Transition metals open up new opportunities for synthesis, because their means of bonding and their reaction mechanisms differ from those of the elements of the s and p blocks. In the last two decades the subject has mushroomed – established reactions are seeing both technical improvements and increasing numbers of applications, and new reactions are being developed.

Organic Synthesis Using Transition Metals, Second Edition considers the ways in which transition metals, as catalysts and reagents, can be used in organic synthesis. It concentrates on the bond-forming reactions that set transition metal chemistry apart from “classical” organic chemistry.

For this second edition the text has been extensively revised and expanded to reflect the significant improvements and advances in the field since the first edition, as well as the large number of new transition metal-catalysed processes that have come to prominence in the last 10 years – for example the extraordinary progress in coupling reactions using “designer” ligands, catalysis using gold complexes, new opportunities arising from metathesis chemistry, and C-H activation. Each chapter is extensively referenced and provides a convenient point of entry to the research literature.

Organic Synthesis Using Transition Metals, Second Edition will find a place on the bookshelves of advanced undergraduates and postgraduates working in organic synthesis, catalysis, medicinal chemistry and drug discovery. It is also be useful for practising researchers who want to refresh and enhance their knowledge of the field.
Organic Synthesis Using Transition Metals
Organic Synthesis Using Transition Metals

Second Edition

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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.
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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 OsO$_4$, 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
Introduction

At irregular intervals, it is announced that organic synthesis is dead, that it is a completed science, that
tall 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), Ziegler and Natta
(1963), Wilkinson and Fischer (1973), Sharpless, Noyori and Knowles (2001), Grubbs, Schrock and
Chauvin (2005) and, most recently, Heck, Negishi and Suzuki (2010).

Advances in the area have not been uniform. With the challenge of greenness, atom economy and sus-
tainability, the most progress has been made in the area of catalysis. Progress in the use of stoichiometric
transition-metal reagents and with transition-metal complex intermediates has lagged, while progress in catal-
ysis 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 con-
tinue 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.
2 Organic Synthesis Using Transition Metals

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 Mg²⁺, 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 C₁ 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 Ni(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
MR

\[ \eta^1-\text{alkyl} \]

\[ \eta^1-\text{vinyl} \]

\[ \eta^1-\text{alkynyl} \]

\[ \eta^1-\text{aryl} \]

\[ \eta^1-\text{acyl} \]

\[ \text{carbene} \]

\[ \text{carbyne} \]

\[ \text{vinylidene} \]

\text{Figure 1.1} \hspace{1em} \eta^1-\text{Complexes.}

\text{Figure 1.2} \hspace{1em} \eta^2-\text{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”, \( \eta \), it is sometimes called the eta number.

\( \eta^1 \)-Complexes contain a metal–carbon single bond (Figure 1.1). The organic group may be alkyl, vinyl, alkylnyl, 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 carbines. Cumulenes are also known, such as in vinylidene complexes.

\( \eta^2 \)-Complexes do not have analogues amongst the main group metals. They are formed by the interaction of the metal with the \( \pi \)-orbitals of alkenes and alkynes (Figure 1.2). They may also be drawn as their metallacyclopropane 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 Ziese’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 \( \pi^* \)-orbital of the alkene can accept electrons from filled d-orbitals on the metal, while the filled \( \pi \)-orbital of the alkene can donate back to empty metal orbitals. This is known as the Chatt—Dewar—Duncanson model.\(^{16}\)

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

\text{Figure 1.3} \hspace{1em} \text{Ziese’s salt. Reprinted with permission from Love, R. A.; Koetzle, T. F. et al. Inorg. Chem. 1975, 14, 2653. © 1975 American Chemical Society.}
4 Organic Synthesis Using Transition Metals

Figure 1.4 The Chatt–Dewar–Duncanson model.

Figure 1.5 The \( \eta^3 - \eta^1 \) equilibrium in allyl complexes.

Figure 1.6 \( \eta^4 \), \( \eta^5 \) and \( \eta^6 \)-complexes.

\( \eta^4 \)-diene, \( \eta^5 \)-dienyl and \( \eta^6 \)-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 \( \eta^5 \)-dienyl complexes, the best known is the \( \eta^5 \)-cyclopentadienyl ligand. Such is its ubiquity, that it has its own symbol: Cp. The best known of the cyclopentadienyl compounds is ferrocene (Cp\(_2\)Fe) with two Cp rings, the original sandwich compound. The permethyl derivative, pentamethylcyclopentadienyl, is known as Cp\(^*\). The most important class of \( \eta^6 \)-complexes by far is the \( \eta^6 \)-arene complexes in which a metal is coordinated to the face of a benzene derivative through the \( \pi \)-system. \( \eta^1 \)-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 \( \sigma^* \)-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 \( \pi^* \)-orbital (Figure 1.7). This is the case for the simple metal carbonyls including Ni(CO)\(_4\), Fe(CO)\(_5\) and Cr(CO)\(_6\).
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 $\text{OsO}_4$. A variety of nitrogen species may complex to the metal including the rather special case of the nitrosyl ligand, $\text{NO}^+$, 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. 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. 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.](image)
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 Trisixephos. 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. 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). 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.
Bidentate phosphines have been used for many years (Figure 1.11). They provide the complex with greater stability because, for complete ligand dissociation, two metal–phosphine bonds must be broken, rather than one. Simple bidentate ligands consist of two diphenylphosphino units linked by an alkyl chain or group (1.26–1.30). More complex ligands use more elaborate linkers. Bis(diphenylphosphino)ferrocene, with a ferrocenyl linker, has proved to be a useful ligand. Most other linkers are based upon aromatic motifs. BINAP 1.33, most often employed as a chiral ligand for asymmetric catalysis, has sometimes been used. Xantphos 1.34 and DPEphos 1.35 form a special subset of bidentate ligands. In square planar complexes, such as complexes with palladium(II), due to the geometrical demands of the linker, the two phosphines are capable of being trans.\textsuperscript{21} The other bidentate ligands tend to be cis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{bidentate_phosphines}
\caption{Bidentate phosphines.}
\end{figure}

