation (Sections VI.A and B), has also been directed against this fouling problem. Development of organotin-based anti-fouling systems dates back to the early 1960s, since when organotins have been used firstly in conjunction with conventional Cu_2O-based paints (which are *ca* 10 times less effective than organotins) and now, more recently, in tin-only formulations[244]. This area has been extensively reviewed in recent years[216,245–247].

The organotin compounds employed in anti-fouling paints are usually Ph_3SnX (X = OH, F, Cl, OAc), Bu_3SnX (X = F, Cl), and $(Bu_3Sn)_2O$, although many other systems have been evaluated[248,249]. The problem associated with the physical dispersion of these chemicals within a paint is that the rate at which the biocide is leached from its matrix is initially high, possibly in excess of an optimum value, which in time, as near-surface material is depleted, will fall to below a value which yields effective toxin concentrations. The working lifetime of such systems is typically 1–2 years before repainting becomes necessary.

The lifetime of an anti-fouling paint has been greatly increased by controlling the rate of release of toxin into the environment. Two approaches to this problem have been effectively developed. Firstly, the organotin has been impregnated into an elastomeric matrix, e.g. neoprene[250–252], a situation which is particularly suited to the protective rubber domes encasing sonar equipment, but has also been adapted to protect ships hulls, and protective periods of up to 9 years or more have been recorded[253].

The alternative methodology, which is more suited to the protection of ships hulls, is a self-polishing paint in which the organotin is an integral part of the matrix. The most celebrated of these formulations involves tributyltin methacrylate[254], but many other organotin polymers have been evaluated[255–257]. The organotin at the paint surface is hydrolytically cleaved from the polymer to release it into the environment. The resulting polymer, depleted in surface organotin, is relatively hydrophilic owing to the remaining charged head groups and is slowly dissolved from the surface by sea water, revealing a new layer of organotin polymer to replenish the toxic environment close to the ship's hull. This scenario is shown schematically in Figure 23. The nature of the organotin species within these polymeric systems has been investigated by a number of spectroscopic techniques[258,259].

Despite the widespread use of organotin anti-fouling paints, there has been increasing concern in recent years about the impact of these chemicals on the environment. This concern is not primarily related to the use of paints on ocean-going vessels, where the release of organotin is, literally, a drop in the ocean, but their use on vessels which are moored for long periods in harbours, marinas, lakes, and river estuaries, i.e. in relatively static aqueous surroundings. In such environments, large local concentrations of organotins can accrue in the water, with concomitant effects on many passive forms of marine life. Particular concern has been expressed on the effect of aqueous tributyltin on oyster farming[18,260–262]. The current legislative position with regard to tributyltin-based

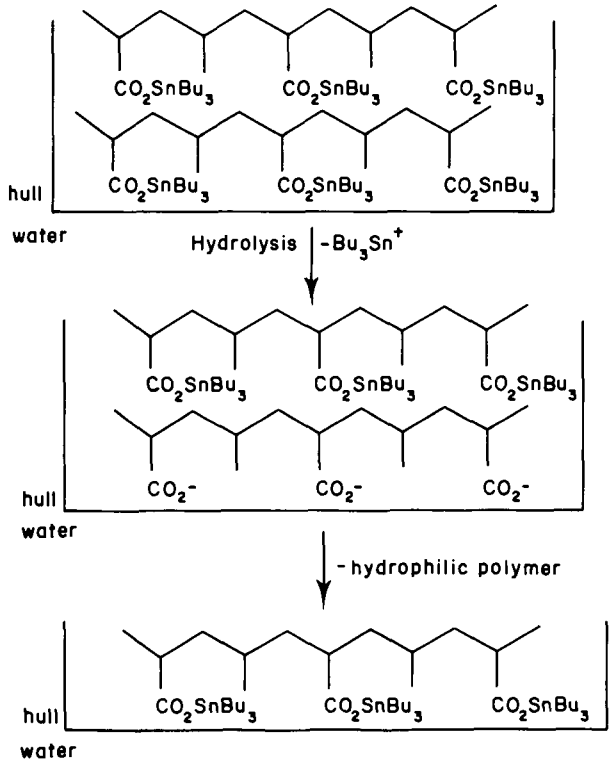


FIGURE 23. Schematic representation of the mechanism of self-polishing triorganotin antifouling paints

anti-fouling paints is summarized in Table 21. Aspects of the environmental chemistry, distribution, and analysis of tributyltin anti-fouling paints have recently been published[263,264].

TABLE 21. Regulation of tributyltin anti-fouling paints[a]

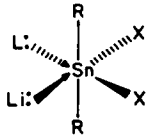
Country	Comment
France	1982: use on vessels shorter than 25 m banned.
UK	1986: prohibited retail sale and supply of paints with $>7.5\%$ (w/w) tin in copolymer formulations or $>2.5\%$ (w/w) tin in non-copolymer systems. 1987: retail sale of all tributyltin-containing paints banned.
Germany	Use of organotins in freshwater anti-fouling paints currently prohibited.
Switzerland	Use of organotins in freshwater anti-fouling paints currently banned.
USA	Environmental Protection Agency currently reviewing use of tributyltins.
Canada	Use of tributyltin preservatives on fishing nets not allowed. 1987: Pest Control Products Act requires registration of tributyltin compounds, and specifies (i) release rates into the environment and (ii) bans use of vessels <19.5 m.

[a]Taken from Ref. 264 and references therein.

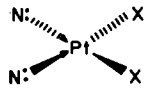
D. Pharmaceuticals

The most active area of research into the biological chemistry of organotin compounds in recent years on their anti-tumour activity, following the first reports by Brown[265] in 1972 that tumour growth in rodents was retarded by doses of Ph_3SnOAc. It is now established that it is diorganotin compounds which show maximum anti-tumour activity combined with low mammalian toxicity, and *ca* 50% of the R_2SnX_2 compounds tested show some activity based on current criteria[266], although this is almost always less than for the established *cis*-platin family of compounds which act as a yardstick for new metal-centred drugs. However, unlike *cis*-platin, diorganotin compounds show less nephrotoxicity[267]. Numerous compounds have now been screened against a variety of tumours, and several reviews of the results exist[216,268–271]. Probably the most extensively studied group of compounds are adducts of type $R_2SnX_2{\cdot}L_2$ (X = halogen, pseudohalogen; L = *O*- or *N*-donor ligand)[272–276], but other general classes included derivatives of fluorocarbons[277], bis(stannyl)methanes[278], dithiophosphinates[279], compounds containing the R_2SnO_2 moiety in different guises[280,281], carboxylic acids[282], amino acids[94], purines[94], pyrimidines[283], and peptides[68,94,293]. Attempts to improve the bioavailability of the organotin by formation of water-soluble compounds[284] or by their inclusion into β-cyclodextrin[285] have also been reported.

