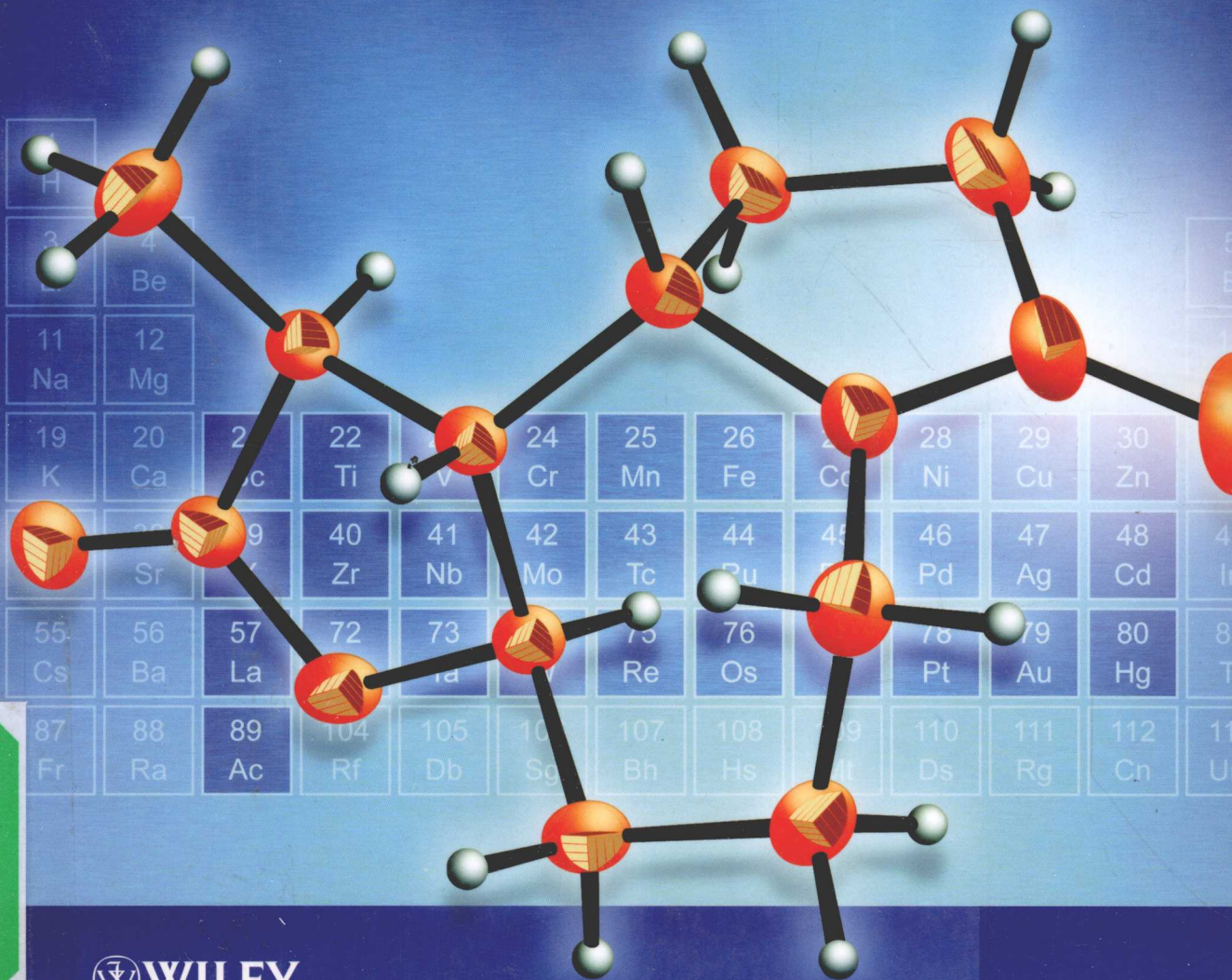


Second Edition

ORGANIC SYNTHESIS USING TRANSITION METALS

Roderick Bates



 **WILEY**

Organic Synthesis Using Transition Metals

Second Edition

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Nanyang Technological University, Singapore



 **WILEY**

A John Wiley & Sons, Ltd., Publication

This edition first published 2012
© 2012 John Wiley & Sons, Ltd

First Edition published in 2000

Registered office

John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

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Library of Congress Cataloging-in-Publication Data

Bates, Roderick.

Organic synthesis using transition metals / Roderick Bates. – 2nd ed.
p. cm.

Includes bibliographical references and index.

ISBN 978-1-119-97894-7 (hardback) – ISBN 978-1-119-97893-0 (paper)

1. Transition metals. 2. Organic compounds—Synthesis. I. Title.

QD172.T6B383 2012

547'.056—dc23

2012003765

A catalogue record for this book is available from the British Library.

