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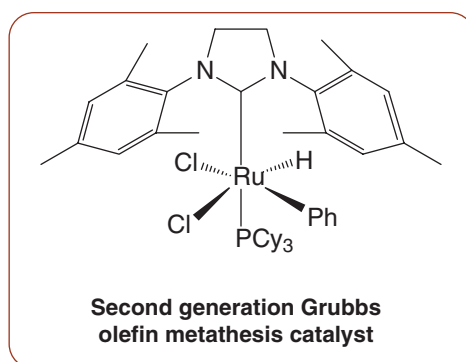
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# Carbon–Carbon Bond–Forming and Other Reactions of Transition Metal Organometallic Compounds



A number of transition metal–catalyzed carbon–carbon bond-forming reactions have been developed into highly useful tools for organic synthesis. The great power of many transition metal–catalyzed reactions is that they provide ways to form bonds between groups for which there are very limited or perhaps no other carbon–carbon bond-forming reactions available. For example, using certain **transition metal catalysts** we can form bonds between alkenyl (vinyl) or aryl substrates and  $sp^2$ - or  $sp$ -hybridized carbons of other reactants. We shall provide examples of a few of these methods here, including the **Heck–Mizokori reaction**, the **Miyaura–Suzuki coupling**, the **Stille coupling**, and the **Sonogashira coupling**. These reactions are types of **cross-coupling reactions**, whereby two reactants of appropriate structure are coupled by a new carbon–carbon  $\sigma$  bond.

**Olefin metathesis** is another reaction type, whereby the groups of two alkene reactants exchange position with each other. We shall discuss olefin metathesis reactions that are promoted by **Grubbs’ catalyst**.

Another transition metal–catalyzed carbon–carbon bond-forming reaction we shall discuss is the **Corey–Posner, Whitesides–House reaction**. Using this reaction an alkyl halide can be coupled with the alkyl group from a **lithium dialkyl cuprate** reagent (often called a **Gilman reagent**). This reaction does not have a catalytic mechanism.

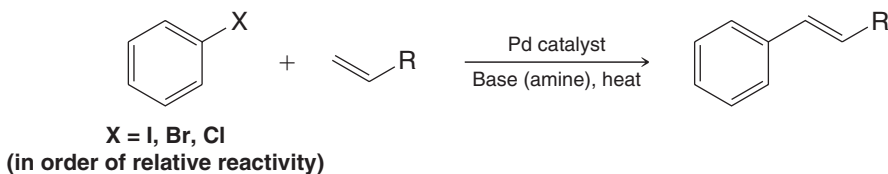
All of these reactions involve transition metals such as palladium, copper, and ruthenium, usually in complex with certain types of ligands. After we see the practical applications of these reactions for carbon–carbon bond formation, we shall consider some general aspects of transition metal complex structure and representative steps in the mechanisms of transition metal–catalyzed reactions. We shall consider as specific examples the mechanism for a transition metal–catalyzed hydrogenation using a rhodium complex called Wilkinson’s catalyst, and the mechanism for the Heck–Mizokori reaction.

## G.1 Cross-Coupling Reactions Catalyzed by Transition Metals

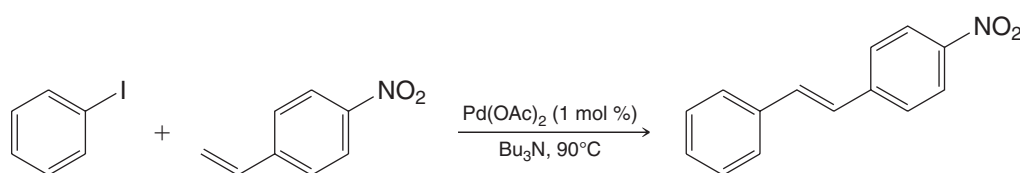
### G.1A The Heck–Mizokori Reaction

The Heck–Mizokori reaction involves palladium-catalyzed coupling of an alkene with an alkenyl or aryl halide, leading to a substituted alkene. The alkene product is generally trans due to a 1,2-elimination step in the mechanism.

#### General Reaction

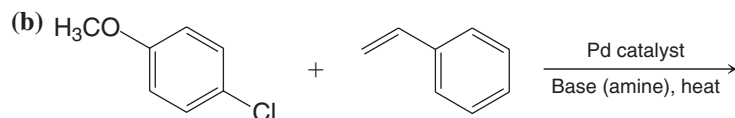
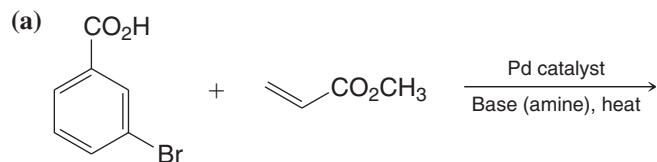


#### Specific Example



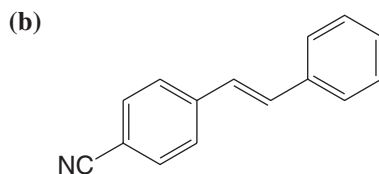
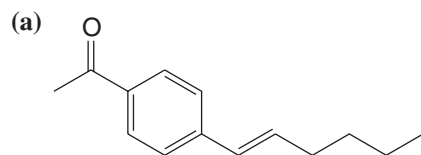
What product would you expect from each of the following reactions?

Review Problem G.1



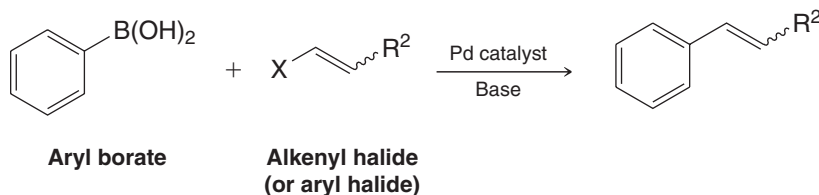
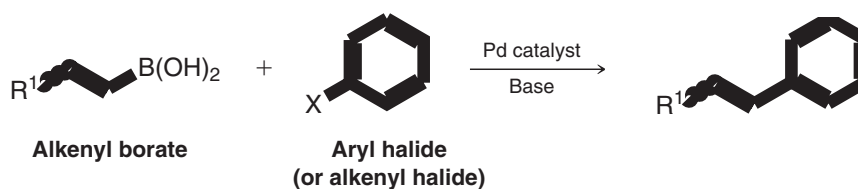
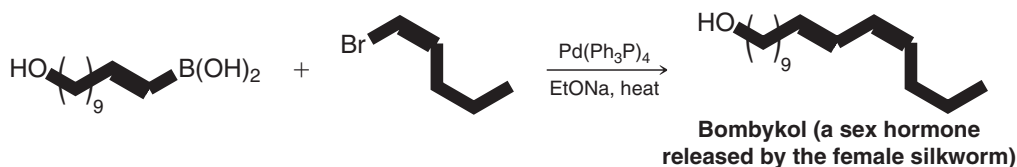
What starting materials could be used to synthesize each of the following compounds by a Heck–Mizokori reaction?

Review Problem G.2

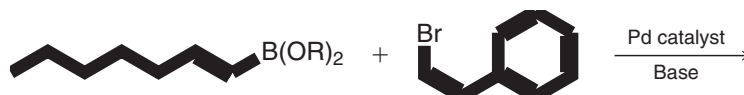


### G.1B The Miyaura–Suzuki Coupling

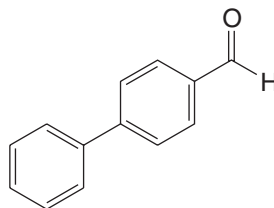
The Miyaura–Suzuki coupling joins an alkenyl or aryl borate with an alkenyl or aryl halide in the presence of a palladium catalyst. The stereochemistry of alkenyl reactants is preserved in the coupling.

