Transition Metals in the Synthesis of Complex Organic Molecules

Third Edition

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Preface

Since the second edition of this book was published in 1999, thousands of papers have appeared in the literature describing all aspects of transition metals in organic synthesis including novel reactions, new catalysts, ligands, and reaction conditions and applications in synthesis of complex organic molecules. With better computational methods to probe the mechanisms of transition metal promoted reactions, a deeper understanding of the often very complex pathways for catalytic reactions has been obtained. This third edition updates the very dynamic and exponentially growing field of transition metal chemistry including literature references up to early 2008. The number of references included has almost doubled to about 1600.

Transition metal catalyzed polymerization, synthesis of compounds of interest for material research, the use of non-conventional "green" solvents such as water, fluorous solvents, supercritical fluids, and ionic liquids, and reactions employing polymer supported reactants or catalysts have all enjoyed enormous attention. However these reactions are not mechanistically different from the more standard transformations and no significant differences in reactivity or selectivity compared to solution phase reactions in more standard organic solvents can be discerned. The focus of this edition is on the synthesis of small well-defined organic target molecules using more standard reaction conditions.

Chapter 1—*Formalisms, Electron Counting, and Bonding*—and Chapter 2—*Organometallic Reaction Mechanisms*—dealing with the basic principles of transition metal chemistry have not been extensively updated. Chapter 3—*Synthetic Applications of Transition Metal Hydrides*—details advances in homogenous hydrogenations in particular asymmetric hydrogenations, transfer hydrogenations, hydrofunctionalizations, and alkene isomerizations. Chapter 4—*Synthetic Applications of Complexes Containing Metal–Carbon σ-Bonds*—updates and expands on the very rich chemistry of σ-metal complexes especially the synthetically important palladium catalyzed coupling reactions. Chapter 5—*Synthetic Applications of Transition Metal Carbonyl Complexes*—remains the most static of all chapters and only minor revisions have been made. Chapter 6—*Synthetic Applications of Transition Metal Carbene Complexes*—treats stoichiometric and catalytic reactions of metal bound carbenes. The section on metathesis processes has been significantly expanded. The formation and reactivity of metal alkene complexes are described in

Chapter 7—*Synthetic Applications of Transition Metal Alkene, Diene, and Dienyl Complexes.* Chapter 8—*Synthetic Applications of Transition Metal Alkyne Complexes*—covers alkyne complexes in organic synthesis and this chapter has been expanded with examples of the often unique reactions catalyzed by gold, silver, and platinum complexes. In Chapter 9—*Synthetic Applications of η^3-Allyl Transition Metal Complexes*—new examples of η^3-allyl chemistry in synthesis using primarily palladium catalysts. Other transition metals have emerged as competitors or complements to palladium. Finally, Chapter 10—*Synthetic Applications of Transition Metal Arene Complexes*—describes the chemistry of mainly chromium, manganese, iron, and ruthenium η^6-complexes of arenes but also η^2-complexes of osmium and arenes.

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When it became clear that the previous version of this book was badly in need of updating and revision, I enlisted the aid of Professor Björn Söderberg, a former coworker of mine, to take on this task. I felt he was ideally suited for the job, since he had been annually reviewing the field of transition metals in organic synthesis for a number of years, a task I had done for 25 years previous to him. Although strongly based on the previous version, this revision was done almost exclusively by Professor Söderberg, with minimal help from me. Whatever added value this revision has is due to his diligence and hard work.

Louis S. Hegedus, Professor Emeritus
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Formalisms, Electron Counting, and Bonding (How Things Work)

1.1 Introduction

Why should an organic chemist even consider using transition metals in complex syntheses? There are many reasons. Virtually every organic functional group will coordinate to some transition metal, and upon coordination, the reactivity of that functional group is often dramatically altered. Electrophilic species can become nucleophilic and vice versa, stable compounds can become reactive, and highly reactive compounds can become stabilized. Normal reactivity patterns of functional groups can be inverted, and unconventional (*impossible*, under "normal" conditions) transformations can be achieved with facility. Highly reactive, normally unavailable reaction intermediates can be generated, stabilized, and used as efficient reagents in organic synthesis. Most organometallic reactions are highly specific, able to discriminate between structurally similar sites, thus reducing the need for bothersome "protection–deprotection" sequences that plague conventional organic synthesis. Finally, by careful selection of substrate and metal, multistep cascade sequences can be generated to form several bonds in a single process in which the metal "stitches together" the substrate.