The mode of action of the above organotins is still open to considerable question, and may well vary from one compound type to another, i.e. the active versus the passive nature of the coordinated ligands is not yet clarified. However, $R_2SnX_2{\cdot}L_2$ adducts (**62**) probably show activity *via* a different mechanism to the structurally similar family of *cis*-platin drugs (**63**) on which they are modelled. *cis*-Platin activity occurs by loss of halide ions and when



(**62**)



(**63**)

the <Cl—Pt—Cl is less than 95°, allowing subsequent bonding to nitrogenous bases of DNA with a 'bite size' of < 360 pm. Such a mechanism is also, in principle, possible for diorganotins and several derivatives of purine and pyrimidine bases are known (see Section V.C.1). Crystallographic data for both active and inactive $R_2SnX_2{\cdot}L_2$ adducts reveal <Cl—Sn—Cl > 103°, which should lead to inactivity by the *cis*-platin mechanism. Instead, it has been noted that for *N*-donor ligands (L) compounds with Sn—N bonds > 239 pm are active, whereas compounds which contain stronger Sn—N bonds are not[286], implying that it is dissociation of the *N*-donor groups rather than halogens that is important.

In the case of diorganotin dipeptide activity, it has been suggested that a strong Sn—N bond (see Section V.B) which is capable of persisting in aqueous media allows the ligand to deliver the organotin to the active site before release of the R_2Sn^{2+} toxin. In cases where the ligands are rapidly cleaved from tin, R_2SnO precipitates from solution, rendering the compound inactive[94].

A second pharmaceutical application for organotins is in the chemotherapy of leishmaniasis, a parasitic infection of the skin, where dioctyltin maleate has shown promisingly high activity[287].

E. Miscellaneous

Minor biocidal applications of organotins include disinfectants (tbto, Bu_3SnO_2CPh)[288,289], controlled-release molluscicides showing activity against, for example, bilharzia[290], anti-microbial slimicides in the paper industry[291], moth proofing of textiles[292,293], and rodent-repellant coatings for wires and cables[294].

VII. CONCLUSIONS

It is the nature of science that, in many instances, an empirical approach to problem solving—'try it and see if it works'—leads to a more rapid advancement than does a detailed investigation of the cause or mechanism of a particular phenomenon. Such has been the case with bio-organotin chemistry, where the philosophy of synthesis and testing, fuelled by a competitive market place, has out-distanced our understanding of the fundamental chemical and biochemical processes which are at the heart of their usefullness. It is therefore paradoxical, at least as far as the triorganotin story is concerned, that while collective achievement to date has greatly clarified the biochemistry of these systems, environmental concerns have, or by the end of the century probably will have, reduced the extent to which their biological properties can be utilized. The current worldwide legislative activity relating to tributyltin anti-fouling paints is more likely to be a beginning than an end as far as triorganotin biocides are concerned.

The future for bio-organotin chemicals lies, inasmuch as current data permit such speculation, in the field of less toxic diorganotin compounds and their anti-tumour properties. It is to be hoped that as much effort is placed in understanding the biochemistry of this activity as will no doubt be put into the synthesis and screening of new compounds. To this end, far greater cooperation between chemist, biologist and biochemist is desirable than generally exists at present, and such links should be encouraged.

From the purely chemical point of view, our understanding of organotin chemistry is in a healthy state. Synthetic procedures and structural trends are predictable with increasing certainty, even if a few pleasurable surprises await us. The chemist is therefore ably primed to develop new technological applications as they arise and, despite the current concerns about triorganotin compounds, the future should be viewed with optimism for new horizons, not with despair for the passing of an old friend.

VIII. REFERENCES

1. A. G. Davies and P. J. Smith, in *Comprehensive Organometallic Chemistry* (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Pergamon Press, Oxford, 1982, p. 608.
2. C. J. Evans, *Spec. Chem.*, **1**, 12 (1981).
3. C. J. Evans, *Tin Its Uses*, **101**, 12 (1974).
4. W. P. Neumann, *The Organic Chemistry of Tin*, Wiley, London, 1970.
5. R. C. Poller, *The Chemistry of Organotin Compounds*, Logos, London, 1970.
6. A. K. Sawyer (Ed.), *Organotin Compounds*, Vol. 1–3, Marcel Dekker, New York, 1971.
7. P. G. Harrison, *Coord. Chem. Rev.*, **75**, 200 (1986).
8. P. A. Cusack, P. J. Smith, J. D. Donaldson, and S. M. Grimes, *A Bibliography of X-Ray Crystal Structures of Tin Compounds*, Publication 588, International Tin Research Institute, London, 1981.
9. J. A. Zubieta and J. J. Zuckerman, *Prog. Inorg. Chem.*, **24**, 251 (1978).
10. J. J. Zuckerman, *Adv. Organomet. Chem.*, **9**, 22 (1970).
11. B. Wrackmeyer, *Annu. Rep. NMR Spectrosc.*, 519 (1982).
12. J. S. Thayer, *Organometallic Compounds and Living Organisms*, Academic Press, New York, 1984, p. 2.
13. T. Tsubaki and K. Irukayama (Eds), *Minamata Disease: Methylmercury Poisoning in Minamata and Hiigata (Japan)*, Kodansha, Tokyo, 1977.