**General Reactions****Specific Example****Review Problem G.3**

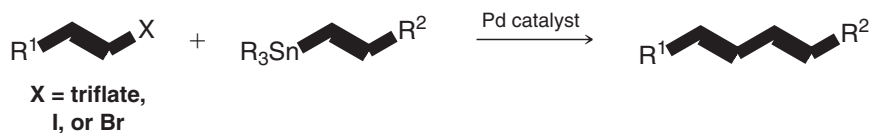
What is the product of the following Miyaura–Suzuki coupling?

**Review Problem G.4**

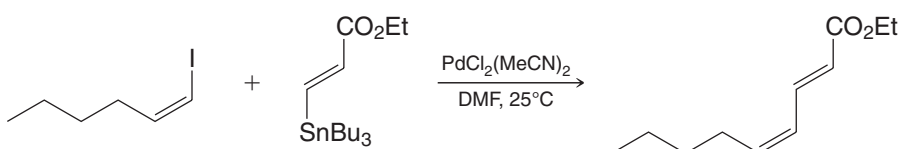
What starting materials could be used to synthesize the following compound by a Miyaura–Suzuki coupling?

**G.1C The Stille Coupling and Carbonylation**

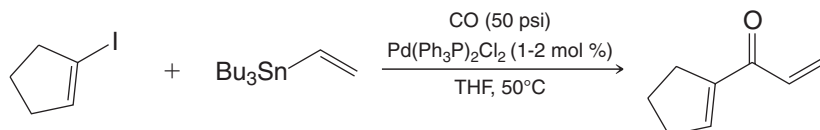
The Stille coupling is a cross-coupling reaction that involves an organotin reagent as one reactant. In the presence of appropriate palladium catalysts, alkenyl and aryl tin reactants can be coupled with alkenyl triflates, iodides, and bromides, as well as allylic chlorides and acid chlorides.

**General Reaction**



**Specific Example**

Ketones can be synthesized by a variation of the Stille coupling that involves coupling in the presence of carbon monoxide. The following reaction is an example.



What is the product of each of the following reactions?

Review Problem G.5

- (a) Reaction (a) shows a cyclic molecule containing a ketone, an iodide, and a tributylstannyl group reacting with a Pd catalyst.
- (b) Reaction (b) shows 4-tert-butylphenyl triflate reacting with 4-(tributylstannyl)phenyl triflate in the presence of a Pd catalyst.
- (c) Reaction (c) shows 4-tert-butylphenyl triflate reacting with allyl tributylstannane in the presence of CO and a Pd catalyst.
- (d) Reaction (d) shows 4-nitrobenzoyl chloride reacting with ethyl acrylate tributylstannane in the presence of a Pd catalyst.

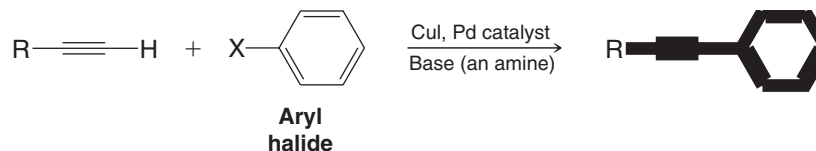
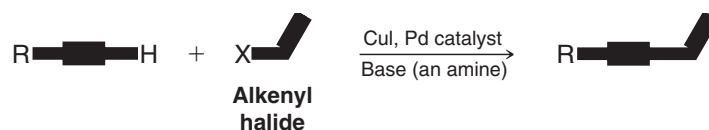
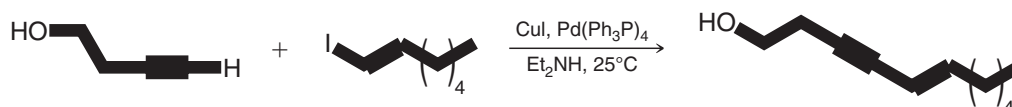
What starting materials could be used to synthesize each of the following compounds by a Stille coupling reaction?

Review Problem G.6

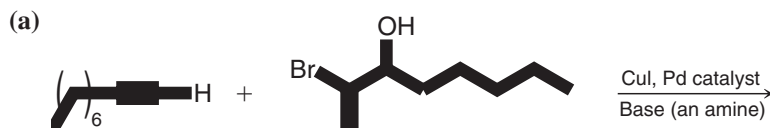
- (a) Target compound (a) is 4-tert-butylstyrene.
- (b) Target compound (b) is 1,1-diphenylethylene.

**G.1D The Sonogashira Coupling**

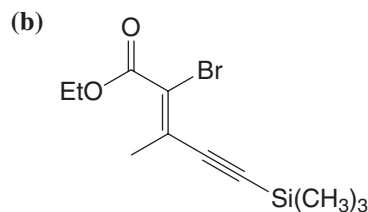
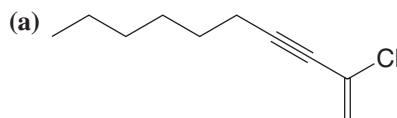
The Sonogashira coupling joins an alkyne with an alkenyl or aryl halide in the presence of catalytic palladium and copper. A copper acynide is formed as an intermediate in the reaction. (When palladium is not used, the reaction is called the Stephens–Castro coupling, and it is not catalytic.) In addition to providing a method for joining an alkyne directly to an aromatic ring, the Sonogashira coupling provides a way to synthesize enynes.

**General Reactions****Specific Example****Review Problem G.7**

Provide the products of each of the following reactions.

**Review Problem G.8**

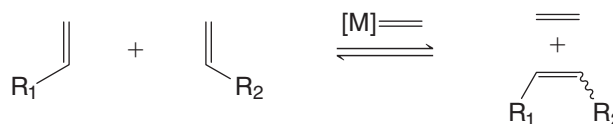
What starting materials could be used to synthesize each of the following compounds by a Sonogashira coupling reaction?



## G.2 Olefin Metathesis: Ruthenium Carbene Complexes and Grubbs' Catalysts

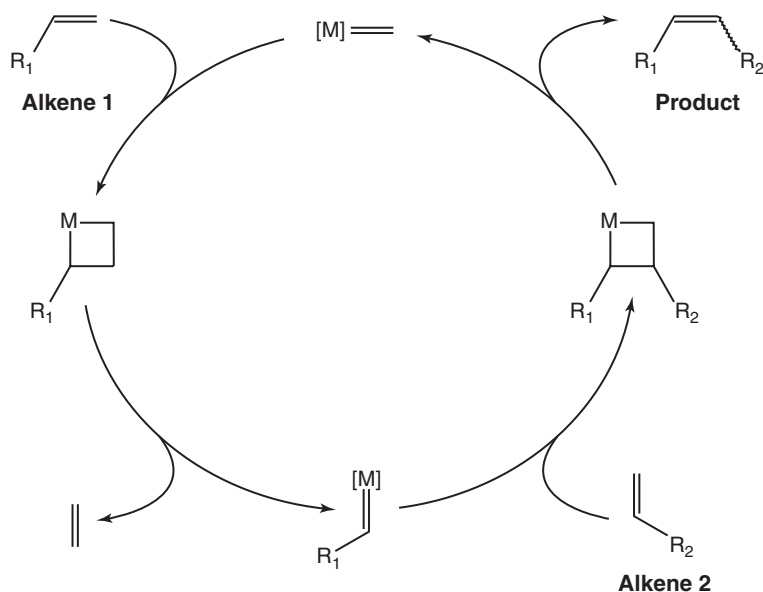
Pairs of alkene double bonds can trade ends with each other in a remarkable molecular “dance” called olefin metathesis (*meta*, Greek: to change; *thesis*, Greek: position).

The overall reaction is the following.