HB ISBN: 9781119978947

PB ISBN: 9781119978930

Typeset in 10/12pt Times by Aptara Inc., New Delhi, India

Printed and bound in Malaysia by Vivar Printing Sdn Bhd

The cover shows the X-ray crystallographic structure of stemoamide, a *stemona* natural product, determined by Dr. Li Yongxin in the X-Ray Crystallography Laboratory of the Division of Chemistry and Biological Chemistry, Nanyang Technological University, Singapore. Syntheses of Steoamide can be found in chapter 4, scheme 44 and chapter 8, scheme 112.

About the Author

Roderick Bates received his PhD at Imperial College, London with Professor Steven Ley, using organoiron complexes for organic synthesis. After a postdoctoral stint at Colorado State University with Professor L. S. Hegedus working on chromium carbenes, he moved to the University of North Texas as an Assistant Professor and began independent research, working on palladium catalysed coupling reactions, organocobalt chemistry and applications of allenes. After some years spent in Thailand at Chulalongkorn University and the Chulabhorn Research Institute and a short stay in the ill-fated Department of Chemistry at Exeter, he joined Nanyang Technological University in Singapore as a pioneer member of the brand-new Division of Chemistry and Biological Chemistry. He is currently an Associate Professor and has research interests in the use of transition metals in natural product synthesis, and stereocontrol in alkaloid chemistry.

Preface

The gradual realization that complexes of transition metals have a place in organic synthesis has caused a quiet revolution. Organic chemists have used certain transition metal substances, such as palladium on carbon and OsO₄, for many years. These kinds of reactions are not the subject of this book, as they appear in every standard text. The aim of this book is to provide an outline of the principle reactions of transition metal complexes that are used in organic synthesis, both catalytic and stoichiometric, with examples to show how they can be applied, and sufficient mechanistic information to allow them to be understood. The examples of syntheses are intended to place them in the context of the entire synthesis where space permits, so a great deal of non-transition metal chemistry can also be found in these pages. The molecular targets include natural products, novel structures and molecules of industrial, especially pharmaceutical, interest. The scale of the reaction for some of these molecules is indicated to show that these reactions are of more than just academic interest.

Tremendous progress has been made since the first edition of this work. The introduction of new ligands ("designer ligands") has hugely expanded the scope of coupling reactions and is starting to impact other areas, while the introduction of NHC ligands has opened new possibilities in reactions of many types, from coupling to metathesis. Ten years ago, this field of chemistry was dominated by palladium; now other metals, once neglected, have become firmly established. In particular, the organic chemistry of gold has become a major area. Metathesis chemistry has gone from strength to strength. An old but also once neglected area, the activation of C-H bonds by transition metals, has achieved huge prominence and has earned itself its own chapter. Two more general trends have emerged. One is that the emphasis on catalytic reactions, rather than stoichiometric reactions has increased. While it is undeniable that catalytic reactions are the ones that will be used in industry, the stoichiometric chemistry of transition metal complexes can still provide transformations that are both elegant and interesting and, hence, retain their place. The other is the much greater acceptance of transition metal mediated reactions in the mainstream of organic synthesis. In the first edition, most syntheses might feature a single such transformation; it is now increasingly common for syntheses to include multiple, different transition metal mediated reactions. The different aspects of such syntheses can be found in various chapters of this text.

Roderick Bates
January 2012

Contents

About the Author	xiii
Preface	xv
1 Introduction	1
1.1 The Basics	2
1.2 The Basic Structural Types	2
1.2.1 Phosphines	5
1.2.2 Phosphites	8
1.2.3 <i>N</i> -Heterocyclic Carbenes	9
1.2.4 Other Ligands	10
1.2.5 Quantifying Ligand Effects	10
1.2.6 Heterogeneous Catalysis	10
1.3 Just How Many Ligands Can Fit around a Metal Atom?	10
1.3.1 Method 1: Covalent	11
1.3.2 Method 2: Ionic	11
1.3.3 Examples	12
1.4 Mechanism and the Basic Reaction Steps	13
1.4.1 Coordination and Dissociation	13
1.4.2 Oxidative Addition and Reductive Elimination	15
1.4.3 Transmetallation	15
1.4.4 Alkene and Alkyne Insertion	15
1.4.5 CO Insertion	16
1.4.6 β -Hydride Elimination	16
1.4.7 Oxidative Cyclization	17
1.5 Catalysis	17
References	19
2 Coupling Reactions	21
2.1 Carbon–Carbon Bond Formation	21
2.1.1 The Main-Group Metal, M	22
2.1.2 Limitation	23
2.1.3 Reactivity of the Leaving Group	23
2.1.4 Selectivity	25
2.1.4.1 Selectivity Based on Halogen Reactivity	25
2.1.4.2 Steric Hindrance	25
2.1.4.3 Electronic Effects	26
2.2 Lithium and Magnesium: Kumada Coupling	27
2.3 Zinc: The Negishi Reaction	32
2.4 Aluminium and Zirconium	35