\textbf{Figure 1.10} A gold(I) biphenylphosphine complex. Reprinted with permission from Herrero-Gómez, E.; Nieto-Oberhuber, C. et al. Angew. Chem., Int. Ed. 2006, 45, 5455. © 2006 Wiley-VCH Verlag GmbH & Co. KGaA.
The use of chiral phosphines has been the principle way to achieve asymmetric reactions in organometallic chemistry. A small selection of the huge number of chiral phosphines reported so far is presented in Figure 1.12. While chiral monodentate species have been used, most of the ligands are bidentate. Their designs can be divided into three groups. One group has the chirality present in the chain that links the two phosphorus atoms. Many of these are axially chiral. The two enantiomers of BINAP, \(1.36/1.37\), are the first in this group, and many derivatives and modifications of BINAP have been reported. Others, such as chiraphos \(1.40\) and skewphos \(1.41\) have stereogenic carbon atoms in the chain. A second group, represented here by Me-DUPHOS \(1.42\) has the chirality in the phosphorus substituents, rather than the chain. A third and rarer group exploits the chirality of the phosphorus atom. DIPAMP \(1.43\), the first effective ligand for asymmetric hydrogenation, is in this group. Applications of asymmetric catalysis are included in several chapters. For a deeper discussion, the reader is referred to more specialized textbooks. ²²

### 1.2.2 Phosphites

Phosphites are closely related to phosphines, but have P–O bonds in place of P–C bonds (Figure 1.13). While they have been found to be useful ligands in certain reactions (see Section 4.4 and Sections 11.1.1 and 11.2.2), they have not been subject to the same widespread use or development as phosphines.

![Figure 1.13 Phosphites.](image-url)
1.2.3  

**N-Heterocyclic Carbenes**

Carbene complexes have been known since the 1960s. Their chemistry revolves around the reactions of the carbene moiety (Chapter 8). The isolation of the first stable carbene by Arduengo,\(^\text{23}\) and the realization that such carbenes could function as useful ligands for transition metals, in a similar way to phosphines, opened up a new chapter in organometallic chemistry.\(^\text{24,25}\) Arduengo's first stable carbenes were formed by the deprotonation of imidazolium salts (Schemes 1.1 and 1.2). The carbene carbon is built into a stabilizing nitrogen heterocycle. The stabilization is principally electronic, by the two nitrogen atoms. The \(N\)-substituents provide steric stabilization that is not, however, essential.\(^\text{26}\) They are, therefore, referred to as \(N\)-heterocyclic carbenes or NHCs. The many NHC ligands that have followed have largely been variations on Arduengo's original (Figure 1.14). The \(N\)-mesityl, rather than \(N\)-admantyl, has been commonly used, although families of \(N\)-alkyl carbenes have been produced. The double bond in the \(N\)-heterocycle may be absent, as in the Grubbs second-generation catalyst (Chapter 8). The heterocycle may also be varied, as in TPT \(1.50\). Numerous more complex carbenes, including chelating bis-carbenes, have also been synthesized.

![Scheme 1.1](image1.png)

**Scheme 1.1**

![Scheme 1.2](image2.png)

**Scheme 1.2**

![Figure 1.14](image3.png)

\(1.47\) IMes  
\(1.48\) SIMes  
\(1.49\) ClIMes  
\(1.50\) TPT

**Figure 1.14**  
N-heterocyclic carbene (NHC) ligands.
1.2.4 Other Ligands

Many other species have been employed as ligands, including amines and nitrogen heterocycles, sulfides and sulfoxides, halides, alkoxides and nitriles. Dienes, such as 1,5-cyclooctadiene, are commonly used as ligands.

1.2.5 Quantifying Ligand Effects

The two principle effects of the ligand are electronic and steric. The concept of cone angle is used to describe the size of a ligand (Table 1.1). It is the angle of a cone that has its point at the metal and just contains the phosphine ligand. As this angle will vary depending on the metal–ligand bond length, the standard is taken as the nickel tricarbonyl derivative, (OC)$_3$NiL.

Is cone angle still adequate to describe the increasingly complex phosphine ligands, and the new NHC ligands that are far from cone shaped? New quantifiers are being proposed.