14. Anon., *Br. Med. J.*, **1**, 515 (1958).
15. T. Alajouanine, L. Derobert, and S. Thieffrey, *Rev. Neurol.*, **98**, 85 (1958).
16. A. J. Crowe, *Drugs Future*, **12**, 255 (1985).
17. G. J. M. van der Kerk and J. G. A. Luijten, *J. Appl. Chem.*, **4**, 314 (1954); **6**, 56 (1956).
18. Anon., *New Sci.*, No. 1469, 20 (1985).
19. A. Bokranz and H. Plum, *Fortschr. Chem. Forsch.*, **16**, 356 (1971).
20. W. P. Neumann, *Justus Libigs Ann. Chem.*, **653**, 157 (1962).
21. K. Sisido, Y. Takeda, and Z. Kinugawa, *J. Am. Chem. Soc.*, **83**, 538 (1961).
22. F. S. Holland, *Appl. Organomet. Chem.*, **1**, 185 (1987).
23. P. J. Smith, *Toxicological Data on Organotin Compounds*, Publication 538, International Tin Research Institute, London, 1978.
24. H. Schweinfurth, *Tin Its Uses*, **143**, 9 (1985).
25. J. M. Barnes and L. Magos, *Organomet. Chem. Rev.*, **3**, 137 (1968).
26. J. M. Barnes and H. B. Stoner, *Pharmacol. Rev.*, **11**, 211 (1959).
27. G. K. Sandhu and G. K. Sandhu, *J. Chem. Sci.*, **9**, 36 (1983).
28. M. R. Krigman and A. P. Silverman, *Neurotoxicology*, **5**, 129 (1984).
29. R. B. Laughlin and O. Linden, *Ambio*, **14**, 88 (1985).
30. P. Lange, G. Henninghausen, and U. Karnstedt, *Arch. Toxicol.*, Suppl., **4**, 132 (1980).
31. A. H. Penninks and W. Seinen, *Adv. Immunopharmacol., Proc. 2nd Int. Conf.*, **2**, 41 (1982).
32. A. H. Penninks and W. Seinen, *Tijdschr. Diergeneeskd.*, **109**, 209 (1984).
33. A. H. Penninks, P. M. Punt, M. Bol-Schoenmakers, H. J. M. van Rooijen, and W. Seinen, *Rev. Silicon Germanium Tin Lead Cmpd.*, **9**, 367 (1986).
34. K. R. Ruehl and J. M. Cranmer, *Neurotoxicology*, **5**, 187 (1984).
35. Y. Arakawa and O. Wada, *Biochem. Biophys. Res. Commun.*, **123**, 543 (1984).
36. G. G. Bierkamper, E. Aizenman, and W. R. Millington, *Neurotoxicology*, **5**, 245 (1984).
37. L. W. Chang and R. S. Dyer, *J. Toxicol. Environ. Health*, **16**, 641 (1985).
38. L. W. Reiter and P. H. Ruppert, *Neurotoxicology*, **5**, 177 (1984).
39. G. R. Wenger, *Neurol. Neurobiol.*, **13**, 503 (1985).
40. S. O. Idemudia and D. E. McMillan, *Neurotoxicology*, **7**, 109 (1986).
41. P. J. Craig, in Comprehensive Organometallic Chemistry (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Pergamon Press, Oxford, 1982, p. 979.
42. F. E. Brinkman and J. M. Bellama (Eds), *Organometals and Organometalloids: Occurrence and Fate in the Environment*, ACS Symposium Series, No. 82, American Chemical Society, Washington, DC, 1978.
43. G. N. Howell, M. J. O'Connor, A. M. Bond, H. A. Hudson, P. J. Hanna, and S. Strother, *Aust. J. Chem.*, **39**, 1167 (1986).
44. W. F. Mauders, G. J. Olsen, F. E. Brinkman, and J. M. Bellama, *J. Chem. Soc., Chem. Commun.*, 538 (1984).
45. P. J. Craig and S. Rapsomanikis, *Environ. Sci. Technol.*, **19**, 726 (1986).
46. P. J. Craig and S. Rapsomanikis, *Environ. Technol. Lett.*, **5**, 407 (1984).
47. A. K. Sijpesteijn, J. G. A. Luijten, and G. J. M. van der Kerk, in *Fungicides* (Ed. D. C. Torgeson), Vol. 2, Academic Press, New York, 1969, p. 352.
48. J. E. Cremer, *Biochem J.*, **68**, 685 (1958).
49. E. C. Kimmel, R. H. Fish, and J. E. Casida, *J. Agric. Food Chem.*, **25**, 1 (1977).
50. H. B. Stoner, J. M. Barnes, and J. I. Duff, *Br. J. Pharmacol.*, **10**, 16 (1955).
51. G. Henninghausen, P. Lange, and J. Merkod, *Arch. Toxicol.*, Suppl., **4**, 175 (1980).
52. R. G. Wulf and K. H. Byington. *Arch. Biochem. Biophys.*, **167**, 176 (1975).
53. N. J. Snoeij, A. A. J. van Iersel, A. H. Penninks, and W. Seinen, *Toxicology*, **39**, 71 (1986).
54. T. Tsuda, H. Nakanishi, S. Aoki, and J. Takebayashi, *Toxicol. Environ. Chem.*, **12**, 137 (1986).
55. N. J. Snoeij, A. A. J. van Iersel, A. H. Penninks, and W. Seinen, *Toxicol. Appl. Pharmacol.*, **81**, 274 (1985).
56. A. H. Penninks and W. Seinen, *Toxicol. Appl. Pharmacol.*, **56**, 221 (1980).
57. J. M. Brown, A. C. Chapman, D. Harper, D. J. Mowthorpe, A. G. Davies, and P. J. Smith, *J. Chem. Soc., Dalton Trans.*, 338 (1972).
58. K. C. Molloy, T. G. Purcell, K. Quill, and I. W. Nowell, *J. Organomet. Chem.*, **267**, 337 (1984).
59. C. Glidewell and D. Liles, *Acta Crystallogr., Sect. B*, **34**, 129 (1978).
60. I. Hamman, K. H. Büchel, K. Bungarz, and L. Born, *Pflanzenschutz-Nachr.*, **31**, 1 (1978).
61. K. C. Molloy and K. Quill, *J. Chem. Soc., Dalton Trans.*, 1417 (1985).