2.5	Tin: The Stille Reaction	37
2.5.1	Vinyl Stannanes	41
2.5.2	Aryl and Heteroaryl Stannanes	42
2.5.3	The Intramolecular Stille Reaction	42
2.5.4	Coupling of Acid Chlorides	42
2.5.5	Stille Coupling of Triflates	44
2.5.6	Stille Coupling of Alkyl Halides	44
2.5.7	Stille Reaction Troubleshooting	44
2.6	Boron: The Suzuki Reaction	46
2.6.1	Alkenyl Borane Coupling Reactions	48
2.6.2	Alkyl Borane Coupling Reactions	50
2.6.3	Aryl Borane Coupling Reactions	52
2.6.4	Suzuki Coupling of Alkyl Halides	56
2.7	Silicon: The Hiyama Reaction	57
2.8	Copper: The Sonogashira Reaction	61
2.9	Other Metals	67
2.10	Homocoupling	67
2.11	Enolate and Phenoxide Coupling	69
2.12	Heteroatom Coupling	70
2.12.1	Palladium-Catalysed Synthesis of Amine Derivatives	72
2.12.2	Palladium-Catalysed Synthesis of Ethers	76
2.12.3	Ullmann Coupling	78
2.12.4	Formation of Other C–X bonds	81
	References	82
3	C–H Activation	89
3.1	Arenes and Heteroarenes	91
3.1.1	Fujiwara–Heck Reaction	91
3.1.2	Biaryl Coupling	93
3.2	Aldehydes	100
3.3	Borylation and Silylation	102
3.4	Allylic Functionalization	103
3.5	Unfunctionalized C–H Bonds	105
3.5.1	Carbon–Heteroatom Bond Formation	105
3.5.2	Carbon–Carbon Bond Formation	109
	References	115
4	Carbonylation	117
4.1	Carbonylative Coupling Reactions: Synthesis of Carbonyl Derivatives	117
4.2	Carbonylative Coupling Reactions: Synthesis of Carboxylic Acid Derivatives	122
4.3	Carbonylation of Alkenes and Alkynes	127
4.3.1	The Carbonylative Heck Reaction	127
4.3.2	Other Carbonylation Reactions of Alkenes and Alkynes	129
4.4	Hydroformylation	130
4.4.1	Directed Hydroformylation	135
4.4.2	Asymmetric Hydroformylation	138

4.5	Stoichiometric Carbonylation Using Carbonyl Complexes	139
4.5.1	Iron and Cobalt Carbonyl Anions	139
4.5.2	Ferrilactones and Ferrilactams	142
4.5.3	Molybdenum and Tungsten Carbonyls	145
4.6	Carboxylation	146
4.7	Decarbonylation and Decarboxylation	148
	References	150
5	Alkene and Alkyne Insertion Reactions	153
5.1	The Heck Reaction	153
5.1.1	The Organic Halide	153
5.1.2	Leaving Groups	155
5.1.3	Catalysts, Ligands and Reagents	158
5.1.4	The Alkene: Scope and Reactivity	159
5.1.5	The Alkene: Regio- and Stereoselectivity	160
5.1.6	Cyclic Alkenes	161
5.1.7	Isomerization	162
5.1.8	The Intramolecular Heck Reaction	163
5.1.9	The Asymmetric Heck Reaction	164
5.1.10	Tandem Reactions	169
	5.1.10.1 Alkynes	169
	5.1.10.2 Trisubstituted Alkenes	171
	5.1.10.3 Rigid Alkenes	172
5.1.11	Heck-Like Reactions of Organometallics	174
5.2	Insertion Reactions Involving Zirconium and Titanium	175
5.2.1	Hydrozirconation and Carbozirconation	175
5.2.2	Alkene and Alkyne Complexes	177
5.2.3	Zirconium-Mediated Carbomagnesiation	182
5.2.4	The Kulinkovich Reaction	185
	References	188
6	Electrophilic Alkene and Alkyne Complexes	191
6.1	Electrophilic Palladium Complexes	191
6.1.1	Tandem Reactions Involving CO or Alkene Insertion	198
6.1.2	Tandem Reactions with Oxidative Addition	207
6.2	Other Metals: Silver, Gold, Platinum and Rare Earths	210
6.2.1	Reactions of Alkenes	210
6.2.2	Reactions of Allenes	213
6.2.3	Reactions of Alkynes	216
6.2.4	The Hashmi Phenol Synthesis	223
6.2.5	Ene–Yne Cyclization	225
6.3	Iron	229
6.3.1	Fp Complexes of Alkenes	229
6.3.2	Fp Complexes of Alkynes	234
6.3.3	Alkylation of Allyl Fp Complexes and Formal Cycloadditions	234
6.4	Cobaloxime π -Cations	235
	References	237