1.2.6 Heterogeneous Catalysis

The vast majority of the transition-metal catalysed reactions in this book use transition-metal species that are soluble in the reaction medium. These are often well-defined and characterized complexes. It does not have to be this way. Sources of transition metals that are insoluble in the reaction medium, especially heterogeneous sources of palladium, can be very effective. Palladium on inert supports, such as carbon, has been employed for many decades for hydrogenation reactions. They can also be employed for carbon–carbon bond-forming reactions. Other heterogeneous sources, such as perovskites, which are better known as components of car exhaust systems, have also been used. Catalysts of this type may act as sources of palladium, releasing palladium as complexes or nanoparticles into the reaction medium, then reclaiming it. Often, these systems leave less residual metal contamination in the final product and, therefore, are particularly useful industrially.

1.3 Just How Many Ligands Can Fit around a Metal Atom?

This is a fairly easy question to answer. If we think about elements such as carbon, nitrogen and oxygen, we know that their valency can be explained by the importance of filling the outer valence
shell with eight electrons and obtaining an inert-gas configuration. As they have to fill up an s orbital and three p orbitals, this means acquiring eight electrons, including the electrons that they already possess.

Transition metals have to fill an s orbital, three p orbitals and five d orbitals. This requires eighteen electrons. This is the eighteen-electron rule. These electrons must either belong to the metal atom already or must be supplied by the ligand. We must also adjust for the charge.

There are two methods for adding up electrons, both are based on counting the electrons contributed to the complex from the metal and the ligands. The methods have been referred to as the “covalent” and “ionic” methods as they differ in the notional origin of the electrons. It has to be clearly understood that this is the notional origin, not the actual origin. A hydride ligand is assigned as bringing 1 or 2 electrons to the complex respectively, whether its actual origin was from LiAlH$_4$, H$_2$ or HCl. The same answer is obtained whichever method is used. The important thing is to not get the two methods mixed up! Examples of both methods are given in Figures 1.15–1.18.

1.3.1 Method 1: Covalent

*Electrons from the metal:* This is equal to its group number. Just count from the far left-hand column (group 1) of the periodic table (Table 1.2).

*Electrons from the ligands:* this depends, naturally on the ligands. For hydrocarbon ligands, the number is equal to the hapto number. Single-bonded ligands (hydride, halide etc) count as 1 (although a bridging halide counts as 2 – a lone-pair donor), while carbenes and carbynes count as 2 and 3, respectively. Lone-pair donors, such as phosphines and CO, count as 2.

*Charge:* electrons have a negative charge. A positive charge on your complex means a missing electron, so subtract one. A negative charge means an extra electron, so add one.

1.3.2 Method 2: Ionic

*Electrons from the metal:* first, the oxidation state of the metal must be assigned. Oxidation state is a formalism, but a useful formalism. The assignment can be done by the notional stripping off of ligands to reveal a notional metal ion. Ligands that are donors of pairs of electrons, or multiple pairs of electrons are removed with their pair(s) of electrons and do not effect the charge of the metal. Examples include alkenes, dienes and arenes (all of which have an even hapto number), CO, phosphines and carbenes. Ligands with a sigma bond are stripped off as anions even if this makes no chemical sense. Examples are alkyl, allyl, dienyl and even acyl ligands (all of which have an odd hapto number), hydride, halide and carbynes. The number of electrons contributed by the metal is then its group number (count from the far left-hand column (group 1) of the periodic table) minus the oxidation state. This is also the number of d electrons, d$^\dagger$. This number is useful for comparing metals with different oxidation states across groups of the periodic table.

<table>
<thead>
<tr>
<th>Table 1.2</th>
<th>Transition metals and numbers of electrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sc</td>
<td>Ti</td>
</tr>
<tr>
<td>Y</td>
<td>Zr</td>
</tr>
<tr>
<td>La</td>
<td>Hf</td>
</tr>
</tbody>
</table>
12 Organic Synthesis Using Transition Metals

Electrons from the ligands: The number of electrons supplied by a ligand is related to how the ligand was notionally stripped off above. Hydrocarbon ligands with even hapto numbers were stripped off as neutral molecules, so the number of electrons donated is equal to their hapto number. Hydrocarbon ligands with odd hapto numbers were stripped off as anions, so the number of electrons donated is equal to their hapto number plus one. Thus, an allyl group is a donor of four electrons. Lone-pair donors donate two electrons; sigma-bonded ligands stripped off as anions also donate two electrons.

Charge: The assignment of the oxidation state has already taken the charge into account, so there is no further adjustment.

1.3.3 Examples

The rule is often broken. d⁸-Complexes of metals towards the right-hand side of the d-block often form stable square-planar complexes, such as (Ph₃P)₂PdCl₂. Bulky ligands may prevent a complex reaching 18 electrons: palladium forms an eighteen-electron complex with triphenylphosphine to give the popular catalyst (Ph₃P)₄Pd, but only a fourteen-electron complex with the bulkier tri(t-buty)phosphine, (t-Bu₃P)₂Pd. Complexes with fewer than 18 electrons are not impossible; it is just that they tend to be less stable. What is important to remember is that stable complexes are unreactive. To get them to participate in chemistry, it is usually first necessary to get them away from their stable state (meaning, in most cases, 18 electrons) by forcing them to dissociate a ligand.