62. S. J. Blunden, P. J. Smith, and B. Sugavanam, *Pestic. Sci.*, **15**, 253 (1984).
63. S. J. Blunden, B. N. Patel, P. J. Smith, and B. Sugavanam, *Appl. Organomet. Chem.*, **1**, 241 (1987).
64. A. Tzschach, E. Reiss, P. Held, and W. Bollmann, *E. Ger. Pat.*, 63490 (1968); *Chem. Abstr.*, **92**, P71059 (1980).
65. K. R. S. Ascher and N. E. Nemny, *Experientia*, **32**, 902 (1976).
66. R. S. Tobias, *Organomet. Chem. Rev.*, **1**, 93 (1966).
67. A. G. Davies, J. P. Goddard, M. B. Hursthouse, and N. P. C. Walker, *J. Chem. Soc., Chem. Commun.*, 597 (1983).
68. G. Ruisi, A. Silvestri, M. T. Lo Gudice, R. Barbieri, G. Atassi, F. Huber, K. Grätz, and L. Lamartina, *J. Inorg. Biochem.*, **25**, 229 (1985).
69. R. H. Fish, E. C. Kimmel, and J. E. Casida, *J. Organomet. Chem.*, **93**, C1 (1975).
70. R. H. Fish, E. C. Kimmel, and J. E. Casida in *Organotin Compounds: New Chemistry and Applications* (Ed. J. J. Zuckerman), *Adv. Chem. Ser.*, No. 157, 197 (1976).
71. A. G. Davies, in *Organotin Compounds: New Chemistry and Applications* (Ed. J. J. Zuckerman), *Adv. Chem. Ser.*, No. 157, 34 (1976).
72. J. E. Casida, E. C. Kimmel, B. Holm, and G. Widmark, *Acta Chem. Scand.*, **25**, 1497 (1971).
73. J. W. Bridges, D. S. Davies, and R. T. Williams, *Biochem. J.*, **105**, 1261 (1967).
74. D. Barug, *Chemosphere*, **10**, 1145 (1981).
75. A. G. Davies and P. J. Smith, *Adv. Inorg. Radiochem.*, **23**, 49 (1980).
76. K. D. Freitag and R. Bock, *Pestic. Sci.*, **5**, 731 (1974).
77. L. L. Cook, K. S. Jacobs, and L. W. Reiter, *Toxicol. Appl. Pharmacol.*, **72**, 75 (1984).
78. E. H. Blair, *Environ. Qual. Saf. Suppl.*, **3**, 406 (1975).
79. R. A. Brown, M. C. Nazario, and R. S. DeTirado, *Environ. Res.*, **13**, 56 (1977).
80. Y. Arakawa, O. Wada, and T. H. Yu, *Toxicol. Appl. Pharmacol.*, **60**, 1 (1981).
81. L. L. Cook, K. E. Stine, and L. W. Reiter, *Toxicol. Appl. Pharmacol.*, **76**, 344 (1984).
82. N. F. Cardarelli, B. M. Quitler, A. Allen, E. Dobbins, E. P. Libby, P. Hager, and L. R. Sherman, *Aust. J. Exp. Biol. Med. Sci.*, **62**, 199 (1984).
83. L. R. Sherman, *Rev. Silicon Germanium Tin Lead Cmpd.*, **9**, 323 (1986).
84. M. Frankel, D. Gertner, D. Wagner, and A. Zilkha, *J. Org. Chem.*, **30**, 1596 (1965).
85. B. Y. K. Ho and J. J. Zuckerman, *Inorg. Chem.*, **12**, 1552 (1973).
86. W. T. Hall and J. J. Zuckerman, *Inorg. Chem.*, **16**, 1239 (1977).
87. G. Roge, F. Huber, H. Preut, A. Silvestri, and R. Barbieri, *Atti Congr. Naz. Chim. Inorg.*, **15**, 241 (1982).
88. G. Roge, F. Huber, A. Silvestri, and R. Barbieri, *Z. Naturforsch., Teil B*, **37**, 1456 (1982).
89. F. Huber, G. Roge, R. Barbieri, and F. Di Bianca, *J. Organomet. Chem.*, **233**, 185 (1982).
90. G. Roge, F. Huber, H. Preut, A. Silvestri, and R. Barbieri, *J. Chem. Soc., Dalton Trans.*, 595 (1983).
91. M. J. Hynes and M. O'Dowd, *Biochem. Soc. Trans.*, **13**, 490 (1985).
92. M. J. Hynes and M. O'Dowd, *J. Chem. Soc., Dalton Trans.*, 563 (1987).
93. B. Y. K. Ho, K. C. Molloy, J. J. Zuckerman, F. Reidinger, and J. A. Zubieta, *J. Organomet. Chem.*, **187**, 213 (1980).
94. F. Huber, G. Roge, L. Carl, G. Atassi, F. Spreafico, S. Filippeschi, R. Barbieri, A. Silvestri, E. Rivarola, G. Ruisi, F. Di Bianca, and G. Alonzo, *J. Chem. Soc., Dalton Trans.*, 523 (1985).
95. G. K. Sandhu, R. Gupta, S. S. Sandhu, and R. V. Parish, *Polyhedron*, **4**, 81 (1985).
96. G. K. Sandhu, R. Gupta, S. S. Sandhu, R. V. Parish, and K. Brown, *J. Organomet. Chem.*, **279**, 373 (1985).
97. G. K. Sandhu, G. Kaur, J. Holeček, and A. Lyčka, *J. Organomet. Chem.*, **332**, 75 (1987).
98. P. J. Smith, R. L. Hyams, J. S. Brooks, and R. W. Clarkson, *J. Organomet. Chem.*, **171**, C29 (1979).
99. C. D. Hager, F. Huber, R. Barbieri, and A. Silvestri, *Z. Anorg. Allg. Chem.*, **471**, 194 (1980).
100. O. A. Bamgboye, T. T. Bamgboye, and P. G. Harrison, *J. Organomet. Chem.*, **306**, 17 (1986).
101. R. Barbieri, F. Di Bianca, A. Silvestri, E. Rivarola, and F. Huber, *Atti Congr. Naz. Chim. Inorg.*, **15**, 237 (1982).
102. K. C. Molloy, K. Quill, and I. W. Nowell, *J. Chem. Soc., Dalton Trans.*, 101 (1987).
103. K. C. Molloy, S. J. Blunden, and R. Hill, *J. Chem. Soc., Dalton Trans.*, 1259 (1988).
104. G. Domazetis, R. J. Magee, and B. D. James, *Inorg. Chim. Acta*, **32**, L48 (1979).
105. G. Domazetis, R. J. Magee, and B. D. James, *J. Organomet. Chem.*, **173**, 357 (1979).
106. J. D. Cashion, G. Domazetis, and B. D. James, *J. Organomet. Chem.*, **185**, 433 (1980).