7 Reactions of Alkyne Complexes	241
7.1 Alkyne Cobalt Complexes	241
7.2 Propargyl Cations: The Nicholas Reaction	244
7.3 The Pauson–Khand Reaction	246
7.3.1 Asymmetric Pauson–Khand Reaction	248
7.3.2 The Hetero-Pauson–Khand Reaction	249
7.4 Synthesis Using Multiple Cobalt Reactions	250
References	251
8 Carbene Complexes	253
8.1 Fischer Carbenes	253
8.1.1 Demetallation	258
8.1.2 The Dötz Reaction	258
8.1.3 Not the Dötz Reaction	263
8.1.4 Fischer Carbene Photochemistry	267
8.2 Vinylidene Complexes	269
8.3 Metathesis Reactions Involving Carbene Complexes	273
8.3.1 Tebbe’s Reagent	274
8.3.2 Alkene (Olefin) Metathesis	278
8.3.3 Ring-Closing Metathesis	279
8.3.4 Cross-Metathesis	291
8.3.5 Ring-Opening Metathesis	296
8.3.6 Asymmetric Metathesis	297
8.3.7 Ene–Yne Metathesis	300
8.3.8 Ene–Yne–Ene Metathesis	303
8.3.9 Tandem Reactions	306
8.3.10 Metathesis Side Reactions	306
8.4 Carbyne Complexes	310
8.4.1 Alkyne Metathesis	310
8.5 Carbene Complexes from Diazo Compounds	312
8.5.1 Nucleophilic Trapping	313
8.5.2 C–H Insertion Reactions of Carbene Complexes	315
8.5.3 C–H Insertion Reactions of Nitrene Complexes	316
References	319
9 η^3- or π-Allyl Complexes	325
9.1 Stoichiometric Reactions of π -Allyl Complexes	325
9.2 Catalysis: Mostly Palladium	328
9.2.1 Regioselectivity	331
9.2.2 Internal versus Terminal Attack	333
9.2.3 Stereoselectivity	335
9.2.4 Asymmetric Allylation	337
9.2.5 Synthesis Using Palladium Allyl Chemistry	341
9.2.6 Base-Free Allylation	343
9.2.7 Allylation with Decarboxylation	347
9.2.8 Allyl as a Protecting Group	350
9.2.9 Other Routes to η^3 - or π -Allyl Palladium Complexes	352
9.3 Propargyl Compounds	357
References	357

10 Diene, Dienyl and Arene Complexes	361
10.1 η^4 -Diene Complexes	361
10.1.1 Electrophilic Attack	364
10.1.2 Nucleophilic Attack	366
10.1.3 Deprotonation	370
10.2 η^5 -Dienyl Complexes	371
10.2.1 Nucleophilic Attack	372
10.3 η^6 -Arene Complexes	377
10.3.1 Nucleophilic Attack	380
10.3.2 Deprotonation	385
10.4 η^2 -Arene Complexes	387
References	389
 11 Cycloaddition and Cycloisomerization Reactions	 391
11.1 Formal Six-Electron, Six-Atom Cycloadditions	391
11.1.1 The [4 + 2] Cycloaddition	391
11.1.2 The [2 + 2 + 2] Cycloaddition	394
11.2 Cycloadditions Involving Fewer than Six Atoms	402
11.2.1 Four-Membered Rings	402
11.2.2 Five-Membered Rings through TMM Methods	402
11.2.3 Other Five-Membered Ring Formations	405
11.3 Cycloadditions Involving More than Six Atoms	407
11.3.1 The [5 + 2] Cycloaddition	407
11.3.2 The [4 + 4] Cycloaddition	410
11.3.3 The [6 + 2] and [6 + 4] Cycloadditions	411
11.4 Isomerization	414
11.5 Cycloisomerization and Related Reactions	415
References	426
 Abbreviations	 431
 Index of Principle Transition Metal Catalysts and Reagents	 433
 Index	 437