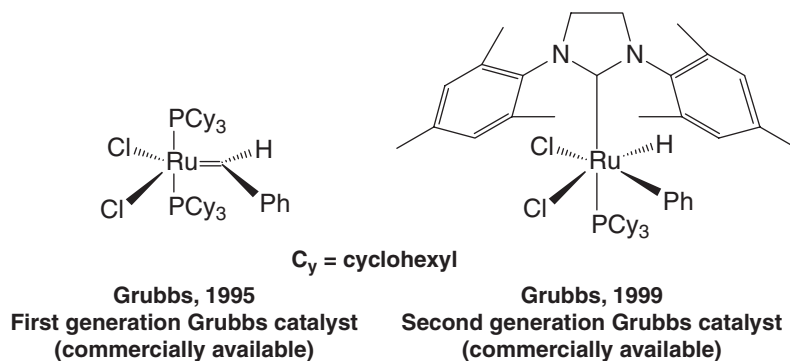


**[M]** represents a ruthenium alkylidene complex

The generally accepted catalytic cycle for this “change partners” dance was proposed by Yves Chauvin and is believed to involve metallocyclobutane intermediates that result from reaction of metal alkylidenes (also called metal carbenes) with alkenes. The catalysts themselves are metal alkylidenes, in fact. Chauvin's catalytic cycle for olefin metathesis is summarized here.



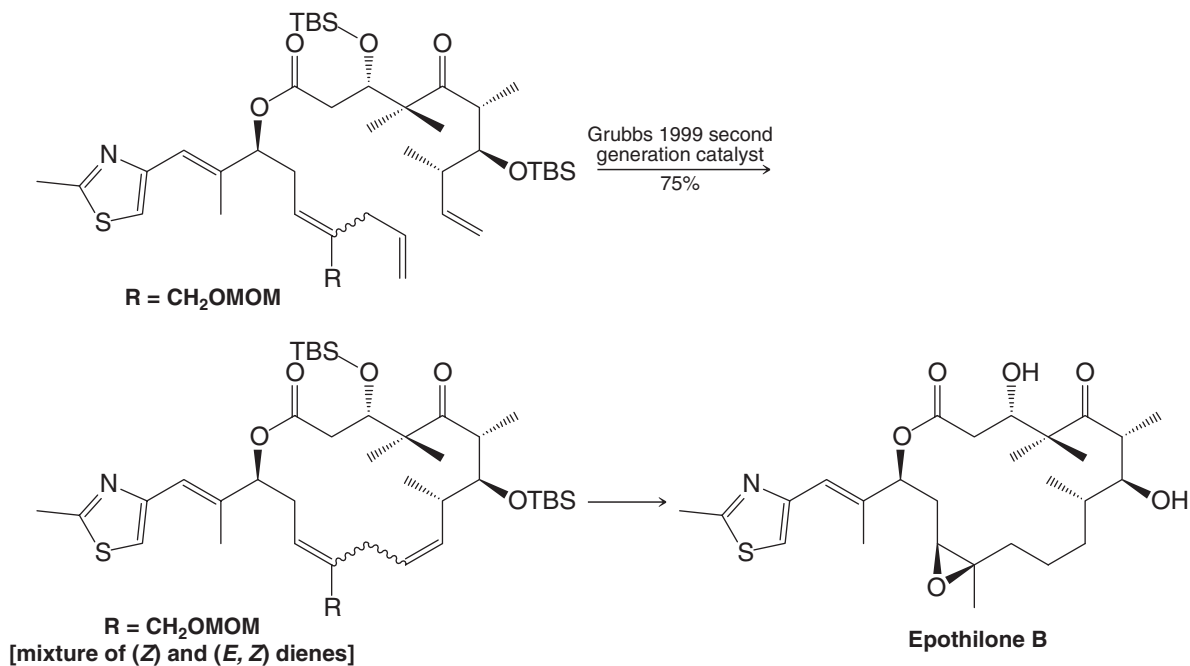
Richard Schrock investigated the properties of some of the first catalysts for olefin metathesis. His work included catalysts prepared from tantalum, titanium, and molybdenum. The catalysts predominantly in use today, however, are ruthenium catalysts developed by Robert Grubbs, Grubbs' so-called first generation and second generation catalysts are shown here.



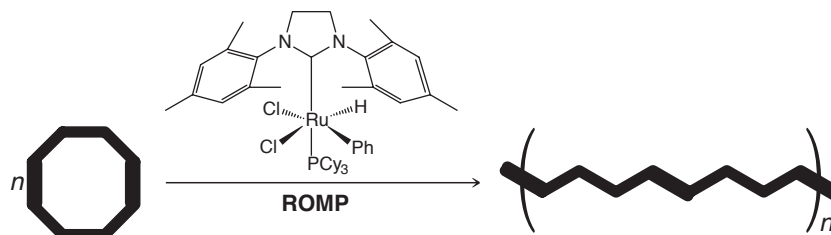
Olefin metathesis has proved to be such a powerful tool for synthesis that the 2005 Nobel Prize in Chemistry was awarded to Chauvin, Grubbs, and Shrock for their work in this area. One example is ring-closing olefin metathesis as applied to synthesis of the anticancer agent epothilone B by Sinha, shown below.



2005 Nobel Prize

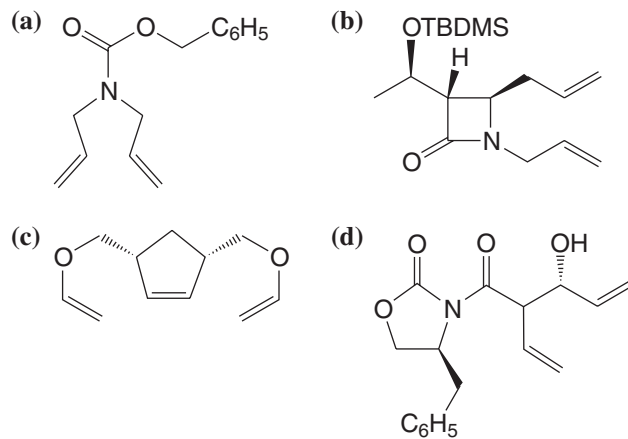


Another example is ring-opening olefin metathesis polymerization (ROMP), as can be used for synthesis of polybutadiene from 1,5-cyclooctadiene.



### Review Problem G.9

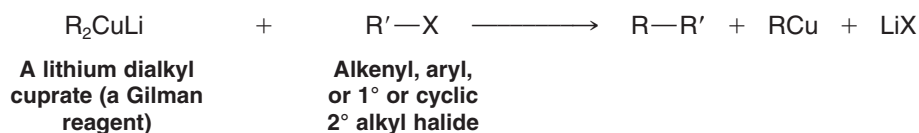
What products would form when each of the following compounds is treated with  $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ , one of Grubbs' catalysts?



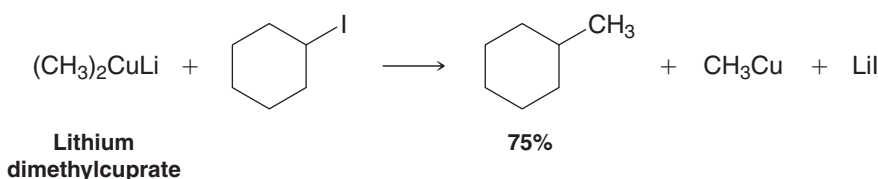
### G.3 The Corey–Posner, Whitesides–House Reaction: Use of Lithium Dialkyl Cuprates (Gilman Reagents) in Coupling Reactions

The Corey–Posner, Whitesides–House reaction involves the coupling of a lithium dialkylcuprate (called a Gilman reagent) with an alkyl, alkenyl, or aryl halide. The alkyl group of the lithium dialkylcuprate reagent may be primary, secondary, or tertiary. However, the halide with which the Gilman reagent couples must be a primary or cyclic secondary alkyl halide if it is not alkenyl or aryl.

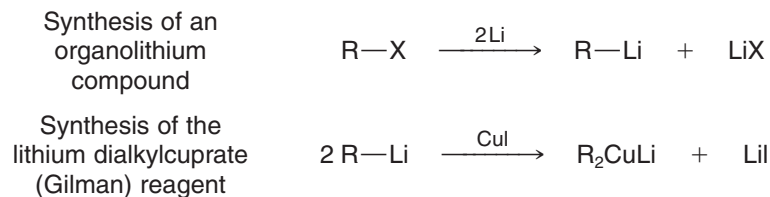
#### General Reaction



#### Specific Example

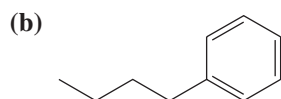
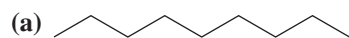


The required lithium dimethylcuprate (Gilman) reagent must be synthesized by a two-step process from the corresponding alkyl halide, as follows.