107. R. Barbieri, A. Silvestri, F. Huber, and C.-D. Hager, *Can. J. Specrosc.*, **26**, 194 (1981).
108. G. Domazetis, R. J. Magee, and B. D. James, *J. Organomet. Chem.*, **162**, 239 (1978).
109. G. Domazetis and M. F. Mackay, *J. Cryst. Mol. Struct.*, **9**, 57 (1979).
110. R. Barbieri and M. Musmeci, *J. Inorg. Biochem.*, **32**, 89 (1988).
111. P. A. Cusack, P. J. Smith, and J. D. Donaldson, *J. Chem. Soc., Dalton Trans.*, 439 (1982).
112. S. Calogero, G. Valle, P. A. Cusack, P. J. Smith, and J. D. Donaldson, *Inorg. Chim. Acta*, **67**, 95 (1982).
113. L. G. Costa, *Toxicol. Appl. Pharmacol.*, **79**, 471 (1985).
114. L. Pellerito, M. T. Lo Guidice, G. Ruisi, N. Bertazzi, R. Barbieri, and F. Huber, *Inorg. Chim. Acta*, **17**, L21 (1976).
115. F. Huber, H. J. Haupt, H. Preut, R. Barbieri, and M. T. Lo Guidice, *Z. Anorg. Allg. Chem.*, **432**, 51 (1977).
116. B. K. Nicholson, *J. Organomet. Chem.*, **265**, 153 (1984).
117. R. Barbieri, L. Pellerito and F. Huber, *Inorg. Chim. Acta*, **30**, L321 (1978).
118. L. Pellerito, M. T. Lo Guidice, G. C. Stocco, J. D. Donaldson, S. M. Grimes, and P. J. Smith, *Polyhedron*, **4**, 747 (1985).
119. L. Pellerito, G. Ruisi, M. T. Lo Guidice, R. Cefalù, J. D. Donaldson, S. M. Grimes, and P. J. Smith, *Inorg. Chim. Acta*, **62**, 149 (1982).
120. H. Preut, B. Mundus, F. Huber, and R. Barbieri, *Acta Crystallogr., Sect. C*, **42**, 536 (1986).
121. P. G. Harrison and N. W. Sharpe, *Inorg. Chim. Acta*, **108**, 7 (1985).
122. L. Pellerito, G. Ruisi, N. Bertazzi, M. T. Lo Guidice, and R. Barbieri, *Inorg. Chim. Acta*, **17**, L9 (1976).
123. C. J. Cardin and A. Roy, *Inorg. Chim. Acta*, **107**, 57 (1985).
124. G. Valle, G. Plazzogna, and R. Ettore, *J. Chem. Soc., Dalton Trans.*, 1271 (1985).
125. R. Barbieri, E. Rivarola, F. Di Bianca, and F. Huber, *Inorg. Chim. Acta*, **57**, 37 (1982).
126. R. Barbieri, F. Di Bianca, E. Rivarola, and F. Huber, *Inorg. Chim. Acta*, **108**, 141 (1985).
127. L. Pellerito, G. Ruisi, M. T. Lo Guidice, J. D. Donaldson, and S. M. Grimes, *Inorg. Chim. Acta*, **58**, 21 (1982).
128. A. Patel and R. C. Poller, *Rev. Silicon Germanium Tin Lead Cmpd.*, **8**, 263 (1985).
129. S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985).
130. S. J. Blunden, P. A. Cusack, and P. J. Smith, *J. Organomet. Chem.*, **325**, 141 (1987).
131. M. Pereyre, J.-P. Quintard and A. Rahm, *Tin in Organic Synthesis*, Butterworths, London, 1987.
132. A. F. Hussain and R. C. Potter, *J. Organomet. Chem.*, **118**, C11 (1976).
133. L. D. Hall, P. R. Steiner, and D. C. Miller, *Can. J. Chem.*, **57**, 38 (1978).
134. O. J. Taylor and J. L. Wardell, *Abstr. 5th Int. Conf. Organomet. Coord. Chem. Ge, Sn, Pb, Univ. Padua*, 1986, p. 138; cited in ref. 130.
135. T. Ogawa and M. Matsui, *Carbohydr. Res.*, **56**, C1 (1977).
136. S. J. Blunden, P. J. Smith, P. J. Beynon, and D. C. Gillies, *Carbohydr. Res.*, **88**, 9 (1981).
137. K. M. Taba, R. Köster, and W. V. Dahlhoft, *Synthesis*, 399 (1984).
138. S. David, A. Thiéffry, and A. Vayrières, *J. Chem. Soc., Perkin Trans. I*, 1796 (1981).
139. A. J. Crowe and P. J. Smith, *J. Organomet. Chem.*, **110**, C57 (1976).
140. Y. Tsuda, M. E. Haque, and K. Yoshimoto, *Chem. Pharm. Bull.*, **31**, 1612 (1983).
141. J. D. Donaldson, S. M. Grimes, L. Pellerito, M. Assunta Girasolo, P. J. Smith, A. Cambria, and M. Fama, *Polyhedron*, **6**, 383 (1987).
142. A. G. Davies, A. J. Price, H. M. Dawes, and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 297 (1986).
143. S. David, C. Pascard, and M. Cesario, *Nouv. J. Chim.*, **3**, 63 (1979).
144. C. W. Holzapfel, J. M. Koekemoer, C. F. Marais, G. J. Kruger, and J. A. Pretorius, *S. Afr. J. Chem.*, **35**, 80 (1982).
145. T. Chivers, J. H. G. van Roode, J. N. R. Ruddick, and J. R. Sams, *Can. J. Chem.*, **15**, 3702 (1977).
146. J. P. Ashmore, T. Chivers, K. A. Kerr, and J. H. G. van Roode, *Inorg. Chem.*, **16**, 191 (1977).
147. T. H. Tan, J. R. Dalziel, P. A. Yeats, J. R. Sams, R. C. Thompson, and F. Aubke, *Can. J. Chem.*, **50**, 1843 (1972).
148. D. Cunningham, P. Firtear, K. C. Molloy, and J. J. Zuckerman, *J. Chem. Soc., Dalton Trans.*, 1523 (1983).
149. K. C. Molloy, M. B. Hossain, D. van der Helm, D. Cunningham, and J. J. Zuckerman, *Inorg. Chem.*, **20**, 2402 (1981).
150. D. Cunningham, L. A. Kelly, K. C. Molloy, and J. J. Zuckerman, *Inorg. Chem.*, **21**, 1416 (1982).