### Example 1: Cp(Ph₃P)CoMe₂

<table>
<thead>
<tr>
<th>Ligands:</th>
<th>Cp = 5</th>
<th>Ph₃P = 2</th>
<th>Me = 2 x 1 = 2</th>
<th>Metal: Co = 9</th>
<th>Charge = 0</th>
<th>Total = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal: Co = +3</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Oxidation state = +3

### Example 2:

<table>
<thead>
<tr>
<th>Ligands: 4 x CO = 4 x 2 = 8</th>
<th>ketone lone pair = 2</th>
<th>η¹-aryl = 1</th>
<th>Metal: Mn = 7</th>
<th>Charge = 0</th>
<th>Total = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligands: 4 x CO = 4 x 2 = 8</td>
<td>ketone lone pair = 2</td>
<td>η¹-aryl = 2</td>
<td>Metal: Mn(+1) = 6</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Oxidation state = +1
1.4 Mechanism and the Basic Reaction Steps

To adapt the well-known phrase of Lord Rutherford, organic chemistry without mechanism is just stamp collecting. Mechanisms have been proposed for all of the major reactions catalysed or mediated by transition metals and used in organic synthesis. In many cases, the proposed mechanisms are supported by sound and thorough studies. In other cases, this is not so. The reader should approach any published mechanism (including those in this book) with caution. Unless the mechanism is backed up by the proper experiments such as kinetics and isotopic labeling, it should be regarded as speculative and fully open to reinterpretation. Nevertheless, thinking about mechanisms is one of the most valuable activities and an excellent source of new ideas.

Mechanisms for reactions catalysed or mediated by transition metals are multistep. While the overall result can be complex and bewildering, the individual steps are taken from a quite small and relatively simple list. Some of these are common to “classical” organic chemistry; others are specific to the transition metals. While the basic reactions such as nucleophilic and electrophilic attack do operate, the presence of transition metals means that another set of basic reaction steps also operate. Combinations of these steps give us the overall reactions that we use.

1.4.1 Coordination and Dissociation

The most fundamental step is the simple coordination and dissociation of ligands (Scheme 1.3). This is important because a stable complex cannot coordinate the substrate, but must first dissociate a ligand. Although some ligands are sufficiently labile to dissociate under mild conditions, in other cases it is necessary to use heat or light to achieve this. Often, reaction conditions are dictated by this initial dissociation.
The equilibrium between the coordinated and dissociated species may be driven towards the dissociated side, to generate the more reactive complex, by the addition of a second metal ion (Scheme 1.4). The purpose of the second ion is to absorb the dissociated ligand, thus driving the equilibrium according to le Chatelier’s principle. In the case of phosphine ligands, this can be done using copper(I) salts (see Section 2.5.7). In the case of chloride ligands, this can be done, effectively irreversibly, but the addition of silver(I) salts (see Section 6.2 and Section 11.3.1). In this latter situation, what is achieved is the exchange of the chloride for a more labile anionic ligand, often triflate, but also perchlorate, tetrafluoroborate and hexafluoroantimonate.

\[
\begin{align*}
\text{L}_n\text{M} &\text{-PPh}_3 + \text{CuX} \leftrightarrow \text{L}_n\text{M} + \text{PPh}_3\text{PCuX} \\
\text{L}_n\text{M} &\text{-Cl} + \text{AgOTf} \rightarrow \text{L}_n\text{M} &\text{-OTf} + \text{AgCl}
\end{align*}
\]

**Scheme 1.4**

Dissociation may also be made easier by replacing a strongly bound ligand with a weakly bound ligand in a separate step (Scheme 1.5). This can be achieved by destruction of a ligand. This is often done by oxidation of a CO ligand to CO\(_2\) using an amine oxide. The vacant site is then taken up by the more labile amine ligand. Another strategy is to substitute a less-labile ligand for a more-labile ligand in a separate step, so that the substrate avoids the more brutal conditions required for dissociation.

\[
\begin{align*}
\text{L}_n\text{M} &\text{-CO} \rightarrow_{\text{Me}_3\text{N}-\text{O}} \text{L}_n\text{M} &\text{-NMe}_3 + \text{CO}_2 \\
\text{Mo(CO)}_6 &\rightarrow_{\text{hv}, \text{MeCN}} \text{Mo(CO)}_3(\text{NCMe})_3
\end{align*}
\]

**Scheme 1.5**

Exchange of ligands may also be employed to modify the reactivity of a complex. Substitution of CO by NO\(^+\) will make a complex much more electrophilic (see Scheme 10.19). Substitution of CO by PPh\(_3\) will achieve the opposite.

Complexation can also raise stereochemical issues. When a \(\pi\)-system is involved, the metal may attach to either face (Scheme 1.6). Selectivity is often observed, and can be exploited. The selectivity may be due to steric effects or neighbouring group effects.\(^{32}\)

**Scheme 1.6**
1.4.2 Oxidative Addition and Reductive Elimination

Oxidative addition is the most important method for the formation of a metal–carbon single bond, although it is not limited to just this. In oxidative addition, a transition-metal fragment, which must have less than eighteen electrons, inserts into the X–Y bond, and the oxidation state of the metal increases by 2 (Scheme 1.7). Usually X is an organic group and Y is a leaving group, such as a halide. There are, however, many other possibilities, including the simple one where both X and Y are hydrogen. The reverse process is reductive elimination in which the metal fragment is expelled by formation of an X–Y bond, and the oxidation state of the metal drops by 2.