All of the reagents in a Corey–Posner, Whitesides–House reaction are consumed stoichiometrically. The mechanism does not involve a catalyst, as in the other reactions of transition metals that we have studied.

Show how 1-bromobutane could be converted to the Gilman reagent lithium dibutylcuprate, and how you could use it to synthesize each of the following compounds.



Review Problem G.10

### G.4 Some Background on Transition Metal Elements and Complexes

Now that we have seen examples of some important reactions involving transition metals, we consider aspects of the electronic structure of the metals and their complexes.

Transition metals are defined as those elements that have partly filled *d* (or *f*) shells, either in the elemental state or in their important compounds. The transition metals that are of most concern to organic chemists are those shown in the green and yellow portion of the periodic table given in Fig. G.1, which include those whose reactions we have just discussed.

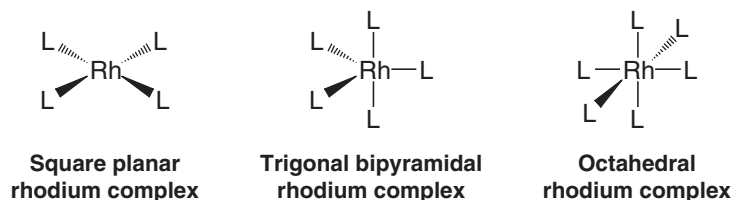
Transition metals react with a variety of molecules or groups, called *ligands*, to form *transition metal complexes*. In forming a complex, the ligands donate electrons to vacant

	1/IA											
1	1											
	H											
	1.00797	2/IIA										
2	3	4										
	Li	Be										
	6.941	9.01218										
3	11	12										
	Na	Mg	3/IIIB	4/IVB	5/VB	6/VIB	7/VIIB	8/VIIIB	9/VIIIB	10/VIIIB	11/IB	12/IIB
4	19	20	21	22	23	24	25	26	27	28	29	30
	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
	39.098	40.08	44.9559	47.90	50.9414	51.996	54.9380	55.847	58.9332	58.71	63.546	65.38
5	37	38	39	40	41	42	43	44	45	46	47	48
	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
	85.4678	87.62	89.9059	91.22	92.9064	95.94	98.9062	101.07	102.9055	106.4	107.868	112.40
6	55	56	57	72	73	74	75	76	77	78	79	80
	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg
	132.9054	137.34	138.9055	178.49	180.9479	183.85	186.2	190.2	192.22	195.09	196.9665	200.59
	1	2	3	4	5	6	7	8	9	10	11	12
	Valence electrons											

**Figure G.1** Important transition elements are shown in the green and yellow portion of the periodic table. Given across the bottom is the total number of valence electrons (*s* and *d*) of each element.

orbitals of the metal. The bonds between the ligand and the metal range from very weak to very strong. The bonds are covalent but often have considerable polar character.

Transition metal complexes can assume a variety of geometries depending on the metal and on the number of ligands around it. Rhodium, for example, can form complexes with four ligands in a configuration called *square planar*. On the other hand, rhodium can form complexes with five or six ligands that are trigonal bipyramidal or octahedral. These typical shapes are shown below, with the letter L used to indicate a ligand.



## G.5 Electron Counting in Metal Complexes

Transition metals are like the elements that we have studied earlier in that they are most stable when they have the electronic configuration of a noble gas. In addition to *s* and *p* orbitals, transition metals have five *d* orbitals (which can hold a total of 10 electrons). Therefore, the noble gas configuration for a transition metal is *18 electrons*, not 8 as with carbon, nitrogen, oxygen, and so on. When the metal of a transition metal complex has 18 valence electrons, it is said to be *coordinatively saturated*.\*

\*We do not usually show the unshared electron pairs of a metal complex in our structures, because to do so would make the structure unnecessarily complicated.

To determine the valence electron count of a transition metal in a complex, we take the total number of valence electrons of the metal in the elemental state (see Fig. G.1) and subtract from this number the oxidation state of the metal in the complex. This gives us what is called the  $d$  electron count,  $d^n$ . The oxidation state of the metal is the charge that would be left on the metal if all the ligands (Table G.1) were removed.



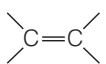


$$d^n = \begin{array}{l} \text{total number of valence electrons} \\ \text{of the elemental metal} \end{array} - \begin{array}{l} \text{oxidation state of} \\ \text{the metal in the complex} \end{array}$$

Then to get the total valence electron count of the metal *in the complex*, we add to  $d^n$  the number of electrons donated by all of the ligands. Table G.1 gives the number of electrons donated by several of the most common ligands.

$$\begin{array}{l} \text{total number of valence electrons} \\ \text{of the metal in the complex} \end{array} = d^n + \begin{array}{l} \text{electrons donated} \\ \text{by ligands} \end{array}$$

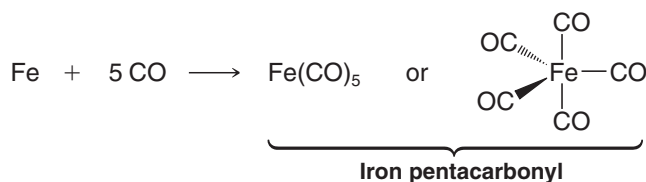
Let us now work out the valence electron count of two examples.

**TABLE G.1** Common Ligands in Transition Metal Complexes<sup>a</sup>

Ligand	Count as	Number of Electrons Donated
<b>Negatively charged ligands</b>		
Hydride, H		H: <sup>-</sup> 2
Alkanide, R		R: <sup>-</sup> 2
Halide, X		X: <sup>-</sup> 2
Allyl anion		4
Cyclopentadienyl anion, Cp		6
<b>Electrically neutral ligands</b>		
Carbonyl (carbon monoxide)	:C≡O:	2
Phosphine	R <sub>3</sub> P: or Ph <sub>3</sub> P:	2
Alkene		2
Diene		4
Benzene		6

<sup>a</sup>Used with permission from the *Journal of Chemical Education*, Vol. 57, No. 1, 1980, pp. 170-175, copyright © 1980, Division of Chemical Education.

**Example A** Consider iron pentacarbonyl, Fe(CO)<sub>5</sub>, a toxic liquid that forms when finely divided iron reacts with carbon monoxide.



From Fig. G.1 we find that an iron atom in the elemental state has 8 valence electrons. We arrive at the oxidation state of iron in iron pentacarbonyl by noting that the charge on the complex as a whole is zero (it is not an ion), and that the charge on each CO ligand is also zero. Therefore, the iron is in the zero oxidation state.

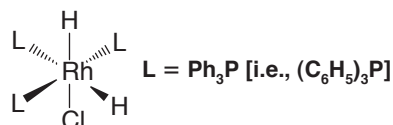
Using these numbers, we can now calculate  $d^n$  and, from it, the total number of valence electrons of the iron in the complex.

$$d^n = 8 - 0 = 8$$

$$\begin{array}{l} \text{total number of} \\ \text{valence electrons} \end{array} = d^n + 5(\text{CO}) = 8 + 5(2) = 18$$

We find that the iron of  $\text{Fe}(\text{CO})_5$  has 18 valence electrons and is, therefore, coordinatively saturated.

**Example B** Consider the rhodium complex  $\text{Rh}[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{H}_2\text{Cl}$ , a complex that, as we shall see later, is an intermediate in certain alkene hydrogenations.