1

Introduction

At irregular intervals, it is announced that organic synthesis is dead, that it is a completed science, that all possible molecules can be made by the application of existing methodology, and that there are no new reactions or methods to discover – everything worth doing has been done. And yet new molecular structures come up to challenge the imagination, most often from nature, and new challenges arise from the demands of society and industry, usually to be more selective, to be more efficient and to be more green. The tremendous progress that has been made in the last few decades, including the hectic period since the first edition of this work appeared, is more than ample to prove the prophecies of doom to be wrong. The art and science of organic synthesis continues to make progress as the new challenges are met. While much of the limelight has been taken up by the expansion of the once small and neglected field of asymmetric organocatalysis, huge progress has also been made in the use of transition metals. The academic and practical significance of this area can be seen by a glance at the list of Nobel prizes for chemistry (even if not all of the laureates had intended to contribute to organic synthesis): Sabatier, shared with Grignard (1912), Ziegler¹ and Natta² (1963), Wilkinson³ and Fischer⁴ (1973), Sharpless,⁵ Noyori⁶ and Knowles⁷ (2001), Grubbs, Schrock⁸ and Chauvin⁹ (2005) and, most recently, Heck, Negishi¹⁰ and Suzuki¹¹ (2010).

Advances in the area have not been uniform. With the challenge of greenness, atom economy and sustainability, the most progress has been made in the area of catalysis.¹² Progress in the use of stoichiometric transition-metal reagents and with transition-metal complex intermediates has lagged, while progress in catalysis has surged ahead. Four areas of transition-metal chemistry have been at the forefront of recent progress. One is the tremendous advances and applications made in the area of alkene metathesis chemistry and its spin-off fields. What was once a mainstay of the petrochemical industry, but a curiosity to synthetic organic chemistry has become a standard method for carbon–carbon bond formation. New metathesis catalysts continue to open up new possibilities. The second, not unrelated, area is the development of new ligands. At one time, except for asymmetric catalysis, triphenylphosphine was the option as a ligand, with a small number of variants available. Driven by the demand for greater efficiency and wider substrate scope, a myriad of complex ligands is now available. While their initial impact was upon coupling reactions, their influence is spreading to other areas. The emergence of the *N*-heterocyclic carbene ligands has provided a second stimulus in this area and opened up further opportunities. In addition to more ligands, a greater number of the transition metals are finding applications in organic synthesis. While palladium probably remains the most widely used metal, its “market share” has shrunk, with the increasing use other metals. Most notable is the glittering rise of gold and gold catalysis. The final area had been present in the literature for decades but only took off recently.

This is the area of C–H activation, based upon the realization that C–H bonds are not passive spectators, but, with the ability of transition metals to insert into them under mild conditions, are potent functional groups.

This is an area of science that is very much alive and moving forwards. Transition-metal chemistry is not only used for academic purposes, but also in the fine chemicals industry. The reader will find references to these real-life applications in the appropriate chapters.

1.1 The Basics

Why? What is special about the transition metals and the chemistry that we can do using them? What makes metals such as palladium, iron and nickel different from metals such as sodium, magnesium and lithium? The answer lies in the availability of d-orbitals, filled or empty, that have energy suitable for interaction with a wide variety of functional groups of organic compounds. In an important example, transition metals can interact with alkenes. In ordinary organic chemistry, simple alkenes are relatively unreactive, being ignored by almost all bases and nucleophiles, requiring a reactive radical or a strong electrophile or oxidizing agent, such as bromine, ozone or osmium tetroxide (watch out – osmium is a transition metal!). But they coordinate to transition metals and their reactivity changes. An important molecule that has almost no “ordinary” organic chemistry is CO. It is ignored by metal ions such as Na^+ and Mg^{2+} , but forms complexes with almost all transition metals and is ubiquitous in transition-metal chemistry. The reactions of CO, catalysed by transition metals, has made it a fundamental C_1 building block for both complex molecules and bulk chemicals.

Organometallic chemistry begins with the work of Frankland in the 1840s who made the first organozinc compounds. Grignard’s work with organomagnesium compounds rapidly became part of the standard repertoire of organic chemists, and remains there today. The pathway for transition metals was not so smooth and took much longer. Indeed, it followed two tracks. One track was in industry, where the understandable objective is a profitable process even if there is no understanding of what is happening in the mechanistic “black box”. This track produced alkene metathesis and hydroformylation. The other track was in academia, restrained by the need to understand. Alongside the isolation of then unexplainable complexes, such as an ethylene complex of platinum by Danish apothecary Zeise,¹³ one of the starting points is with Ludwig Mond in the late nineteenth century.¹⁴ He serendipitously discovered $\text{Ni}(\text{CO})_4$ – an amazing compound in that it is a gas under normal conditions, yet is made from so-solid metallic nickel. In terms of using transition metals for synthetic chemistry, a great advance was by Sabatier at the end of the nineteenth century who showed that finely divided metals such as nickel, palladium or platinum could catalyse the hydrogenation of alkenes. This discovery rapidly led to the manufacture of margarine, for instance. A real turning point was with the determination of the structure of ferrocene by Wilkinson – many decades after Mond. This gave chemists a stable organometallic compound to study and understand. Aided by advances in instrumentation, it was in this period that chemists were able to study organotransition-metal complexes thoroughly and understand the ground rules of their reactivity.