However wonderful this sounds, there are a number of disadvantages as well. The biggest one is that the use of transition metals in organic synthesis requires a new way of thinking, as well as a rudimentary knowledge of how transition metals behave. In contrast to carbon, metals have a number of stable, accessible oxidation states, geometries, and coordination numbers, and their reactivity towards organic substrates is directly related to these features. The structural complexity of the transition metal species involved is, at first, disconcerting. Luckily, a few, easily mastered formalisms provide a logical framework upon which to organize and systematize this large amount of information, and this chapter is designed to provide this mastery.

The high specificity, cited as an advantage above, is also a disadvantage, in that specific reactions are not very general, so that small changes in the substrate can turn

an efficient reaction into one that does not proceed at all. However, most transition metal systems carry "spectator" ligands—ligands that are coordinated to the metal but are not directly involved in the reaction—in addition to the organic substrate of interest, and these allow for the fine-tuning of reactivity, and an increase in the scope of the reaction.

Finally, organometallic mechanisms are often complex and poorly understood, making both the prediction and the rationalization of the outcome of a reaction difficult. Frequently, there is a manifold of different reaction pathways of similar energy, and seemingly minor changes in the features of a reaction cause it to take an entirely unexpected course. By viewing this as an opportunity to develop new reaction chemistry rather than an obstacle to performing the desired reaction, progress can be made.

1.2 Formalisms

Every reaction presented in this book proceeds in the coordination sphere of a transition metal, and it is the precise electronic nature of the metal that determines the course and the outcome of the reaction. Thus, a very clear view of the nature of the metal is critical to an understanding of its reactivity. The main features of interest are (1) the oxidation state of the metal, (2) the number of *d* electrons on the metal in the oxidation state under consideration, (3) the coordination number of the metal, and (4) the availability (or lack thereof) of vacant coordination sites on the metal. The simple formalisms presented below permit the easy determination of each of these characteristics. A caveat, however, is in order. These formalisms are just that—formalisms— not reality, not the "truth," and in some cases, they aren't even chemically reasonable. However, by placing the entire organic chemistry of transition metals within a single formalistic framework, an enormous amount of disparate chemistry can be systematized and organized, and a more nearly coherent view of the field is thus available. As long as it remains consistently clear that we are dealing with formalisms, exceptions will not cause problems.

a. Oxidation State

The oxidation state of a metal is defined as the charge left on the metal atom after *all* ligands have been removed *in their normal, closed-shell, configuration*—that is, *with their electron pairs*. The oxidation state is *not* a physical property of the metal, and it cannot be measured. It is a formalism that helps us count electrons, but no more. Typical examples are shown in **Figure 1.1**. [An alternative formalism, common in the older literature, removes each covalent, anionic ligand as a *neutral* species with a single electron (i.e., homolytically), leaving the other electron on the metal. Although this results
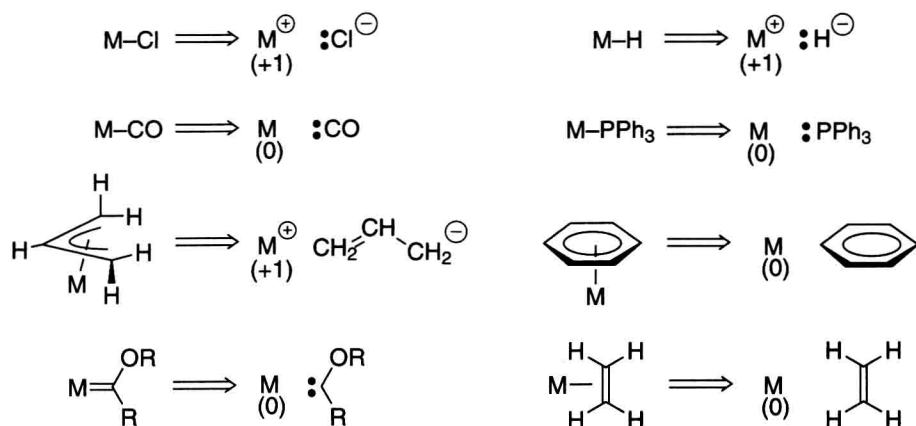
Figure 1.1. Examples of How to Determine the Oxidation State of a Transition Metal

in a different *formal* oxidation state for the metal, it leads to the same conclusions as to the total number of electrons in the bonding shell, and the degree of coordination saturation.]