The oxidation state of rhodium in the complex is +3. [The two hydrogen atoms and the chlorine are each counted as  $-1$  (hydride and chloride, respectively), and the charge on each of the triphenylphosphine ligands is zero. Removing all the ligands would leave a  $\text{Rh}^{3+}$  ion.] From Fig. G.1 we find that, in the elemental state, rhodium has 9 valence electrons. We can now calculate  $d^n$  for the rhodium of the complex.

$$d^n = 9 - 3 = 6$$

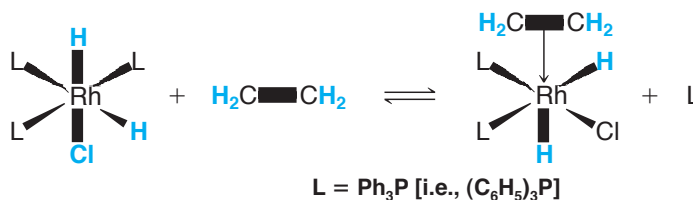
Each of the six ligands of the complex donates two electrons to the rhodium in the complex, and, therefore, the total number of valence electrons of the rhodium is 18. The rhodium of  $\text{Rh}[(\text{C}_6\text{H}_5)_3\text{P}]_3\text{H}_2\text{Cl}$  is coordinatively saturated.

$$\begin{array}{l} \text{total number of valence} \\ \text{electrons rhodium} \end{array} = d^n + 6(2) = 6 + 12 = 18$$

## G.6 Mechanistic Steps in the Reactions of Some Transition Metal Complexes

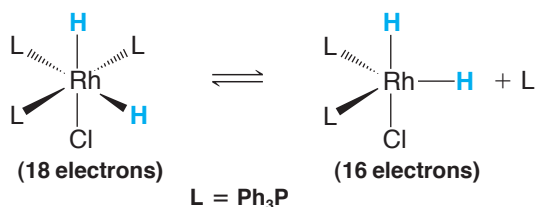
Much of the chemistry of organic transition metal compounds becomes more understandable if we are able to follow the mechanisms of the reactions that occur. These mechanisms, in most cases, amount to nothing more than a sequence of reactions, each of which represents a *fundamental reaction type that is characteristic of a transition metal complex*. Let us examine three of the fundamental reaction types now. In each instance we shall use steps that occur when an alkene is hydrogenated using a catalyst called Wilkinson's catalyst. In Section G.7 we shall examine the entire hydrogenation mechanism. In Section G.8 we shall see how similar types of steps are involved in the Heck–Mizokori reaction.

**1. Ligand Dissociation–Association (Ligand Exchange).** A transition metal complex can lose a ligand (by dissociation) and combine with another ligand (by association). In the process it undergoes *ligand exchange*. For example, the rhodium complex that we encountered in Example B above can react with an alkene (in this example, with ethene) as follows:

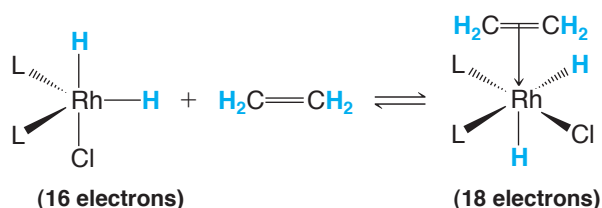




Two steps are actually involved. In the first step, one of the triphenylphosphine ligands dissociates. This leads to a complex in which the rhodium has only 16 electrons and is, therefore, coordinatively *unsaturated*.



In the second step, the rhodium associates with the alkene to become coordinatively saturated again.



The complex between the rhodium and the alkene is called a  $\pi$  complex. In it, two electrons are donated by the alkene to the rhodium. Alkenes are often called  $\pi$  donors to distinguish them from  $\sigma$  donors such as  $\text{Ph}_3\text{P}$ ,  $\text{Cl}^-$ , and so on.

In a  $\pi$  complex such as the one just given, there is also a donation of electrons from a populated  $d$  orbital of the metal back to the vacant  $\pi^*$  orbital of the alkene. This kind of donation is called “back-bonding.”

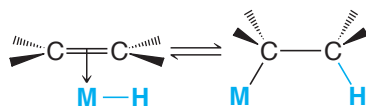
- 2. Insertion–Deinsertion.** An unsaturated ligand such as an alkene can undergo *insertion* into a bond between the metal of a complex and a hydrogen or a carbon. These reactions are reversible, and the reverse reaction is called *deinsertion*.

The following is an example of insertion–deinsertion.

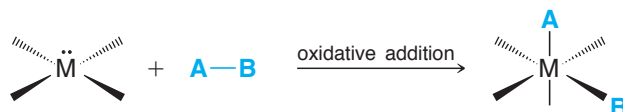


In this process, a  $\pi$  bond (between the rhodium and the alkene) and a  $\sigma$  bond (between the rhodium and the hydrogen) are exchanged for two new  $\sigma$  bonds (between rhodium and carbon, and between carbon and hydrogen). The valence electron count of the rhodium decreases from 18 to 16.

This insertion–deinsertion occurs in a stereospecific way, as a *syn addition* of the  $\text{M}-\text{H}$  unit to the alkene.



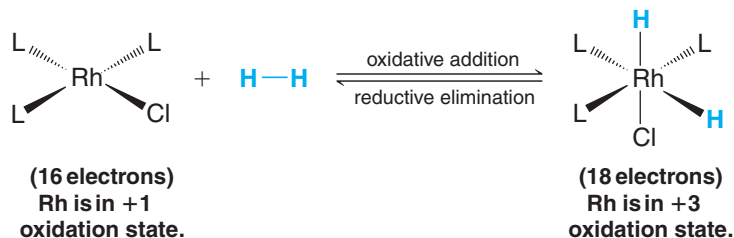
- 3. Oxidative Addition–Reductive Elimination.** Coordinatively unsaturated metal complexes can undergo oxidative addition of a variety of substrates in the following way.\*



\*Coordinatively saturated complexes also undergo oxidative addition.

The substrate, A—B, can be H—H, H—X, R—X, RCO—H, RCO—X, and a number of other compounds.

In this type of oxidative addition, the metal of the complex undergoes an increase in the number of its valence electrons *and in its oxidation state*. Consider, as an example, the oxidative addition of hydrogen to the rhodium complex that follows (L = Ph<sub>3</sub>P).



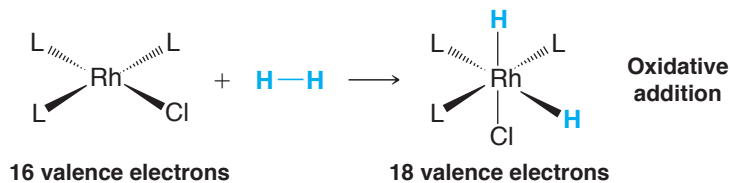
*Reductive elimination* is the reverse of oxidative addition. With this background, we are now in a position to examine the mechanisms of two applications of transition metal complexes in organic synthesis.

## G.7 The Mechanism for a Homogeneous Hydrogenation: Wilkinson's Catalyst

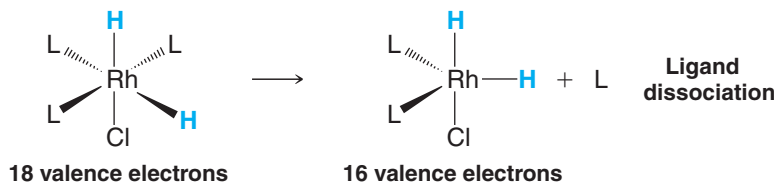
The catalytic hydrogenations that we have examined in prior chapters have been heterogeneous processes. Two phases were involved: the solid phase of the catalyst (Pt, Pd, Ni, etc.), containing the adsorbed hydrogen, and the liquid phase of the solution, containing the unsaturated compound. In homogeneous hydrogenation using a transition metal complex such as Rh[(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>P]<sub>3</sub>Cl (Wilkinson's catalyst), hydrogenation takes place *in a single phase*, i.e., in solution.

When Wilkinson's catalyst is used to carry out the hydrogenation of an alkene, the following steps take place (L = Ph<sub>3</sub>P).