151. R. Barbieri, G. Alonzo, and R. H. Herber, *J. Chem. Soc., Dalton Trans.*, 789 (1987).
152. K. C. Molloy, F. A. K. Nasser, and J. J. Zuckerman, *Inorg. Chem.*, **21**, 1711 (1982).
153. B. Kubo, *Agric. Biol. Chem.*, **29**, 43 (1965).
154. K. C. Molloy and T. G. Purcell, *J. Organomet. Chem.*, **312**, 167 (1986).
155. R. E. Ridenour and E. E. Flagg, *J. Organomet. Chem.*, **16**, 393 (1969).
156. K. C. Molloy, F. A. K. Nasser, C. L. Barnes, D. van der Helm, and J. J. Zuckerman, *Inorg. Chem.*, **21**, 960 (1982).
157. D. Wagner, J. P. H. Verheyden, and J. D. Moffatt, *J. Org. Chem.*, **39**, 24 (1974).
158. L. Pellerito, G. Ruisi, R. Barbieri, and M. T. Lo Guidice, *Inorg. Chim. Acta*, **21**, L33 (1977).
159. G. Ruisi, M. T. Lo Guidice, and L. Pellerito, *Inorg. Chim. Acta*, **93**, 161 (1984).
160. M. Gielen, T. Mancilla, J. Ramharter, and R. Willem, *J. Organomet. Chem.*, **328**, 61 (1987).
161. C. J. Cardin and A. Roy, *Inorg. Chim. Acta*, **125**, 63 (1986).
162. G. Domazetis, R. J. Magee, and B. D. James, *J. Organomet. Chem.*, **197**, 39 (1980).
163. V. D. Ngo, A. Saxena, F. Huber and R. Barbieri, *Abstr. 3rd Int. Symp. effect of Tin upon Malignant Cell Growth, Univ. Padua*, 1986, C8.
164. W. N. Aldridge and B. W. Street, *Biochem. J.*, **91**, 287 (1964).
165. W. N. Aldridge, *Biochem. J.*, **59**, 367 (1958).
166. M. S. Rose and W. N. Aldridge, *Biochem. J.*, **106**, 821 (1968).
167. M. S. Rose, *Biochem. J.*, **111**, 129 (1969).
168. W. N. Aldridge, in *Organotin Compounds: New Chemistry and Applications* (Ed. J. J. Zuckerman), *Adv. Chem. Ser.*, No. 157, 186 (1976).
169. B. M. Elliot and W. N. Aldridge, *Biochem. J.*, **163**, 583 (1977).
170. B. M. Elliot, W. N. Aldridge, and J. W. Bridges, *Biochem. Soc. Trans.*, **6**, 1252 (1978).
171. B. M. Elliot, W. N. Aldridge, and J. W. Bridges, *Biochem. J.*, **177**, 461 (1979).
172. F. Taketa, K. Siebenlist, J. Kasten-Jolly, and N. Polasaari, *Arch. Biochem. Biophys.*, **203**, 466 (1980).
173. A. L. Chu, F. Taketa, A. G. Mauk, and G. D. Bayer, *J. Biomol. Struct. Dyn.*, **3**, 579 (1985).
174. K. R. Siebenlist and F. Taketa, *Biochem. J.*, **233**, 471 (1986).
175. R. Barbieri, M. T. Lo Guidice, G. Ruisi, M. T. Musmeci, *Abstr. 5th Int. Conf. Organomet. Coord. Chem. Ge, Sn, Pb, Univ. Padua*, 1986, C37.
176. W. N. Aldridge and B. W. Street, *Biomchem. J.*, **118**, 171 (1970).
177. A. P. Dawson and M. J. Selwyn, *Biochem. J.*, **138**, 349 (1974).
178. K. Cain and D. E. Griffiths, *Biochem. J.*, **162**, 575 (1977).
179. B. G. Farrow and A. P. Dawson, *Eur. J. Biochem.*, **86**, 85 (1978).
180. A. P. Dawson, B. G. Farrow, and M. J. Selwyn, *Biochem. J.*, **202**, 163 (1982).
181. K. R. Siebenlist and F. Taketa, *Biochemistry*, **22**, 4229 (1983).
182. K. R. Siebenlist and F. Taketa, *Biochemistry*, **22**, 4642 (1983).
183. J. G. R. Elferink, M. Deierkauf, and J. van Steveninck, *Biochem. Pharmacol.*, **35**, 3727 (1986).
184. E. A. Lock and W. N. Aldridge, *J. Neurochem.*, **25**, 871 (1975).
185. M. Wender, B. Zgorzalewicz, A. Piechowski, W. Spieszalski, and M. Bucholc, *Exp. Pathol.*, **23**, 193 (1983).
186. M. R. Rose and E. A. Lock, *Biochem. J.*, **120**, 151 (1970).
187. W. N. Aldridge and B. W. Street, *Biochem. J.*, **91**, 287 (1964).
188. M. J. Selwyn, A. P. Dawson, M. Stockdale, and N. Gains, *Eur. J. Biochem.*, **14**, 120 (1970).
189. M. Stockdale, A. P. Dawson and M. J. Selwyn, *Eur. J. Biochem.*, **15**, 342 (1970).
190. M. S. Rose and W. N. Aldridge, *Biochem. J.*, **127**, 51 (1972).
191. M. J. Selwyn, in *Organotin Compounds: New Chemistry and Applications* (Ed. J. J. Zuckerman), *Adv. Chem. Ser.*, No. 157, 204 (1976).
192. W. N. Aldridge, B. W. Street, and D. N. Skilleter, *Biochem. J.*, **168**, 353 (1977).
193. E. L. Emanuel, M. A. Carver, G. C. Solani, and D. E. Griffiths, *Biochim. Biophys. Acta*, **766**, 209 (1984).
194. M. Porvaznik, B. H. Gray, D. Mattie, A. G. Jackson, and R. E. Omlor, *Lab. Invest.*, **54**, 254 (1986).
195. A. G. Davies and P. J. Smith, in *Comprehensive Organometallic Chemistry* (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Pergamon Press, Oxford, 1982, p. 525.
196. R. Barbieri, *G. Fis.*, **23**, 289 (1982).
197. W. N. Aldridge, *Rev. Silicon Germanium Tin Lead Cmpd.*, Special Issue, Freund Publishing House, Tel-Aviv, 1978, p. 9.