Thus, the use of transition metals enables the organic chemist to do reactions that are difficult or, more often, impossible otherwise, opening up new synthetic pathways and selectivities. Transition-metal organometallics do this through a different set of rules. To understand what is done and what can be done, it is important to be familiar with these rules.

1.2 The Basic Structural Types

While some of the structures found look similar to those formed by s-block and p-block metals, many do not. Many organometallic complexes are classified by the number of contiguous atoms, usually carbon atoms, but

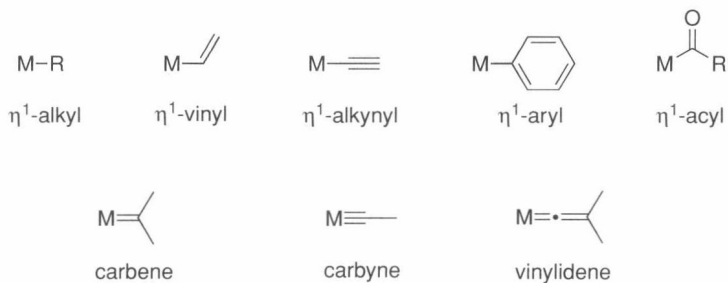


Figure 1.1 η^1 -Complexes.



Figure 1.2 η^2 -Alkene complex.

not always, bound to the metal. This number is known as the hapticity or hapto number. As this is symbolized as a superscript with the Greek letter “eta”, η , it is sometimes called the eta number.

η^1 -Complexes contain a metal–carbon single bond (Figure 1.1). The organic group may be alkyl, vinyl, alkynyl, aryl or acyl. With the exception of the acyl complexes, there are analogous compounds of more familiar metals, such as magnesium and zinc. It is also possible to have complexes with metal–carbon double and triple bonds; these are known as carbenes and carbynes. Cumulenes are also known, such as in vinylidene complexes.

η^2 -Complexes do not have analogues amongst the main group metals. They are formed by the interaction of the metal with the π -orbitals of alkenes and alkynes (Figure 1.2). They may also be drawn as their metallacyclopentane resonance structures, although this representation is less frequently used. The first such complex, isolated in the early nineteenth century, is the platinum–ethylene complex known as Zeise’s salt (Figure 1.3).¹⁵

The reason for the ability of transition metals to bind to alkenes (and alkynes) lies in the fact that electrons can be donated in both directions, resulting in a synergistic effect (Figure 1.4). The π^* -orbital of the alkene can accept electrons from filled d-orbitals on the metal, while the filled π -orbital of the alkene can donate back to empty metal orbitals. This is known as the Chatt—Dewar—Duncanson model.¹⁶

η^3 -Allyl complexes, also known as π -allyl complexes, have three atoms bonded to the metal (Figure 1.5). They are frequently in equilibrium with the corresponding η^1 -allyl complex.

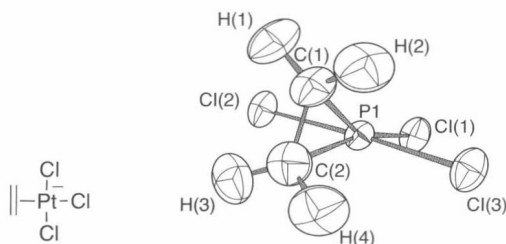


Figure 1.3 Zeise’s salt. Reprinted with permission from Love, R. A.; Koetzle, T. F. et al. *Inorg. Chem.* **1975**, 14, 2653. © 1975 American Chemical Society.

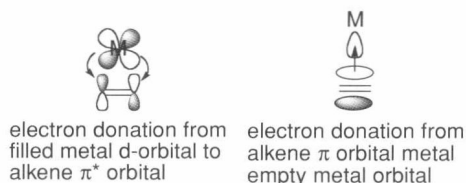


Figure 1.4 The Chatt–Dewar–Duncanson model.



Figure 1.5 The η^3 – η^1 equilibrium in allyl complexes.



Figure 1.6 η^4 , η^5 and η^6 -complexes.

η^4 -diene, η^5 -dienyl and η^6 -arene complexes have four, five or six atoms bonded to the metal (Figure 1.6). The chemistry of these complexes is explored in Chapter 10. Amongst the η^5 -dienyl complexes, the best known is the η^5 -cyclopentadienyl ligand. Such is its ubiquity, that it has its own symbol: Cp. The best known of the cyclopentadienyl compounds is ferrocene (Cp_2Fe) with two Cp rings, the original sandwich compound. The permethyl derivative, pentamethylcyclopentadienyl, is known as Cp^* . The most important class of η^6 -complexes by far is the η^6 -arene complexes in which a metal is coordinated to the face of a benzene derivative through the π -system. η^7 -Complexes are unusual in synthesis: an example may be found in Chapter 11. In all of these complexes, the carbon atoms are coplanar, with the metal occupying one face.