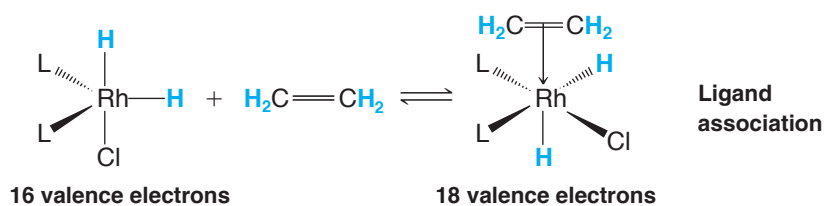
*Step 1*



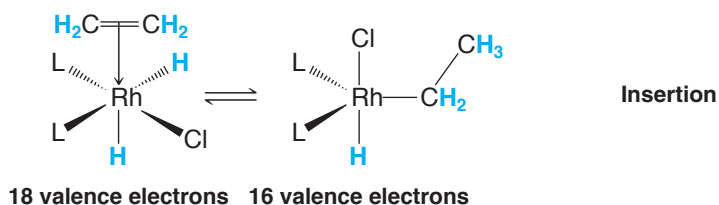
*Step 2*



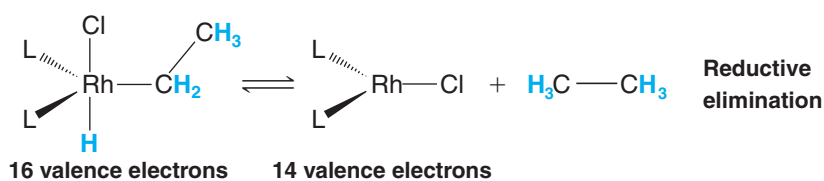
Step 3



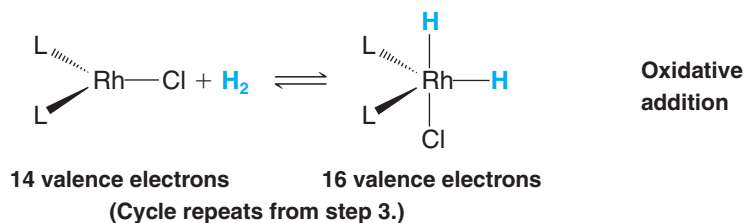
Step 4



Step 5

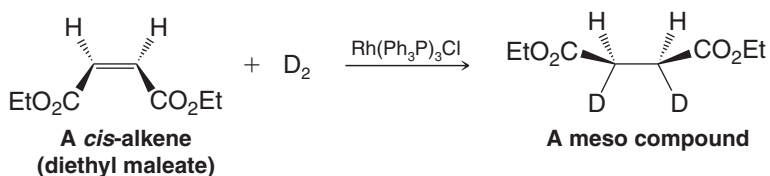


Step 6



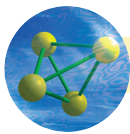
Step 6 regenerates the hydrogen-bearing rhodium complex and reaction with another molecule of the alkene begins at step 3.

Because the insertion step 4 and the reductive elimination step 5 are stereospecific, the net result of the hydrogenation using Wilkinson's catalyst is a *syn addition* of hydrogen to the alkene. The following example (with  $D_2$  in place of  $H_2$ ) illustrates this aspect.



What product (or products) would be formed if the *trans*-alkene corresponding to the *cis*-alkene (see the previous reaction) had been hydrogenated with  $D_2$  and Wilkinson's catalyst?

Review Problem G.11



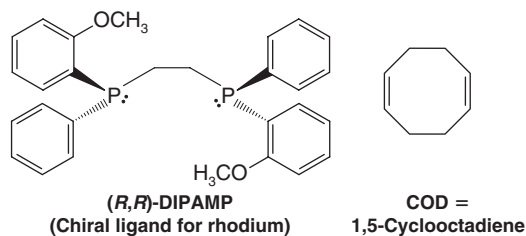
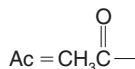
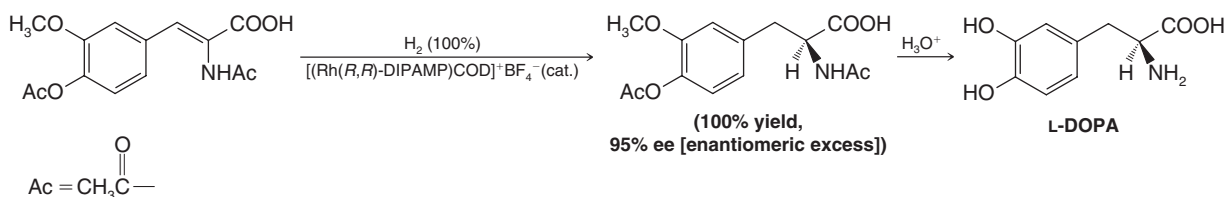
## THE CHEMISTRY OF ...

### Homogeneous Asymmetric Catalytic Hydrogenation: Examples Involving L-DOPA, (S)-Naproxen, and Aspartame

Development by Geoffrey Wilkinson of a soluble catalyst for hydrogenation [tris(triphenylphosphine)rhodium chloride, Section 7.13 and Special Topic G] led to Wilkinson's earning a share of the 1973 Nobel Prize in Chemistry. His initial discovery, while at Imperial College, University of London, inspired many other researchers to create novel catalysts based on the Wilkinson catalyst. Some of these researchers were themselves recognized by the 2001 Nobel Prize in Chemistry, 50% of which was awarded to William S. Knowles (Monsanto Corporation, retired) and Ryoji Noyori (Nagoya

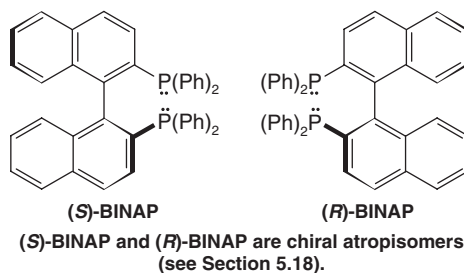
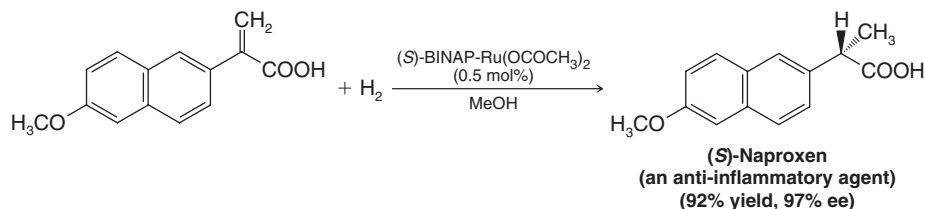
University). (The other half of the 2001 prize was awarded to K. B. Sharpless for asymmetric oxidation reactions. See Chapter 8.) Knowles, Noyori, and others developed chiral catalysts for homogeneous hydrogenation that have proved extraordinarily useful for enantioselective syntheses ranging from small laboratory-scale reactions to industrial- (ton-) scale reactions. An important example is the method developed by Knowles and co-workers at Monsanto Corporation for synthesis of L-DOPA, a compound used in the treatment of Parkinson's disease:

#### Asymmetric Synthesis of L-DOPA



Another example is synthesis of the over-the-counter analgesic naproxen using a BINAP rhodium catalyst developed by Noyori (Sections 5.11 and 5.18).

