

# Organic Synthesis using Transition Metals

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## 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  $\text{OsO}_4$ , for many years. These kinds of reaction 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 enough examples to show how they can be applied and enough mechanisms to allow them to be understood.

The book would have been much more difficult to write without the copies of several papers that were sent to me. For these, I have to thank Professors Minoru Isobe, Siegfried Blechert, Dieter Enders and R.F.W Jackson, as well as the tireless Paitoon Rashatsakhon. The book would have been impossible to write without the use of the excellent library facilities of the Faculty of Science, Mahidol University, here in Bangkok.

R. Bates

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## 1 Introduction

The aim of this book is to provide an overview of the use of transition metals as catalysts and reagents in organic synthesis. In so few pages, it is not and cannot be comprehensive. Even volume 12 of *Comprehensive Organometallic Chemistry II* (L.S. Hegedus, ed., Pergamon Press, Oxford, 1995), which is a goldmine of information, is not really comprehensive. For truly comprehensive coverage of the subject, it is necessary to refer to the annual reviews by Hegedus.<sup>1</sup> The two series of reviews published by the Royal Society of Chemistry provide an additional source of information—one on catalytic<sup>2</sup> and one on stoichiometric applications.<sup>3</sup> A number of other textbooks have been published in this area. A broad survey including an excellent discussion of fundamental mechanisms can be found in *Principles and Applications of Transition Metals* (J.P. Collman, L.S. Hegedus, J.R. Norton, R.G. Finke, University Science Books, Mill Valley, 1987). Two good texts have been published that concentrate on a small number of specific reactions in detail: *Transition Metals in Organic Synthesis* (S.E. Gibson, ed., Oxford University Press, Oxford, 1997) and *Transition Metals in Total Synthesis* (P.J. Harrington, Wiley, New York, 1990). An excellent discussion of the use of all types of homogeneous catalysis in industrial processes is in *Homogeneous Catalysis* (G.W. Parshall, S.D. Ittel, 2nd ed., Wiley, New York, 1992). The catalogues of fine chemicals suppliers, such as *Strem*, are a surprisingly good source of information. Palladium is the most widely used transition metal catalyst and further information can be found in *Palladium Reagents in Organic Synthesis* (R.F. Heck, Academic Press, London, 1985), *Organic Synthesis with Palladium Compounds* (J. Tsuji, Springer, Berlin, 1980) and a chapter by Hegedus in *Organometallics, A Manual* (M. Schlosser, ed., Wiley, New York, 1994). A number of writers have tackled subjects that cut across the chapter boundaries of the present book, such as indoles,<sup>4</sup> ruthenium catalysis<sup>5</sup> and carbocyclizations.<sup>6</sup> The central role of catalysis to achieve efficiency and atom economy has also been expounded.<sup>7</sup> In addition, with the growing acceptance of transition metals by synthetic organic chemists, these reactions are often included in more general texts such as *Cyclization Reactions* (C. Thebtaranonth and Y. Thebtaranonth, CRC Press, Boca Raton, 1994). Many organometallics can be found in the *Encyclopaedia of Reagents for Organic Synthesis* (L. Paquette, ed., Wiley, New York) and in the multivolume works published by Elsevier: *Comprehensive Organic Synthesis* and *Comprehensive Functional Group Transformations*.

This book concentrates on the bond forming reactions that set transition metal chemistry apart from 'classical' organic chemistry. A number of topics are excluded because they are well covered in many general organic texts. These include transition metal mediated oxidation and reduction reactions. The use of chiral complexes as catalysts to induce stereochemistry is also excluded, because this is the subject of another book in this series: *Catalysis in Asymmetric Synthesis* (J.M.J. Williams, Sheffield Academic Press, Sheffield, 2000).