A ligand of special importance is carbon monoxide. The reactivity of CO is a key difference between transition-metal chemistry and classical organic chemistry. Several of the transition metals, such as Mond's nickel, can even form complexes with only CO. The HOMO of CO is its σ^* -orbital, concentrated on the carbon atom, hence CO is most commonly bonded to the metal via its carbon atom. Backbonding then occurs with electron donation from metal d-orbitals into the LUMO of carbon monoxide which is the π^* -orbital (Figure 1.7). This is the case for the simple metal carbonyls including $\text{Ni}(\text{CO})_4$, $\text{Fe}(\text{CO})_5$ and $\text{Cr}(\text{CO})_6$.

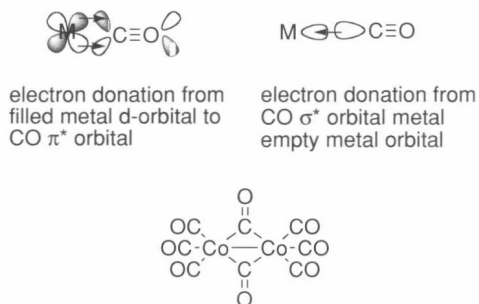


Figure 1.7 Carbonyl complexes.

Carbon monoxide may also be a bridging ligand between two metal atoms. Some of the CO ligands in the complexes $\text{Fe}_2(\text{CO})_9$, $\text{Co}_2(\text{CO})_8$ and $\text{Fe}_3(\text{CO})_{12}$ can behave in this way.

Heteroatoms may also be ligands. These include oxygen, nitrogen, sulfur and halogen atoms. Some of these, such as oxygen, may form double bonds to the metal, as in OsO_4 . A variety of nitrogen species may complex to the metal including the rather special case of the nitrosyl ligand, NO^+ , which can replace CO.

1.2.1 Phosphines

The most widely employed heteroatom ligands are the phosphines. Although they are largely spectators and do not participate directly in bond formation (and when they do, the result is often highly undesirable), they are not innocent bystanders. The size and electronic nature of the three groups attached to phosphorus have a profound effect on the course of the reaction and may make the difference between success and failure. An example is with the Grubbs catalyst (Chapter 8). The bis(triphenylphosphine) complex is of little use. The bis(tricyclohexylphosphine) complex is Nobel-prize winning.

Triphenylphosphine **1.1** has always been the most commonly used ligand, due to cost, availability, ease of handling and habit. While triphenylphosphine **1.1** remains commonly used, it no longer has its old ubiquity. An entire field of research, which might be termed “ligand engineering”, has grown up, centred on the design of new ligands with tailor-made electronic and steric properties (Figure 1.8). In a great many of the early applications of transition metals to organic synthesis, triphenylphosphine was used almost exclusively. An early exception is the use of a modified version, tri-*o*-tolylphosphine **1.2**, in Heck reactions.¹⁷ This was done to suppress quaternization of the phosphine by adding steric hindrance, though its success may actually be due to formation of Herrmann’s catalyst *in situ*.¹⁸ Addition of one or more sulfonate groups to the phenyl rings gives water-soluble analogues, such as **1.3**. Triphenylphosphine has also been modified by changing the donor atom. Both triphenylarsine **1.4** and triphenylstibine **1.5** have been employed. Changing the phenyl groups to furyl groups giving the more electron-rich tri-(2-furyl)phosphine **1.6** can also be beneficial. Alternatively, adding fluorine atoms gives an electron-poor ligand in tris(pentafluorophenyl)phosphine **1.7**. One or more of