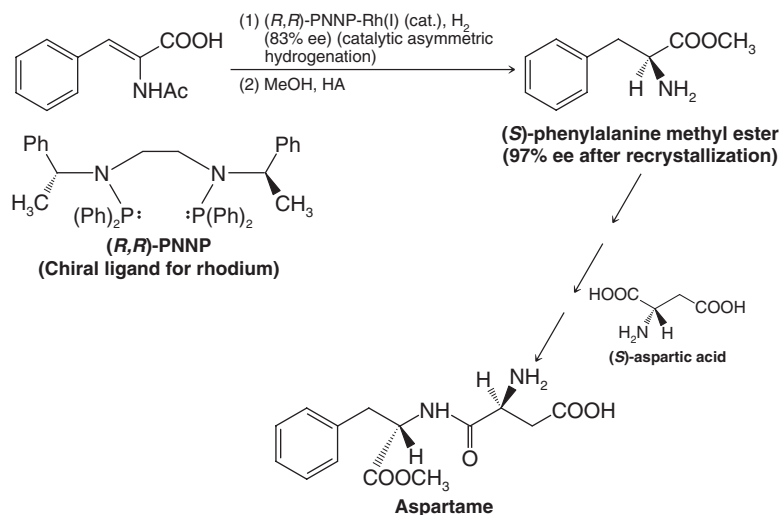
#### Asymmetric Synthesis of (S)-Naproxen



Catalysts like these are important for asymmetric chemical synthesis of amino acids (Section 24.3D), as well. A final example is the synthesis of (*S*)-phenylalanine methyl ester,

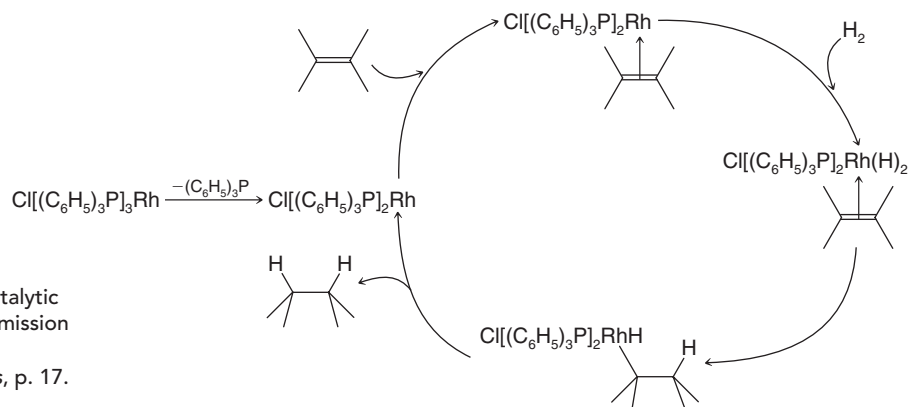
a compound used in the synthesis of the artificial sweetener aspartame. This preparation employs yet a different chiral ligand for the rhodium catalyst.

### Asymmetric Synthesis of Aspartame



The mechanism of homogeneous catalytic hydrogenation involves reactions characteristic of transition metal organometallic compounds. A general scheme for hydro-

genation using Wilkinson's catalyst is shown here. We have seen structural details of the mechanism in Section G.7.



A general mechanism for the Wilkinson catalytic hydrogenation method, adapted with permission of John Wiley & Sons, Inc. from Noyori, *Asymmetric Catalysis in Organic Synthesis*, p. 17. Copyright 1994.

## G.8 The Mechanism for an Example of Cross-Coupling: The Heck–Mizokori Reaction

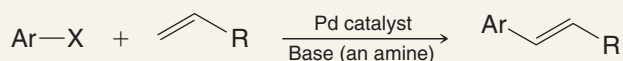
Having seen steps such as oxidative addition, insertion, and reductive elimination in the context of transition metal–catalyzed hydrogenation using Wilkinson's catalyst, we can now see how these same types of mechanistic steps are involved in a mechanism proposed for the Heck–Mizokori reaction. Aspects of the Heck–Mizokori mechanism are similar to steps proposed for other cross-coupling reactions as well, although there are variations and certain steps that are specific to each, and not all of the steps below are involved or serve the same purpose in other cross-coupling reactions.



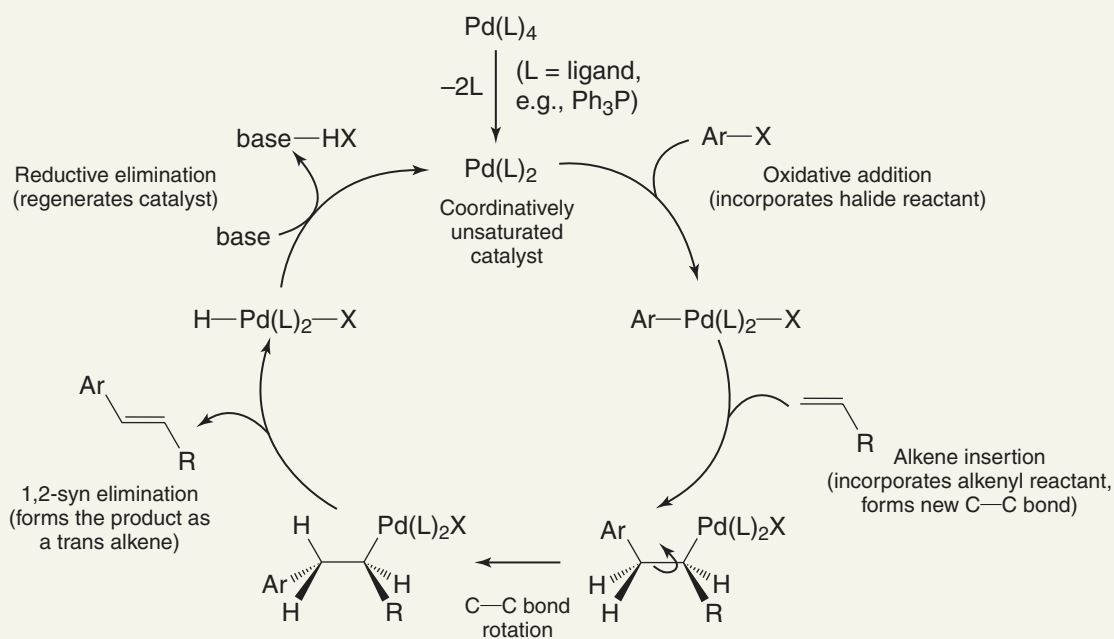
## A MECHANISM FOR THE REACTION

### The Heck–Mizokori Reaction Using an Aryl Halide Substrate

#### GENERAL REACTION



#### MECHANISM



## G.9 Vitamin B<sub>12</sub>: A Transition Metal Biomolecule

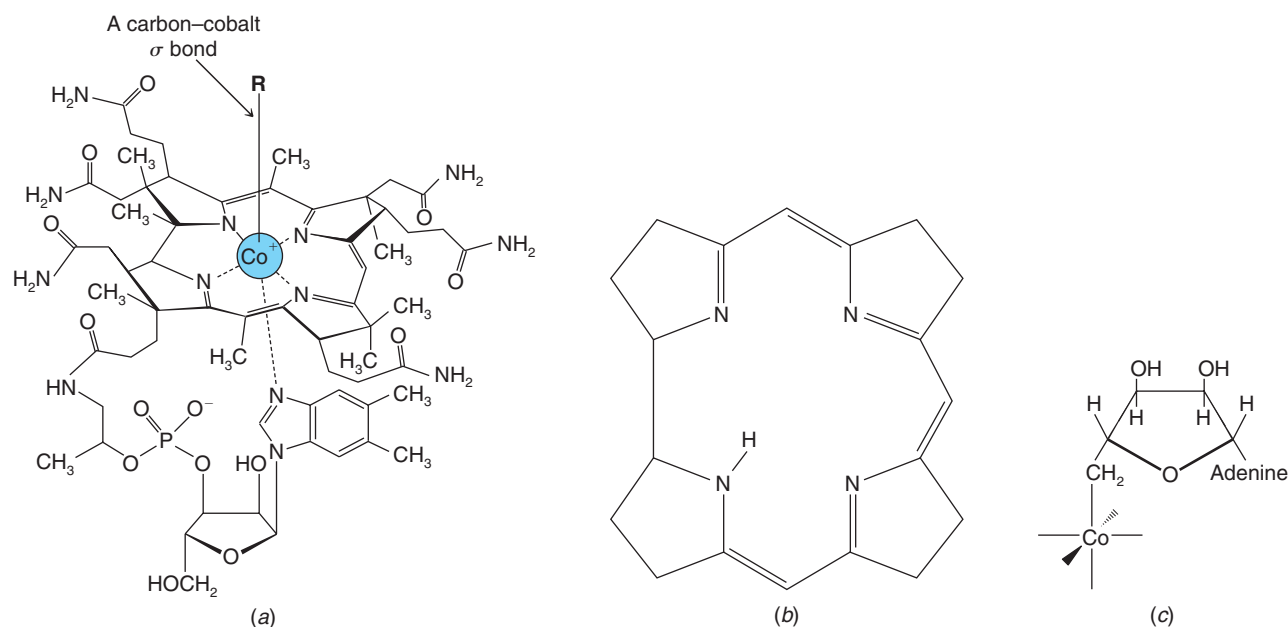
The discovery (in 1926) that pernicious anemia can be overcome by the ingestion of large amounts of liver led ultimately to the isolation (in 1948) of the curative factor, called vitamin B<sub>12</sub>. The complete three-dimensional structure of vitamin B<sub>12</sub> [Fig. G.2(a)] was elucidated in 1956 through the X-ray studies of Dorothy Hodgkin (Nobel Prize, 1964), and in 1972 the synthesis of this complicated molecule was announced by R. B. Woodward (Harvard University) and A. Eschenmoser (Swiss Federal Institute of Technology). The synthesis took 11 years and involved more than 90 separate reactions. One hundred co-workers took part in the project.