\[
\begin{align*}
M + X-Y & \xrightarrow{\text{oxidative addition}} X \quad \text{M} \quad Y \\
& \xleftarrow{\text{reductive elimination}} \quad \text{M} \quad Y
\end{align*}
\]

Scheme 1.7

1.4.3 Transmetallation

Oxidative addition is often followed by transmetallation in which an organic group on a second metal, usually a main group metal, is transferred in exchange for a group such as a halide (Scheme 1.8). This is another important method for formation of a transition metal–carbon bond. There is no change in oxidation state.

\[
\begin{align*}
M_1-X & \xrightarrow{\text{transmetallation}} M_1 \quad X \\
R-M_2 & \quad \text{R} \quad M_2
\end{align*}
\]

Scheme 1.8

1.4.4 Alkene and Alkyne Insertion

A fundamental process for coordinated alkenes and alkynes is insertion (also called migratory insertion), usually into a metal–carbon or metal–hydrogen bond (Scheme 1.9). This is a stereospecifically syn process, so insertion of alkynes results in cis-vinyl complexes. There is no change of oxidation state.

\[
\begin{align*}
M-R & \xrightarrow{\text{insertion}} M-C-C-R \\
M-R & \xrightarrow{\text{insertion}} M-\equiv-C-R
\end{align*}
\]

Scheme 1.9

The insertion of ethylene into a carbon–cobalt bond was carefully studied as part of work on the mechanism of Ziegler–Natta polymerization (Scheme 1.10).33
1.4.5 CO insertion

Similarly, CO insertion (or migratory insertion) is the fundamental transformation of the CO ligand. It is a reversible process and an equilibrium will exist between the \( \eta^1 \)-alkyl and \( \eta^1 \)-acyl complexes (Scheme 1.11). This insertion is not observed for the formation of formyl ligands \((R = H)\), owing to the low thermodynamic stability of the formyl group.

$$\text{Scheme 1.10}$$

1.4.6 \( \beta \)-Hydride Elimination

For alkyl transition-metal complexes, \( \beta \)-hydride elimination is a significant process and many alkyl organometallics are unstable because of this facile transformation. It is the reverse of an alkene-insertion process (Scheme 1.12). As with insertion, there is no change in oxidation state. While the initial product is a \( \eta^2 \)-complex, it is frequently followed by dissociation to give the free alkene. Stereochemically, it is also a syn process and, thus, quite unlike the familiar E2 reaction in classical organic chemistry.

If there is no \( \beta \)-hydrogen available, then \( \beta \)-hydride elimination is (almost) impossible. \( \eta^1 \)-Acyl, aryl and vinyl complexes do not undergo this reaction. The reaction is impossible for alkyl complexes possessing no \( \beta \)-hydrogens at all, such as neopentyl derivatives (Figure 1.19). \( \beta \)-Hydrogens may also be unavailable for geometrical reasons. In the norbornyl complex, \( H_a \) is unavailable as the rigidity of the bicyclic structure prevents a syn relationship with the metal. \( H_b \) is unavailable, as elimination would produce a structure in breach of Bredt’s rule. The same is true if the metal is at the bridgehead position of a norbornane structure, as in the stable tetranorbornyl derivative of cobalt (Figure 1.20).34. Complexes that are unable to undergo \( \beta \)-hydride elimination for these reasons are sometimes referred to as \( \beta \)-blocked.

$$\text{Scheme 1.12}$$

**Figure 1.19** \( \beta \)-Blocked complexes. Reprinted with permission from Byrne, E. K.; Theopold, K. H. J. Am. Chem. Soc. 1989, 111, 3887. © 1989 American Chemical Society.
1.4.7 Oxidative Cyclization

Oxidative cyclization (or oxidative coupling) is also a key reaction of alkene complexes, giving rise to metallacycles (Scheme 1.13). The oxidation state of the metal increases by 2.

Scheme 1.13

1.5 Catalysis

A catalyst is a substance that, when present in a reaction, increases the rate without itself being consumed.\(^{35}\) However, the catalyst cannot change the \(\Delta G\) or \(\Delta H\) of the reaction, or the position of an equilibrium; the change of rate is due to lowering of the activation energy. Most of the reactions catalysed by transition metals cannot occur in the absence of the catalyst. Transition-metal catalysts therefore increase the rate from zero, by opening up new molecular pathways. This is unlike many catalysts in classical organic chemistry. For instance, the formation of esters by the reaction of a carboxylic acid and an alcohol does proceed, albeit at a snail’s pace, even in the absence of a strong acid. The phenomenon of catalysis was discovered (amongst others) by Döbereiner, a Chemist in the German city of Jena, in 1823.\(^ {36}\) He found that when a jet of hydrogen...
gas (generated by the reaction between zinc and sulfuric acid) played upon a piece of platinum foil in air, the gas immediately ignited even though no flame was present. This discovery not only provided the world’s first lighter, but also introduced the concept of catalysis, a term coined by the great Swedish chemist, Berzelius.\textsuperscript{37}

Catalysis has become increasingly important. Many organometallic processes – though not all – are catalytic. Catalysis reduces waste and reduces cost. Ideally, the loading of the catalyst should be as low as possible. Many reactions employed in academic labs are run at 5 mol\%. It seems likely that these could work at much lower loadings. While low catalyst loading is obviously desirable, it must be remembered that there is nothing in the definition of a catalyst about the loading. Thus, a material used in excess can still be a catalyst. Whatever the loading, the test as to whether something is acting as a catalyst is to draw the mechanism as a catalytic cycle (Figure 1.21). If the cycle brings the species back to where it started, then the reaction is catalytic.