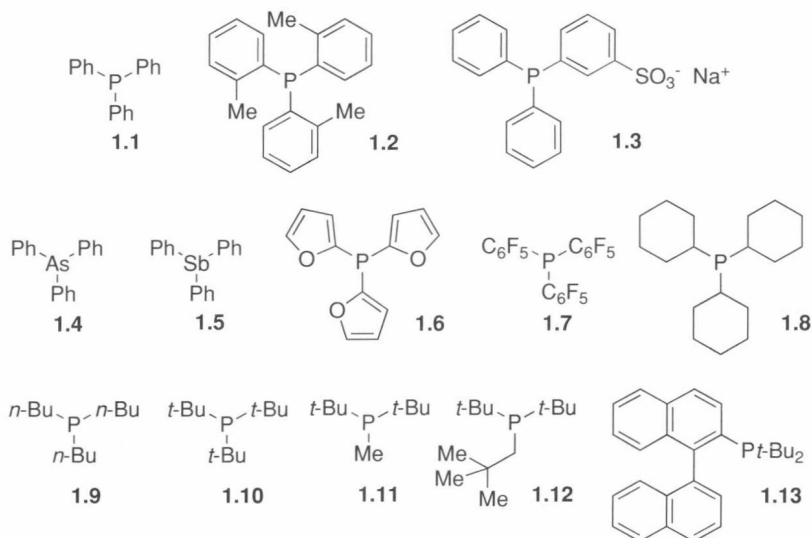


Figure 1.8 Phosphine ligands.

the aryl groups attached to phosphorus may be changed to alkyl groups. Tri(cyclohexyl)phosphine **1.8** has found considerable application from being both more electron rich and more bulky than its aromatic analogue, triphenylphosphine. The related tricyclopentylphosphine is also known. Acyclic alkyl groups have also been used. Tri-*n*-butylphosphine **1.9** is readily available and used in organic procedures, such as Staudinger reactions and Wittig reactions, but is relatively uncommon as a ligand. In contrast, tri-*t*-butylphosphine **1.10**, has proved to be valuable. Its bulk promotes ligand dissociation and, hence, catalytic reactivity. As you can have too much of a good thing, the less-hindered di(*t*-butyl)methylphosphine **1.11** is also available. The neopentyl group and binaphthyl groups has also been used to replace one of the *t*-butyl groups. The binaphthyl modification **1.13** is known as Trixiephos. A disadvantage of using alkyl phosphines is their air sensitivity. All phosphines can be oxidized to the corresponding phosphine oxides, but this tendency is more pronounced with alkyl phosphines. A solution is to store and handle them as a salt, such as the tetrafluoroborate salt.¹⁹ If a small amount of a base is added to the reaction mixture, and many reaction mixtures already contain a base, then the phosphine is liberated *in situ*.

The focus of development of more sophisticated ligands has mainly been concerned with replacing one of the groups on phosphorus with a biphenyl group (Figure 1.9). Johnphos **1.14** and its dicyclohexyl analogue **1.15** contain the unadorned biphenyl moiety. Addition of *ortho*-substituents to the second phenyl group changes the steric and electronic properties, as in Sphos **1.16** and the closely related Ruphos **1.17**, both with alkoxy substituents. Mephos **1.18** and Xphos **1.19** have different alkyl substituents. Davephos **1.20** and its *t*-butyl analogue **1.21** possess a potentially chelating amino group. More highly substituted ligands, such as Brettphos **1.22** and Jackiephos **1.23**, have also been developed. Qphos **1.24**, with a highly substituted ferrocene moiety, can also be considered in this class of ligands.

The popularity of the biphenyl moiety in many ligands is not a mere result of adding bulk. The second aryl ring, twisted at an angle to its partner, may affect the metal directly by coordination, as in the cationic gold complex (Figure 1.10).²⁰ The X-ray structure (anionic counter ion not shown) clearly shows the proximity of the second ring to the metal atom.

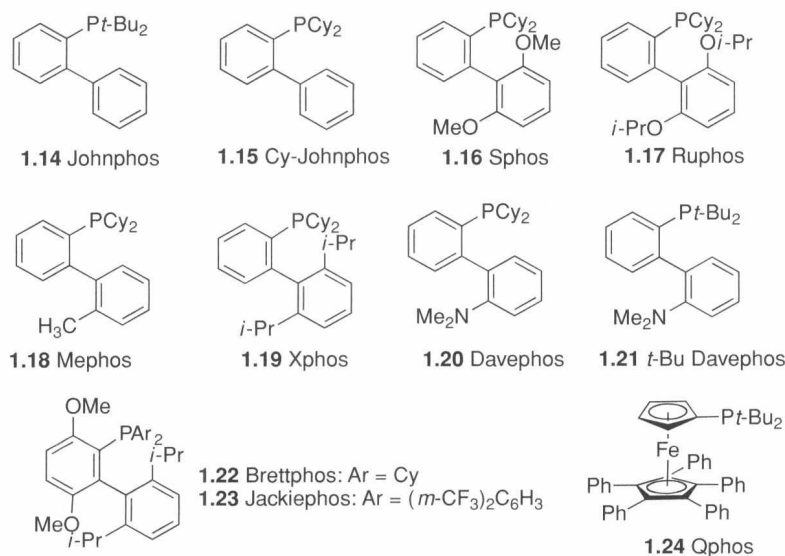


Figure 1.9 Phosphine ligands with a biphenyl motif.