198. W. N. Aldridge, B. W. Street, and J. G. Noltes, *Chem.-Biol. Interact.*, **34**, 223 (1981).
199. K. R. Siebenlist and F. Taketa, *Biochemistry*, **22**, 4229 (1983).
200. K. R. Siebenlist and F. Taketa, *Biochemistry*, **22**, 4642 (1983).
201. V. Massey and C. Veeger, *Biochim. Biophys. Acta*, **48**, 33 (1961).
202. D. E. Griffiths, K. Cain, and R. L. Hyams, *Biochem. Soc. Trans.*, **5**, 205 (1977).
203. F. E. Smith and K. L. Ee, *Experientia*, **36**, 391 (1980).
204. K. Grätz, F. Huber, A. Silvestri, and R. Barbieri, *J. Organomet. Chem.*, **273**, 283 (1984).
205. K. Grätz, F. Huber, A. Silvestri, G. Alonzo, and R. Barbieri, *J. Organomet. Chem.*, **290**, 41 (1985).
206. B. H. Gray, M. Porvaznik, and H. L. Lee, *J. Appl. Toxicol.*, **6**, 363 (1986).
207. J. L. Lefferts, K. C. Molloy, M. B. Hossain, D. van der Helm, and J. J. Zuckerman, *J. Organomet. Chem.*, **240**, 349 (1982).
208. N. F. Cardarelli and S. V. Kanakkanat, *US Pat.*, 4541956 (1985).
209. L. R. Sherman, M. J. Coyer, and F. Huber, *Appl. Organomet. Chem.*, **1**, 355 (1987).
210. A. Saxena, F. Huber, L. Pellerito, and A. Girasolo, *Appl. Organomet. Chem.*, **1**, 413 (1987).
211. A. Saxena, F. Huber, L. Pellerito, A. Girasolo, and G. C. Stocco, *Inorg. Chim. Acta*, **125**, 197 (1986).
212. L. R. Sherman, D. M. Soma, and C. J. Thoman, *Appl. Organomet. Chem.*, **1**, 359 (1987).
213. P. Smith and L. Smith, *Chem. Br.*, 208 (1976).
214. C. J. Evans and S. Karpel, *J. Organomet. Chem. Lib.*, **16**, 1 (1985).
215. S. S. Sandhu, Jr, and G. K. Sandhu, *J. Chem. Sci.*, **6**, 52 (1980).
216. S. J. Blunden, P. A. Cusack, and R. Hill, *The Industrial Uses of Tin Compounds*, Royal Society of Chemistry, London, 1985.
217. S. Balabaskaran, K. Tilakavati, and V. G. Kumar Das, *Appl. Organomet. Chem.*, **1**, 347 (1987).
218. K. R. S. Archer and J. Moscowitz, *Int. Pest. Control*, **11**, 17 (1969).
219. K. R. S. Ascher, *Phytoparasitica*, **7**, 117 (1979).
220. R. Bock, in *Residue Reviews* (Ed. F. A. Gunther), Vol. 79, Springer, New York, 1981.
221. K. R. S. Ascher, M. Eliyahu, E. J. Bulten, and H. A. Meinema, *Appl. Organomet. Chem.*, **1**, 303 (1987).
222. E. E. Kenager, *Proc. 12th Int. Congr. Entomol., London*, 1965, p. 517.
223. A. J. Crowe, *Appl. Organomet. Chem.*, **1**, 143 (1987).
224. A. J. Crowe, *Appl. Organomet. Chem.*, **1**, 331 (1987).
225. D. Barug, *Chemosphere*, **10**, 1145 (1981).
226. R. J. Orsler and G. E. Holland, *Int. Biodeterior. Bull.*, **18**, 95 (1982).
227. A. J. Crowe, R. Hill and P. J. Smith, "Laboratory Evaluation of Tributyltin Compounds as Wood Preservatives" Publication 559, International Tin Research Institute, London, 1979.
228. A. J. Crowe, R. Hill, P. J. Smith and T. R. G. Cox, *Int. J. Wood Preserv.*, **1**, 119 (1979).
229. R. Hill and P. J. Smith, *Int. J. Wood Preserv.*, **3**, 77 (1983).
230. U. Schroer and H. Plum, *Ger. Pat.*, 2659288 (1978).
231. J. D. Thornton and O. Collett, *Mater. Org.*, **14**, 131 (1979).
232. S. J. Blunden and R. Hill, *Inorg. Chim. Acta*, **87**, 83 (1984).
233. B. A. Richardson, *Stone Ind.*, **8**, 22 (1973).
234. B. A. Richardson, *Rec. Annu. Conv. Br. Wood Preserv. Assoc.*, 37 (1970).
235. A. Bravery, N. Parameswaran, and W. Liese, *Mater. Org.*, **10**, 31 (1975).
236. P. J. Smith, A. J. Crowe, D. W. Allen, J. S. Brooks, and R. Formstone, *Chem. Ind. (London)*, 874 (1977).
237. A. G. Davies and P. J. Smith, in *Comprehensive Organometallic Chemistry* (Eds G. Wilkinson, F. G. A. Stone, and E. W. Abel), Pergamon Press, Oxford, 1982, p. 583.
238. R. Hill, International Research Group on Wood Preservation, Doc. No. IRG/WP/3312 (1984).
239. R. Hill, P. J. Smith, and J. N. R. Ruddick, International Research Group on Wood Preservation, Doc. No. IRG/WP/3229 (1983).
240. S. J. Blunden, R. Hill, and J. N. R. Ruddick, *J. Organomet. Chem.*, **267**, C5 (1984).
241. S. J. Blunden, R. Hill, and D. G. Gillies, *J. Organomet. Chem.*, **270**, 39 (1984).
242. T. Hof, *J. Inst. Wood Sci.*, **4**, 19 (1969).
243. C. J. Evans and R. Hill, *J. Oil Colour Chem. Assoc.*, **64**, 215 (1981).
244. M. H. Gitlitz, *J. Coat. Technol.*, **53**, 46 (1981).
245. F. Dawans, *Rev. Inst. Fr. Pet.*, **37**, 767 (1982).
246. J. Kowalski, W. Stánczyk, and J. Chojnowski, *Rev. Silicon Germanium Tin Lead Cmpd.*, **6**, 225 (1982).