The *chemical* properties of the ligands are not always consonant with the oxidation state formalism. In metal hydrides, for example, the hydride ligand is *always* formally considered to be H⁻, even though some transition metal "hydrides" are strong acids! Despite this, the formalism is still useful.

b. *d*-Electron Configuration, Coordination Saturation, and the 18-Electron Rule

Having assigned the oxidation state of the metal in a complex, the number of *d* electrons on the metal can easily be assessed by referring to the periodic table. **Figure 1.2** presents the transition elements along with their *d*-electron count. The transition series is formed by the systematic filling of the *d* orbitals. Note that these electron

Group number		4	5	6	7	8	9	10	11
First row	3*d*	Ti	V	Cr	Mn	Fe	Co	Ni	Cu
Second row	4*d*	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
Third row	5*d*	Hf	Ta	W	Re	Os	Ir	Pt	Au
	0	0	4	5	6	7	8	9	10	—
	I	3	4	5	6	7	8	9	10
Oxidation state	II	2	3	4	5	6	7	8	9
	III	1	2	3	4	5	6	7	8
	IV	0	1	2	3	4	5	6	7

d^n

Figure 1.2. *d*-Electron Configuration for the Transition Metals as a Function of Formal Oxidation State

configurations differ from those presented in most elementary texts in which the $4s$ level is presumed to be lower in energy than the $3d$, and is filled first. Although this is the case for the *free atom* in the elemental state, these two levels are quite close in energy, and, for the *complexes* discussed in this text—which are not free metal atoms, but rather metals surrounded by ligands—the assumption that the outer electrons are d electrons is a good approximation. By referring to the periodic table (or preferably, by remembering the positions of the transition metals), the d-electron count for any transition metal in any oxidation state is easily found.

The d-electron count is critical to an understanding of transition metal organometallic chemistry because of the **18-electron rule**, which states "in mononuclear, diamagnetic complexes, the total number of electrons in the bonding shell (the sum of the metal d electrons plus those contributed by the ligands) never exceeds 18" (at least not for very long—see below).[1] This 18-electron rule determines the *maximum* allowable number of ligands for any transition metal in any oxidation state. Compounds having the maximum allowable number of ligands—that is, having 18 electrons in the bonding shell—are said to be coordinatively saturated—that is, there are *no* remaining coordination sites on the metal. Complexes *not* having the maximum number of ligands allowed by the 18-electron rule are said to be coordinatively unsaturated—that is, they have vacant coordination sites. Since vacant sites are usually required for catalytic processes (the substrate must coordinate before it can react), the degree of coordination is central to many of the reactions presented below.

c. Classes of Ligands

The very large number of ligands that are involved in organotransition metal chemistry can be classified into three families: (1) *formal* anions, (2) *formal* neutrals, and (3) *formal* cations. These families result from the oxidation state formalism requiring the removal of ligands in their closed-shell [with their pair(s) of electrons] state. Depending on the ligand, it can be either electron donating or electron withdrawing, and its specific nature has a profound effect on the reactivity of the metal center. Ligands with additional unsaturation may coordinate to more than one site, and thus contribute more than two electrons to the total electron count. Examples of each of these are presented below, listed in approximate order of decreasing donor ability.