The use of transition metals in synthesis was taken up slowly by organic chemists. This is at first surprising because the industrial use of transition metals has a much longer history: hydroformylation using cobalt began in the 1930s. The Mond process using nickel tetracarbonyl was developed in the nineteenth century.<sup>8</sup> Industry was willing to accept and use processes that it could not understand—black box reactions—as long as they were profitable. Academics were handicapped by the desire to understand the chemistry. This was impossible until ideas about chemical bonding and the necessary instrumentation matured in the years after the Second World War. Even with this in place, the impact of transition metals on organic synthesis came late, possibly because of the many fantastic main group reagents that also appeared, or perhaps because organic chemists do not talk to inorganic chemists often enough.

Predictably, palladium based chemistry made its impact first, as reactions such as the Stille coupling and the Heck reaction solved long standing synthetic problems. Palladium is a familiar element to organic chemists, unlike iridium, for instance. In the past few decades, the subject has mushroomed. Established reactions are gaining both technical improvements and increasing numbers of applications; new reactions are being developed. The practicality of the subject is shown by the number of publications coming from the process development laboratories of pharmaceutical companies.

## 1.1 Structures and mechanisms

Reactions involving transition metals can be divided into two groups: catalytic and stoichiometric. For a reaction to be catalytic, the transition metal fragment must be regenerated in its original reactive form with the same ligands and same oxidation state, although this is not necessarily the same complex that is weighed out when the reaction is set up. In stoichiometric reactions, transition metal complexes are often isolated and handled as discrete synthetic intermediates. At some stage the metal is removed (decomplexation), usually oxidatively.

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. A basic grasp of these concepts is essential in order to be able to obtain the most from transition metals. Transition metal complexes are classified by their hapto number, signified by the Greek letter



$\eta$  (eta) with a superscript. The superscript is the number of atoms (usually carbon atoms) of the ligand that are bonded to the metal.

$\eta^1$ -Complexes contain a metal–carbon sigma bond (Figure 1.1). The organic group may be alkyl, vinyl, alkynyl, acyl or aryl. It is also possible to have metal–carbon double and triple bonds; these are known as carbenes and carbynes. Cumulenes are known, such as in vinylidene complexes.

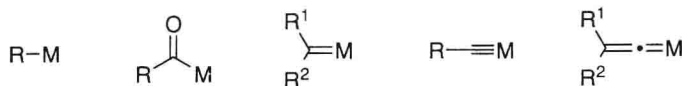


Figure 1.1

$\eta^2$ -Complexes may be formed from alkenes or alkynes by interaction of the  $\pi$ -orbitals with the metal (Figure 1.2). These complexes may also be drawn as their metallacyclopropane resonance structures.



Figure 1.2

$\eta^3$ -Allyl complexes, also known as  $\pi$ -allyl complexes, have three atoms bonded to the metal (Figure 1.3). They are frequently in equilibrium with the corresponding  $\eta^1$ -allyl complexes.



Figure 1.3

$\eta^4$ -Diene and  $\eta^5$ -dienyl complexes are well known (Figure 1.4). The best known  $\eta^5$ -dienyl complexes contain the cyclopentadienyl ligand (Cp), as in ferrocene. The most important class of  $\eta^6$  complexes are arene complexes, such as complexes of benzene.  $\eta^7$ -Complexes are unusual in synthesis. An example is in chapter 10, Scheme 10.22. In all of these complexes, the carbon atoms of the ligand are coplanar, with the metal atom occupying one face of the ligand.

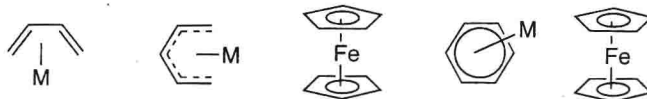


Figure 1.4

An especially significant ligand is carbon monoxide. The high reactivity of CO is a key difference between transition metal chemistry and classical organic chemistry. Other ligands often found include phosphines and halides.

## 1.2 The eighteen electron rule and oxidation state

How many ligands can fit around the metal? In many cases this can be predicted easily. Just as carbon has an octet or eight electron rule, transition metals have an eighteen electron rule. This is the number of electrons required to fill the *s*, *p* and *d* shells. The number of valence electrons of a metal in a complex may be calculated quite easily. There are two methods available, but only one is given here to avoid confusion.