247. C. J. Evans and R. Hill, *Rev. Silicon Germanium Tin Lead Cmpd.*, 7, 57 (1983).
248. R. H. Chandler and J. Chandler, *Fungicides, Preservatives and Anti-fouling Agents for Paints*, R. H. Chandler Ltd, Technical Note, 1977; cited in ref. 216.
249. J. F. Russell, *Bibliography on Anti-fouling Uses of Organotins*, International Tin Research Library Bibliography No. 8, International Tin Research Institute, London, 1981.
250. N. F. Cardarelli, *Controlled Release Pesticide Formulations*, CRC Press, Cleveland, OH, 1976.
251. N. F. Cardarelli and H. F. Neff, *US Pat.* 3639583 (1972).
252. N. F. Cardarelli, *Rev. Silicon Germanium Tin Lead Cmpd.*, **8**, 169 (1985).
253. R. F. Lohr and H. Barry, *Pap. Meet. Am. Chem. Soc. Div. Org. Coat. Plast. Chem.*, **29**, 7 (1969).
254. A. O. Christie, *J. Oil Colour Chem. Assoc.*, **60**, 348 (1977).
255. W. L. Yeager and V. J. Castelli, in *Organometallic Polymers* (Eds C. E. Carraher, Jr, J. E. Sheats, and C. V. Pittman, Jr), Academic Press, London, 1978, p. 175.
256. R. V. Subramanian and K. N. Somasekharan, *J. Macromol. Sci. Chem.*, **A16**, 73 (1981).
257. R. V. Subramanian, B. K. Garg, and J. Corredor, in *Organometallic Polymers* (Eds C. E. Carraher, Jr, J. E. Sheats, and C. V. P. Hman, Jr), Academic Press, London, 1978. p. 181.
258. J. F. Hoffman, K. C. Kappel, L. M. Frenzel, and M. L. Good, in *Organometallic Polymers* (Eds C. E. Carraher, Jr, J. E. Sheats, and C. V. Pittman, Jr), Academic Press, London, 1978, p. 195.
259. E. J. O'Brien, C. P. Monaghan, and M. L. Good, in *Organometallic Polymers* (Eds C. E. Carraher, Jr, J. E. Sheats, and C. V. Pittman, Jr), Academic Press, London, 1978, p. 207.
260. C. Alzieu, Y. Thibaud, M. Heral, and B. Boutier, *Rev. Trav. Inst. Peches Marit.*, **44**, 301 (1980).
261. A. R. D. Stebbing, *Mar. Pollut. Bull.*, **16**, 383 (1985).
262. I. M. Davies, J. C. McKie, and J. D. Paul, *Aquaculture*, **55**, 103 (1986).
263. M. J. Waldock, J. E. Thain, and M. E. Waite, *Appl. Organomet. Chem.*, **1**, 287 (1987).
264. R. J. Maguire, *Appl. Organomet. Chem.*, **1**, 475 (1987).
265. N. M. Brown, *PhD Thesis*, Clemson University, South Carolina (1972).
266. V. L. Narayanan, in *Structure–Activity Relationships of Anti-Tumour Agents* (Eds D. N. Reinhoudt, T. A. Connors, H. M. Pinedo, and K. W. van de Poll), Martinus Nijhoff, The Hague, 1983, p. 5.
267. Anon, *Occupational Exposure to Organotin Compounds*, US DHEW (NIOSH) Publ. No. 77–115, 1976; cited in reference 216.
268. A. Saxena and J. P. Tandon, *Cancer Lett.*, **19**, 73 (1983).
269. G. Atassi, *Rev. Silicon Germanium Tin Lead Cmpd.*, **8**, 219 (1985).
270. N. F. Cardarelli (Ed.), *Tin as a Vital Nutrient*, CRC Press, Boca Raton, FL, 1985.
271. A. Saxena, *Appl. Organomet. Chem.*, **1**, 39 (1987).
272. A. J. Crowe and P. J. Smith, *Chem. Ind. (London)*, **5**, 200 (1980).
273. A. J. Crowe, P. J. Smith, and G. Atassi, *Chem.-Biol. Interact.*, **32**, 171 (1980).
274. A. J. Crowe, P. J. Smith, and G. Atassi, *Inorg. Chim. Acta*, **93**, 179 (1984).
275. N. F. Cardarelli, B. M. Cardarelli, E. P. Libby, and E. Dobbins, *Aust. J. Exp. Biol. Med. Sci.*, **62**, 209 (1984).
276. T. M. Aminabhavi, N. S. Biradar, S. B. Patil, and D. E. Hoffman, *Inorg. Chim. Acta*, **108**, L31 (1985).
277. L. De Clerq, R. Willem, M. Gielen, and G. Atassi, *Bull. Soc. Chim. Belg.*, **93**, 1089 (1984).
278. M. Gielen, K. Jurkschat, and G. Atassi, Bull. Soc. Chim. Belg., **93**, 153 (1984).
279. I. Haiduc, C. Silvestru, and M. Gielen, *Bull. Soc. Chim. Belg.*, **92**, 187 (1983).
280. M. Gielen, R. Willem, T. Mancilla, J. Ramharter, and E. Joosen, *Rev. Silicon Germanium Tin Lead Compd.*, **9**, 349 (1986).
281. C. J. Cardin and A. Roy, *Inorg. Chim. Acta*, **107**, L37 (1985).
282. M. Gielen, E. Joosen, T. Mancilla, K. Jurkschat, R. Willem, C. Roobol, J. Bernheim, G. Atassi, F. Huber, E. Hoffmann, H. Preut, and B. Mahieu, *Main Group Met. Chem.*, **10**, 147 (1987).
283. R. Barbieri, L. Pellerito, G. Ruisi, M. T. Lo Guidice, F. Huber, and G. Atassi, *Inorg. Chim. Acta*, **66**, L39 (1982).
284. M. Gielin, in *Tin as a Vital Nutrient* (Ed. N. F. Cardarelli), CRC Press, Boca Raton, FL, 1985, p. 169.
285. J. Szejtli, *Cyclodextrins and Their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.
286. A. J. Crowe, P. J. Smith, C. J. Cardin, H. E. Page, and F. E. Smith, *Cancer Lett.*, **24**, 45 (1984).
287. W. Peters, E. R. Trotter, and B. L. Robinson, *Ann. Trop. Med. Parasitol.*, **74**, 321 (1980).
288. G. H. Nösler, *Gesundheitswes. Desinfekt.*, **62**, 175 (1970).

289. P. B. Hudson, G. Sanger, and E. E. Sproul, *J. Am. Med. Assoc.*, **169**, 89 (1959).
290. J. Duncan, *Pharmacol. Ther.*, **10**, 407 (1980).
291. W. J. Connolly, *Pap. Trade J.*, **141**, 46 (1957).
292. H. J. Hueck and J. G. A. Luijten, *J. Soc. Dyers Colour.*, **74**, 476 (1958).
293. P. A. Cusack, L. A. Hobbs, P. J. Smith, and J. S. Brooks, *J. Text. Inst.*, **71**, 138 (1980).
294. C. J. Anthony, Jr, and J. R. Tigner, *Wire Prod.*, **43**, 72 (1968).
295. Recent results suggest that this is a result of a redistribution process. R. Hill and S. J. Blunden, *Appl. Organomet. Chem.*, **2**, 251 (1988).

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

Author index

This author index is designed to enable the reader to locate an author's name and work with the aid of the reference numbers appearing in the text. The page numbers are printed in normal type in ascending numerical order, followed by the reference numbers in parentheses. The numbers in *italics* refer to the pages on which the references are actually listed.

The Chemistry of the Metal—Carbon Bond, Volume 5
Edited by F. R. Hartley

Subject index