Formal anionic ligands that act as two electron donors are:

$$R^{\ominus} > Ar^{\ominus} > H^{\ominus} > RC(=O)^{\ominus} > halide^{\ominus} \sim CN^{\ominus}$$
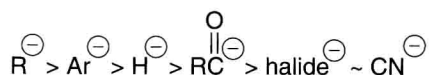
These ligands fill one coordination site through one point of attachment and are called "monohapto" ligands, designated as η^1. The allyl group, $C_3H_5^-$, can act as a monohapto (η^1), two-electron donor, or a trihapto (η^3) (π-allyl) four-electron donor (Figure 1.3). In the latter case, *two* coordination sites are filled, and all three carbons are bonded to the metal, but the ligand as a whole is still a formal mono anion. The
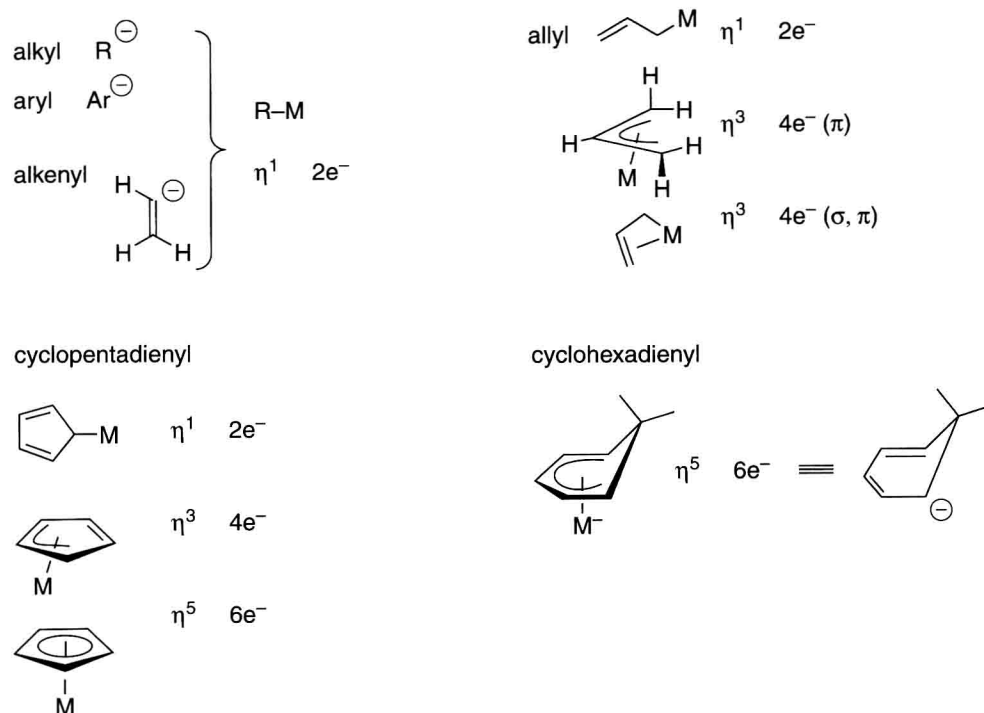
Figure 1.3. Bonding Modes for Mononegative Anionic Ligands

cyclopentadienyl ligand, $C_5H_5^-$, most commonly bonds in an η^5-fashion, filling three coordination sites and acting as a six-electron donor, although η^3 (four electrons, two sites, equivalent to η^3-allyl) and η^4-coordinations are known. The cyclohexadienyl ligand, produced from nucleophilic attack on η^6-arene metal complexes (Chapter 10), is almost invariably a six-electron, mononegative, η^5-ligand that fills three coordination sites. These ligands are illustrated in **Figure 1.3**.

Formal neutral ligands abound, and they encompass not only important classes of "spectator" ligands—ligands such as phosphines and amines introduced to moderate the reactivity of the metal, but which are not *directly* involved in the reaction under consideration—but also ligands such as carbon monoxide, alkenes, alkynes, and arenes, which are often *substrates* (**Figure 1.4**). Ligands such as phosphines and amines are good σ-donors in organometallic reactions, and increase the electron density at the metal, while ligands such as carbon monoxide, isonitriles, and alkenes are π-acceptors, and decrease the electron density at the metal. The reason for this is presented in the next section.

Formally cationic ligands are much less common, since species that bear a full formal positive charge *and* a lone pair of electrons are rare. The nitrosyl group (:NO$^+$) is one of these, being a cationic two-electron donor. It is often used as a spectator ligand, or to replace a carbon monoxide, thus converting a neutral carbonyl complex to a cationic nitrosyl complex.