First, all of the ligands are notionally removed from the metal. The ligands are all removed as neutral species, even if they would normally be considered as anions. Any single bonded species, such as  $\eta^1$ -alkyl groups and halogen atoms contribute one electron to the total, as they do in simple Lewis diagrams. Other organic ligands contribute the same number as their  $\eta$ -number. Lone pair donors, including phosphines and CO (the related molecule NO is unusual in that it can be a one electron or a three electron donor) contribute two electrons (that is, one lone pair). Carbene and carbyne ligands contribute two and three electrons respectively (one for each bond). This gives the total number of electrons contributed by the ligands. The number contributed by the metal can be easily found from the periodic table (Table 1.1).

Table 1.1

3	4	5	6	7	8	9	10	11
Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu
Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
La	Hf	Ta	W	Re	Os	Ir	Pt	Au

Finally, adjustment must be made for the charge. Positive charge represents missing electrons and must be subtracted. Negative charge represents extra electrons and must be added. Two examples are shown in Figure 1.5.

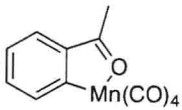
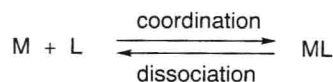
Example 1: $\text{Na}^+ \text{Co}(\text{CO})_4^-$	Example 2: 
Ligands: $4 \times \text{CO} = 4 \times 2$	Ligands: $4 \times \text{CO} = 4 \times 2$
Metal: Co	Ketone lone pair
Charge	$\eta^1$ -aryl
Total	Metal: Mn
	Charge
	Total

Figure 1.5

Oxidation number, although a formalism, is also useful. It is helpful in keeping track of electrons and checking that processes really are catalytic. Oxidation number can be calculated easily by notionally removing ligands in their normal state: lone pair donors such as CO and phosphines, as well as even-numbered hydrocarbon ligands are removed as neutral fragments. Ligands such as chloro are removed as monoanions, as are odd-numbered organic fragments, such as allyl. The resulting charge on the metal is the oxidation state. In Figure 1.5, cobalt is  $(-1)$  and manganese is  $(+1)$ .

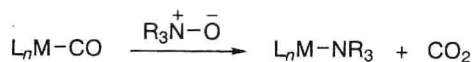
### 1.3 The reactions

Transition metal complexes can undergo a series of reactions that are generally unlike those of main group compounds. The most fundamental is the simple coordination and dissociation of ligands (Scheme 1.1). This is important because eighteen electron complexes do not coordinate additional ligands, including the desired substrate. First, an existing ligand must be dissociated, to generate a reactive sixteen electron complex with a vacant site for a new ligand to coordinate. Although some ligands are sufficiently labile to dissociate, in other cases it is necessary to use heat or photolysis to achieve this. Often the reaction conditions are dictated by the need for this initial dissociation.



Scheme 1.1

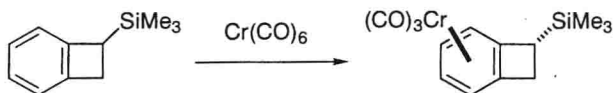
Dissociation may also be achieved by destruction of a ligand. This is often done by oxidation of a CO ligand to  $\text{CO}_2$  using an amine oxide (Scheme 1.2). The vacant site is then taken up by the much more labile amine ligand.



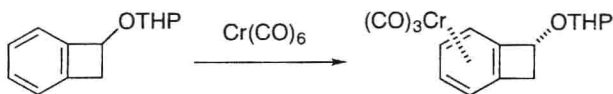
Scheme 1.2

Exchange of ligands may also be employed to modify the reactivity of a complex. Substitution of a CO ligand by a nitrosyl ligand ( $\text{NO}^+$ ) will make the complex more electrophilic.