The term catalyst is widely used. It is often applied to molecules that are not the catalyst, but a precursor for the catalyst. These should be termed “pre-catalysts”. This is particularly the case is industrial processes. A combination of metal salts, reagents, ligands and supports are combined in a reactor. Somehow, they combine \textit{in situ} to generate the catalyst. Due to this combination process, some reactions may have an induction period.

The activity of the catalyst is an important issue. While the reactivity can be judged empirically by looking at the reaction conditions, temperature, concentration, pressure if a gas is involved, for catalysts, the loading is an important factor. In academic laboratories, it is common practice to employ 5 or 10 mol\% as a standard loading. In academic research, cost of chemicals and waste disposal is often less of an issue, and the cost of a catalyst is of lesser importance when the investigator is fifteen steps into a thirty-step sequence! An additional factor is that many academic reactions are run on milligrammes of substrate, and measuring anything less than 5 mol\% of catalyst is very difficult. The situation is quite different in industry. Catalyst loading must be reduced to reduce the cost of the process, to reduce the cost of waste disposal and to minimize the amount of residual metal that may contaminate the final product. In this age, it is time for all academic labs to address the issue of catalyst loading to train students to think in this way for green and cost-effective chemistry.

So how do we measure the activity of the catalyst? This is usually discussed as the turnover number (TON), a concept adapted from enzymology. For mechanistic studies in organometallic chemistry, the turnover number is the number of times the catalyst can go around the catalytic cycle before becoming deactivated.\textsuperscript{38}
In practice, for organic synthesis, the limit is often when the substrate is consumed, even if the catalyst is still active. Hence, for practical purposes, TON quoted will be calculated based upon the number of moles of product formed divided by the number of moles of catalyst employed, so a reaction proceeding in 80% chemical yield with 5 mol% of a catalyst will have a turnover number of \( \frac{80}{5} = 16 \). \(^{39}\) TOF is the turnover number per unit time.

References

25. Although the free carbene ligands were not isolated until the work of Arduengo, their complexes had been prepared as long ago as 1968: Öfele, K. J. Organometal. Chem. 1968, 12, P42; Wanzlick, H.-W.; Schönherr, H.-J. Angew. Chem., Int. Ed. 1968, 7, 141.
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35. The term “catalytic amount” is widely used and understood, even though the definition of a catalyst does not refer to any amount of material.
37. Berzelius provided a more elegant definition: “to awaken affinities, which are asleep at a particular temperature, by their mere presence and not by their own affinities”. For a historical discussion, see Roberts, M. W. *Catalysis Lett.* 2000, 67, 1.
2

Coupling Reactions

2.1 Carbon–Carbon Bond Formation

The coupling of an organometallic and an organic halide should be a useful way of forming a C–C single bond. The reaction is, however, not general, but restricted to special cases. Grignard reagents will react efficiently with some halides, such as allyl halides, while copper reagents can be used in this type of reaction with a wider range of substrates. Even so, that range is not great and copper reagents are thermally unstable, as well as sensitive to air and moisture.

A useful method would not require special conditions, be quite general and use easily prepared starting materials. This can be done with transition-metal catalysis (Scheme 2.1). By far the most widely used metal is palladium, but other metals, especially nickel and, more recently, iron, have also been employed.1

The main variables to consider are the “R” and “R’” groups that can be employed, the main group metals “M” that can be used, the nature of the leaving group “X” and the identity and quantity of the ligand “L”. The basic mechanism for palladium-catalysed coupling is a simple combination of oxidative addition, transmetallation and reductive elimination (Scheme 2.2).

A coordinatively unsaturated palladium(0) complex 2.1, which is the catalytic species, is generated from an 18-electron palladium(0) complex by reversible ligand dissociation. Alternatively, it can be generated by reduction of a palladium(II) complex. Both the L₂Pd and the L₂PdX₂ should be regarded as “pre-catalysts”.

The catalyst or pre-catalyst complex may be assembled in situ from a mixture of a palladium source, such as palladium(II) salt, Pd₂(dba)₃ or even, in a few cases, palladium on carbon, and the ligand. This avoids the need to preform a palladium complex.

If a palladium(II) pre-catalyst is employed, then there must be a reduction step prior to the start of the catalytic process. This has sometimes been done by the addition of a reducing agent, but more commonly, the palladium(II) is reduced by homocoupling of the organometallic partner, RM (Scheme 2.3). This homocoupling reaction is of occasional synthetic use itself (see Section 2.10).