With all of the preceding information in hand, it is now possible to consider virtually any transition metal complex, assign the oxidation state of the metal, assess the
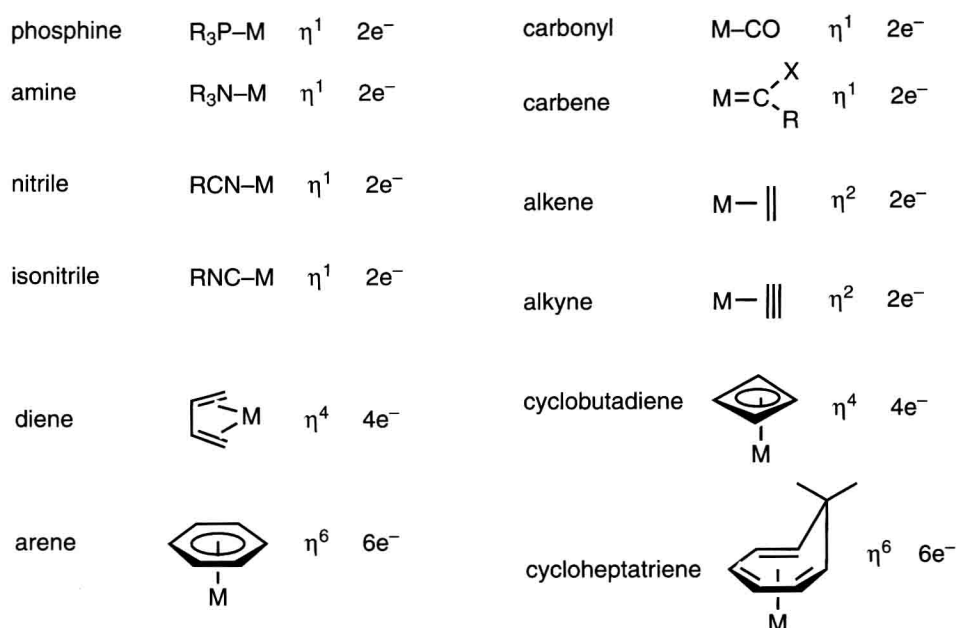
Figure 1.4. Bonding Modes for Neutral Ligands

total number of electrons in the bonding shell, and decide if that complex is coordinatively saturated or unsaturated. For example, the complex $CpFe(CO)_2(C_3H_7)$ is a stable, neutral species, containing two formally mononegative ligands, the propyl (C_3H_7) group, an η^1, $2e^-$ donor ligand, and the Cp ligand, an η^5, $6e^-$ donor ligand, and two neutral carbon monoxide ligands that contribute two electrons each. Since the overall complex is neutral, and has two mononegative ligands, the iron must have a formal 2+ charge, making it Fe(II), d^6. For an overall electron count, there are six electrons from the metal, a total of four from the two CO's, two electrons from the propyl group, and six electrons from the Cp group, for a grand total of $18e^-$. Thus, this complex is an Fe(II), d^6, coordinatively saturated complex. Other examples, with explanatory comments, are given in **Figure 1.5**.

The last example in **Figure 1.5** illustrates one of the difficulties in the strict application of formalisms. Strictly speaking, this treatment of the cyclohexadienyliron tricarbonyl cation is the formally correct one, since the rules state that each ligand shall be removed *in its closed-shell form*, making the cyclohexadienyl ligand a six-electron donor *anion*. However, this particular complex is prepared by a *hydride* abstraction from the neutral cyclohexadieneiron tricarbonyl, making it reasonable to assume that the cyclohexadienyl ligand is a four-electron, donor cation. Furthermore, the cyclohexadienyl group in the complex is quite reactive towards nucleophilic attack (Chapter 7). The true situation is impossible to establish. In reality, the plus charge resides neither exclusively on the metal, as the first, formally correct, treatment would assume, nor completely on the cyclohexadienyl ligand from which the hydride was abstracted, but rather is distributed throughout the entire metal–ligand array. Thus, *neither* treatment represents the true situation, while *both* treatments come to the conclusion that the complex