Complexation reactions taking place on one face of a  $\pi$ -system can be diastereoselective with both steric effects (Scheme 1.3) and neighbouring group effects exercising control (Scheme 1.4).<sup>9</sup>



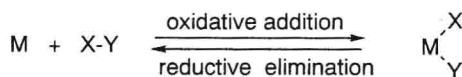
Scheme 1.3



Scheme 1.4

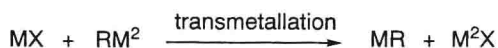
Complexation of organic ligands has dramatic chemical and also stereochemical effects. Many reactions occur specifically *cis* or *trans* to the metal. In addition, the bulk of the metal fragment can shield one face of a nearby uncomplexed functional group, resulting in a diastereoselective reaction (see chapter 9, Schemes 9.2, 9.27, 9.28).

Oxidative addition is the most important method for the formation of a transition metal–carbon bond (Scheme 1.5). In this, a transition metal fragment (which must have less than eighteen electrons) inserts into the  $\text{X—Y}$  bond. Usually X is carbon and Y is a leaving group, such as iodide or triflate. There are many other possibilities, including  $\text{C—H}$  and  $\text{O—H}$  bonds. The reverse process is reductive elimination and this is frequently the final step in an organometallic mechanism. In oxidative addition, the oxidation state of the metal increases by 2, in reductive elimination it is reduced by 2.



Scheme 1.5

Another important method for generation of a transition metal–carbon bond is transmetallation, the transfer of an organic group (R) from a main group metal ( $\text{M}^2$ ) with a leaving group (X) being transferred the other way (Scheme 1.6).



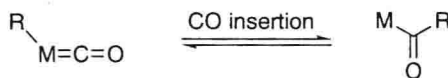
Scheme 1.6

An important reaction of coordinated alkenes and alkynes is insertion, usually into a metal carbon or hydrogen bond (Scheme 1.7).<sup>10</sup> This is a stereospecific *syn* process, so coordinated alkynes yield *cis* vinyl complexes.



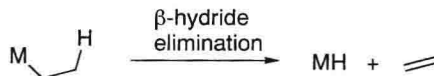
Scheme 1.7

CO insertion is also an important process (Scheme 1.8). It is a reversible reaction. The insertion is not observed for R = H, owing to the low thermodynamic stability of formyl groups.



Scheme 1.8

For alkyl transition metal complexes,  $\beta$ -hydride elimination is a significant process (Scheme 1.9). Many alkyl complexes are unstable because of this quite



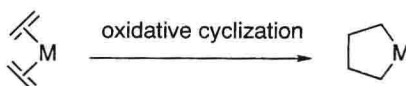
Scheme 1.9

facile reaction, provided that the complex has less than eighteen electrons.  $\beta$ -Hydride elimination is stereospecifically *syn* and it should not be confused with E2 reactions which are *anti*. If there is no *syn* hydrogen available, then  $\beta$ -hydride elimination is impossible. Examples are neopentyl and substituted norbornyl complexes (Figure 1.6). Acyl, vinyl and aryl complexes do not undergo  $\beta$ -hydride elimination.



Figure 1.6

Oxidative cyclization is also an important transformation of coordinated alkenes, and a key route to metallacycles (Scheme 1.10).



Scheme 1.10

## 1.4 Handling

Many organic chemists are discouraged from using transition metals by the air-sensitivity of some of the complexes. Glove boxes are essential equipment in many inorganic chemistry laboratories, but rarely found in organic laboratories. They are vital in many cases for extensive manipulation of air-sensitive compounds, although many of the complexes can be easily handled in air, at least for short times. For organic synthesis, extensive manipulation is not required, merely the transferring of the air-sensitive compound from the storage bottle to the reaction flask. This can often be effectively done using an Atmosbag<sup>®</sup> available from Aldrich or Fluka, or even a simple inverted nitrogen funnel. After the complex has been weighed (by difference) into an inert gas flushed flask, subsequent manipulation can be done using the normal anaerobic techniques that would be appropriate for lithium diisopropylamide (LDA) or butyl lithium.