So how do we know which catalyst to employ? It is determined by looking for precedent and by doing experiments. Key variables are the ligand to metal ratio, and the identity of the ligand. Historically, Ph₃P has been the most widely used, but that doesn’t mean it is best (although it is cheapest). A less widely explored variable is the metal.
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Scheme 2.1

\[ R-M \xrightarrow{Pd \text{ cat.}} R'-X \xrightarrow{R-R', M-X} R'-R' M-X \]

2.1.1 The Main-Group Metal, M

A wide variety of main group metals, M, have been employed (Scheme 2.4). In terms of the main group metal, M, reactivity follows electropositivity. When highly electropositive metals such as lithium and magnesium are employed, transmetallation can be expected to be fast, but problems of low functional-group tolerance as well as air and moisture sensitivity arise. Less-reactive metals are more often employed: lithium and magnesium (Kumada or Corriu–Kumada reaction), zinc (Negishi reaction), aluminium, zirconium, tin (Stille coupling).
Coupling Reactions

boron (Suzuki or Suzuki–Miyaura reaction) and silicon (Hiyama reaction) are the principal ones. Copper(I) derivatives of alkyynes, generated \textit{in situ}, are important coupling partners (Sonogashira reaction). A number of other metals have also been surveyed, but have yet to achieve significant use in synthesis. The uses of these different metals are discussed later in this chapter. Each has their own advantages and disadvantages.

### 2.1.2 Limitation

The most significant limitation has been the difficulty of using alkyl halides: \( R'X \), where \( R' \) is a simple alkyl group. The coupling of alkyl halides posed a considerable challenge. While the synthetic importance of such a process is unquestionable, the ease with which \( \beta \)-hydride elimination from the \( \eta^1 \)-intermediate \( 2.2a \) occurred (Scheme 2.5), presented great difficulties. In addition, alkyl halides are more reluctant to undergo oxidative addition than vinyl or aryl halides. A number of solutions to the problem gradually emerged, based upon either substrate structure or ligand choice. Examples may be found in the following sections specific to each reaction type.

![Scheme 2.5](image)

### 2.1.3 Reactivity of the Leaving Group

The group \( X \), which may be termed as a “leaving group” is most often a halogen. The order of reactivity is, generally, \( X = I > Br \gg Cl \), the same order as for nucleophilic substitution. Organofluorine derivatives do not couple under normal circumstances. It is, therefore, commonly found that coupling reactions proceed much more easily with the more reactive iodo or bromo derivatives, rather than the chloro derivatives. This is, however, not universally true because it depends on which step in the mechanism is the rate-determining step. It will be true if oxidative addition is the rate determining step. Oxidative addition to iodides has been shown to be faster. A study of the Stille coupling of 2-halo pyridines 2.4, however, found the opposite order of reactivity (Table 2.1). In the time that it took for coupling of 2-chloropyridine to go to 75% completion, the same reaction with 2-iodopyridine had only progressed half as far. It was found that addition of lithium chloride to the reaction mixture with 2-iodopyridine enhanced reactivity. The added halide actually makes

<table>
<thead>
<tr>
<th>X</th>
<th>Conversion at 1440 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>36%</td>
</tr>
<tr>
<td>Cl</td>
<td>75%</td>
</tr>
<tr>
<td>I, with added LiCl</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Table 2.1
the rate of coupling of the iodide faster than that of the chloride. This indicates a second effect, believed to be the formation of more reactive anionic chloropalladium(0) complexes.

Historically, the low reactivity of most aryl and vinyl chlorides in coupling reactions meant that such substrates were only used in special cases. As chlorides are cheaper than bromides and iodides, overcoming this obstacle became an important goal. The key was in the ligand. More reactive complexes, which are capable of catalyzing this reaction, can be generated by employing specialist ligands.

The usefulness of halogens is often limited by difficulties in preparing the desired aryl and alkenyl halides. In addition, lack of reactivity can also be a problem. Alternatives to halides have been developed. The most widely used is the triflate group, that can be easily prepared from phenols for the coupling of aryl groups (Scheme 2.6), or from carbonyl compounds for the coupling of alkenyl groups (Scheme 2.7). Triflates can be somewhat unstable. Other sulfonates, such as mesylates and tosylates, can be used in some circumstances. Not only do these sulfonates tend to be more stable, they are also cheaper. Phosphate derivatives are another alternative. Diazonium salts have also been used. These salts have the advantage of high reactivity, but the disadvantage of low stability. Thiol derivatives, especially thioesters, have also been successfully coupled.
Under some circumstances, even ethers can be coupled. Dihydrofuran and dihydropyran were employed in a synthesis of a pheromone 2.17 of Pectinophora gossypiella, the pink bollworm (Scheme 2.8). The pheromone is exclusively the Z isomer at the 7,8-alkene, but a 1:1 E/Z mixture at the 11,12-alkene. Coupling of dihydrofuran 2.12 with n-butylmagnesium bromide 2.11 using dpppNiCl₂ as the catalyst resulted in coupling with loss of alkene stereochemistry, while coupling of the subsequent Grignard reagent with dihydropyran using (Ph₃P)₂NiCl₂ as the catalyst resulted in complete retention of alkene stereochemistry yielding, after chain extension with oxetane and acetylation, the desired pheromone mixture 2.17.

### 2.1.4 Selectivity

Achieving selective coupling at one position in a molecule, while leaving another potentially reactive position untouched is synthetically important. There are several ways to achieve this goal. One is to use several different halogens or other leaving groups and exploit the inherent reactivity difference. Another is to employ the same halogen in several sites, but exploit electronic or steric factors.