Certain complexes deserve special mention. All of the metal carbonyls should be regarded as particularly toxic. Nickel tetracarbonyl is highly dangerous owing to its high volatility which may be the reason that it is now rarely used. Iron pentacarbonyl is only a little less volatile and chemists should use the solid dimer,  $\text{Fe}_2(\text{CO})_9$ , if possible. Chromium hexacarbonyl, although solid, is also toxic and volatile (it is easily purified by sublimation).

Tetrakis(triphenylphosphine) palladium may be the most widely used complex. It is sufficiently air-stable to weigh out, but it must be stored under an inert gas, in the dark. The colour is an excellent indicator of purity. Good material is bright yellow. This complex is expensive, although it is easily prepared. Procedures for making it and other palladium complexes have been collected by Heck (*Palladium Reagents in Organic Synthesis*) and are described in a chapter by Hegedus (*Organometallics, A Manual*).

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## 2 Coupling reactions

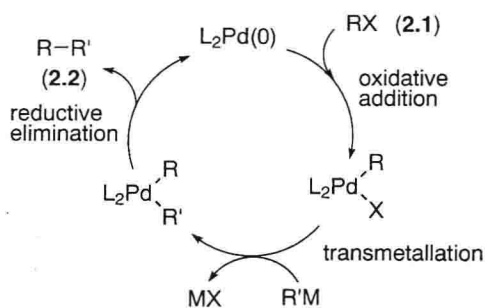
### 2.1 Introduction

Superficially, the reaction between a main group organometallic and an organic halide appears to be a good method for C—C bond formation (Scheme 2.1). In practice, however, it is limited to the use of organocopper reagents and some special cases.



**Scheme 2.1** R, R' = organic groups, X = leaving group, M = main group metal.

These coupling reactions are much improved if a transition metal catalyst, usually a complex of palladium but sometimes nickel, is included. Some reviews of specialized applications have been published.<sup>1</sup> The leaving groups most often used are bromide, iodide, triflate and, in certain cases, chloride. The main group metals, M, most commonly used are tin, zinc, boron and, for alkynes, copper. Other elements sometimes used are lithium, magnesium, aluminium, zirconium and silicon. The basic mechanism of the coupling reaction is a straightforward combination of three key steps (Scheme 2.2): oxidative addition of the organic halide (2.1) to a palladium complex, transmetalation of R' from the main group organometallic to palladium and reductive elimination to release the coupled product and regenerate the original palladium species. It is generally found that the rate determining step is the transmetalation step, although this is not so in every case.<sup>2</sup>



**Scheme 2.2**

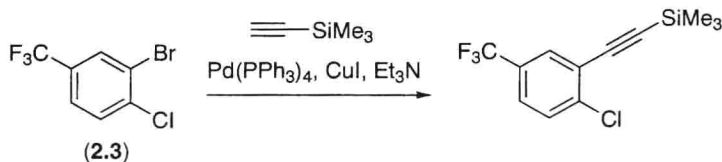
The ligand for palladium, L, is usually triphenylphosphine (which is cheap). In some cases the use of other ligands, such as triphenylarsine and tri(2-furyl)

phosphine, have proved advantageous (see section 2.5.2). The ligand may also be a solvent molecule, especially good donors such as acetonitrile and DMF. Reactions can be done in water using soluble sulfonated phosphines.<sup>3</sup>

Within this scheme, there are a great many variables. A bewildering array of catalysts has been employed, both palladium(0) complexes, such as  $\text{Pd}(\text{PPh}_3)_4$  and  $\text{Pd}_2\text{dba}_3$ , (dba is dibenzylidene acetone) and palladium(II) salts, such as  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ . In both cases, the active species will be palladium(0), as the palladium(II) will be rapidly reduced to palladium(0) *in situ*. In some cases a palladium(II) catalyst is used but prereduced to palladium(0) before the start of the main reaction. Some novel catalysts that should be applicable are discussed in chapter 4 (Heck reaction).<sup>4</sup>

The organic group bearing the halide is the major limitation. This group must not be an alkyl group capable of  $\beta$ -hydride elimination (see section 1.3). Attempts to couple such groups generally lead to alkene formation. Coupling reactions are therefore best with aryl, alkenyl, alkynyl and acyl groups. In contrast, for the organic group of the organometallic, no such limitation applies as reductive elimination is faster than  $\beta$ -hydride elimination.

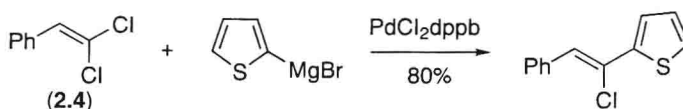
The halide is often iodide or bromide. The order of reactivity of the halides is, as might be predicted, iodide > bromide > chloride. The bromide of arene (**2.3**) can be coupled selectively in the presence of the chloride, with the trifluoromethyl group, not surprisingly, also being unscathed (Scheme 2.3).



Scheme 2.3

An alternative leaving group to a halide is a triflate.<sup>5</sup> Triflates are used most often in the Stille coupling. Addition of lithium chloride is almost always required. Iodonium ions and diazonium salts have also been used. Chlorides are infrequently used because of their low reactivity. Acid chlorides, however, are reactive substrates.<sup>6</sup>

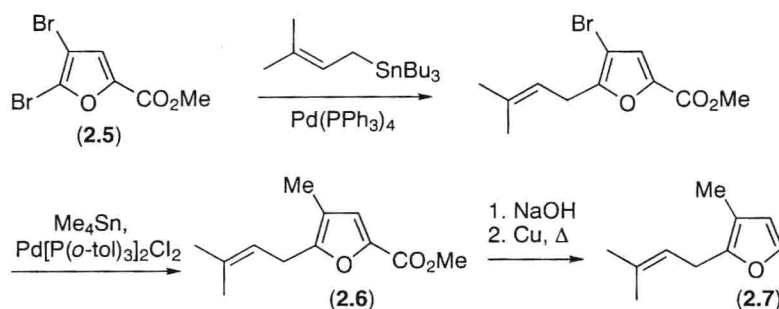
The steric and electronic surroundings of the leaving group have a profound impact on its reactivity.<sup>7</sup> The less hindered halogen will react preferentially, as in the couplings of the 1,1-dihaloalkene (**2.4**) (Scheme 2.4).<sup>8</sup>



Scheme 2.4 dppb is 1,4-bis(diphenylphosphino)butane.



The electronic surroundings of the leaving group have been less appreciated, but are just as important, if not more so. In general, halogens in positions that are easily displaced by nucleophiles (in addition elimination reactions), are more reactive than others. This is most clearly seen in molecules possessing more than one halide. There are many examples of regioselective coupling reactions. For instance, the dibromopyrrole (**2.5**) couples initially at the  $\alpha$ -bromine (analogous to a 1,6-nucleophilic addition), and later at the  $\beta$ -bromine (Scheme 2.5).<sup>9</sup> The product (**2.6**) may be converted by standard methods to rosefuran (**2.7**).



Scheme 2.5

The importance of the positions of electron withdrawing and electron donating groups has been shown quantitatively (Figure 2.1).<sup>10</sup> Coupling *para* to a nitro group is strongly favoured over *meta*. The *para* position is the more electron poor position. Similarly, *ortho* is favoured over *meta*, but this is slower than the reaction at the *para* position, owing to steric hindrance. Electronically opposite trends and substantially lower rates were seen with the electron donating acetamide and amino groups.

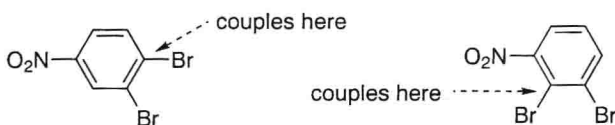


Figure 2.1

The reasons for this selectivity are not fully clear, and may vary from case to case. It is certainly true that electron withdrawing groups on aryl rings accelerate oxidative addition and a good Hammett correlation has been observed.<sup>11</sup> This is consistent with oxidative addition involving donation of electron density from the transition metal to the substrate. Therefore it is not