#### 2.1.4.1 Selectivity Based upon Halogen Reactivity

Given the usual order of reactivity amongst the halogens, I ≫ Br ≫ Cl, it is often possible to achieve selective coupling at the position of one halogen in the presence of a less-reactive halogen. Arene 2.18 underwent selective Sonogashira coupling at only the bromine-substituted position (Scheme 2.9).

This selectivity has been exploited in a synthesis of terprenin 2.26, an immunosuppressant compound (Scheme 2.10). The iodobromide 2.20 underwent selective Suzuki coupling with one boronic acid 2.21 at the iodo position, then a second boronic acid 2.23 at the bromo position. This two-step process could be carried out in one pot. The unusual catechol protecting group was not wasted, but converted into a prenyl ether at the end of the synthesis by hydrolysis and a Wittig reaction.

For synthetic purposes, it would often be more efficient to introduce the same halogen by a single double-halogenation step, then exploit reactivity differences due to position. Factors that affect this form of regioselectivity would be steric hindrance, coordination and electronics.

#### 2.1.4.2 Steric Hindrance

The steric environment around X is also important. Reaction tends to be favoured at the less-hindered position, other factors being equal, as in the coupling reactions of gem-dihalides 2.27 (Scheme 2.11) and 2.30 (Scheme 2.12). An application of this selectivity can be found in Scheme 2.48.

![Scheme 2.9](image-url)
2.1.4.3 Electronic Effects

Coupling reactions often appear to be favoured at the more electron-poor halogenated position. One reason can be that oxidative addition is favoured at such sites.\(^{16}\) This is because oxidative addition involves donation of electron density from the low-valent metal to the substrate, a process made easier by the presence of suitably placed electron-withdrawing groups. This has been systematically studied for the Sonogashira reaction for a series of nitrogen substituted arenes (Scheme 2.13).\(^{17}\) For the nitro compound 2.32, para-coupling is favoured over meta. Ortho-coupling is also (in 2.34) favoured over meta, but the para-coupling is thirty times faster. The ortho and para positions are the more electron poor. For the anilines (Scheme 2.14), meta-coupling is favoured in both cases, as the meta position is the least electron rich, but they are still less reactive than the nitro compounds. The reaction times for the anilines were longer than for the nitro compounds, even at reflux.
The dibromofuran 2.40 was subjected to a sequence of Stille coupling reactions, the second one requiring a more robust catalyst, leading to rosefuran 2.43 after hydrolysis and copper-catalysed thermal decarboxylation (Scheme 2.15). A quite different synthesis of rosefuran may be found in Scheme 11.48.

In other cases, the reason for the selectivity may not be primarily electronic, but a coordination effect. This may be the case in a synthesis of Ailanthoidiol using the Sonogashira reaction (see Scheme 2.115).

2.2 Lithium and Magnesium: Kumada Coupling

When organolithium or Grignard reagents are coupled, the reaction is known as the Kumada reaction, or Kumada–Corriu reaction (Schemes 2.16 and 2.17). Functional-group tolerance is often low, as organolithium and magnesium reagents show high reactivity to a wide range of functional groups. If, however, the catalyst
Organic Synthesis Using Transition Metals

Scheme 2.16

Scheme 2.17

Scheme 2.18

Scheme 2.19

is sufficiently reactive that coupling is fast, surprisingly good functional-group tolerance can be achieved. Nevertheless, this reaction is most often used for the synthesis of molecules with little functionality. With vinyl halides, alkene geometry is retained.

A nickel-catalysed coupling of a Grignard reagent with a bromopyrazole 2.50 was employed as the last step in a synthesis of withasomnine 2.51 (Scheme 2.18).\textsuperscript{20} Nickel catalysis was also employed to make terthiophene on a 700 g scale (Scheme 2.19).\textsuperscript{21}

The Kumada reaction was employed for the synthesis of dendralenes, cross-conjugated alkenes, which show interesting reactivity (Scheme 2.20).\textsuperscript{22} The products even include the labile [3]dendralene 2.56 which has a half-life of just 10 h at 25 $^\circ$C.

A Kumada allylation gave the desired isoindoline 2.59 on a multigramme scale (69.5 g as its HCl salt) accompanied by small amounts of the isomerization product 2.61 (Scheme 2.21). Transition-metal catalysed isomerization is discussed in Section 11.4. Formation of this by-product could be minimized by correct choice of ligand and the metal:ligand ratio.\textsuperscript{23}

Kumada coupling reactions of alkyl chlorides, possessing $\beta$-hydrogens also proceed using palladium catalysis in the presence of either electron-rich phosphines\textsuperscript{24} and NHC ligands (Scheme 2.22).\textsuperscript{25} Simple dienes, such as butadiene, may also act as useful ligands in promoting coupling of this sort (Schemes 2.23 and 2.24).\textsuperscript{26} This form of catalysis shows a surprising preference for primary alkyl halides over aryl halides.

Grignard reagents are also formed during addition of nucleophiles, with magnesium counter ions, to benzynes. A Grignard reagent, generated in this way, was employed in a synthesis of Dictyodendrin A.\textsuperscript{27} Given the array of aryl groups in this telomerase inhibitor natural product, it is no surprise that palladium-catalysed coupling was also used later in the synthesis (Schemes 2.25 and 2.26).
Scheme 2.20

Scheme 2.21

Scheme 2.22

Scheme 2.23

Scheme 2.24

Scheme 2.25