Vitamin B<sub>12</sub> is the only known biomolecule that possesses a carbon–metal bond. In the stable commercial form of the vitamin, a cyano group is bonded to the cobalt, and the cobalt is in the +3 oxidation state. The core of the vitamin B<sub>12</sub> molecule is a *corrin ring* [Fig. G.2(b)] with various attached side groups. The corrin ring consists of four pyrrole

subunits, the nitrogen of each of which is coordinated to the central cobalt. The sixth ligand [(below the corrin ring in Fig. G.2(a)] is a nitrogen of a heterocyclic group derived from 5,6-dimethylbenzimidazole.

The cobalt of vitamin B<sub>12</sub> can be reduced to a +2 or a +1 oxidation state. When the cobalt is in the +1 oxidation state, vitamin B<sub>12</sub> (called B<sub>12s</sub>) becomes one of the most powerful nucleophiles known, being more nucleophilic than methanol by a factor of 10<sup>14</sup>.

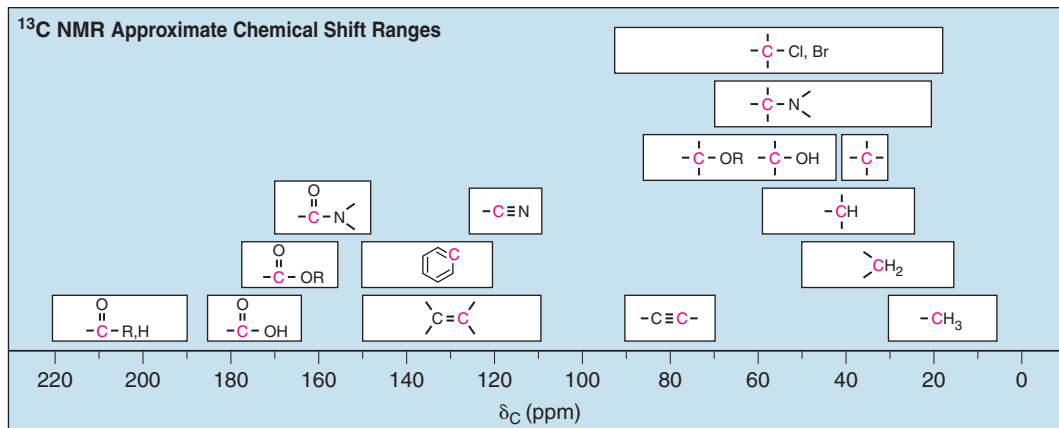
Acting as a nucleophile, vitamin B<sub>12s</sub> reacts with adenosine triphosphate (Fig. 22.2) to yield the biologically active form of the vitamin [Fig. G.2(c)].



**Figure G.2** (a) The structure of vitamin B<sub>12</sub>. In the commercial form of the vitamin (cyanocobalamin), R=CN. (b) The corrin ring system. (c) In the biologically active form of the vitamin (5'-deoxyadenosylcobalamin), the 5' carbon atom of 5'-deoxyadenosine is coordinated to the cobalt atom. For the structure of adenine, see Section 25.2.

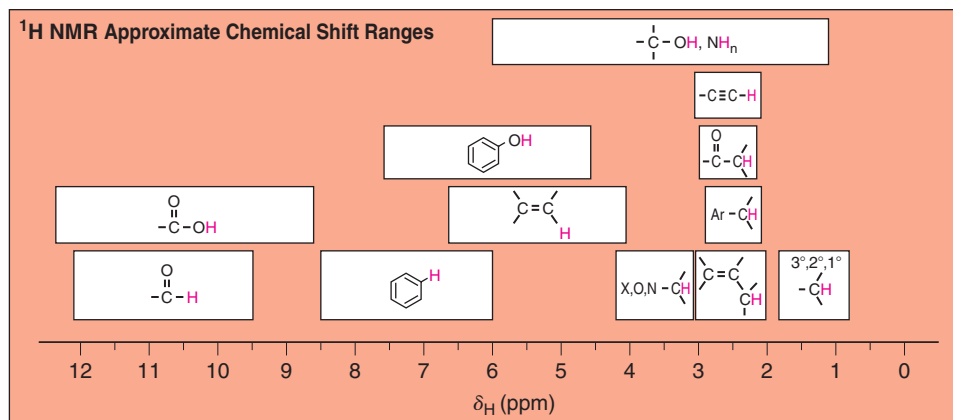






**TABLE 9.2** Approximate Carbon-13 Chemical Shifts

Type of Carbon Atom	Chemical Shift ( $\delta$ , ppm)
1° Alkyl, $\text{RCH}_3$	0–40
2° Alkyl, $\text{RCH}_2\text{R}$	10–50
3° Alkyl, $\text{RCHR}_2$	15–50
Alkyl halide or amine, $\text{-C-X}$ (X = Cl, Br, or N—)	10–65
Alcohol or ether, $\text{-C-O-}$	50–90
Alkyne, $\text{-C}\equiv\text{C}$	60–90
Alkene, $\text{C=C}$	100–170
Aryl,	100–170
Nitrile, $\text{-C}\equiv\text{N}$	120–130
Amide, $\text{-C(=O)-N-}$	150–180
Carboxylic acid or ester, $\text{-C(=O)-O-}$	160–185
Aldehyde or ketone, $\text{-C(=O)-}$	182–215



**TABLE 9.1** Approximate Proton Chemical Shifts

Type of Proton	Chemical Shift (ppm)	Type of Proton	Chemical Shift (ppm)
1° Alkyl, $\text{RCH}_3$	0.8–1.2	Alkyl bromide, $\text{RCH}_2\text{Br}$	3.4–3.6
2° Alkyl, $\text{RCH}_2\text{R}$	1.2–1.5	Alkyl chloride, $\text{RCH}_2\text{Cl}$	3.6–3.8
3° Alkyl, $\text{R}_3\text{CH}$	1.4–1.8	Vinylic, $\text{R}_2\text{C}=\text{CH}_2$	4.6–5.0
Allylic, $\text{R}_2\text{C}=\text{C}-\text{CH}_3$   R	1.6–1.9	Vinylic, $\text{R}_2\text{C}=\text{CH}$   R	5.2–5.7
Ketone, $\text{RCCH}_3$    O	2.1–2.6	Aromatic, $\text{ArH}$	6.0–8.5
Benzylic, $\text{ArCH}_3$	2.2–2.5	Aldehyde, $\text{RCH}$    O	9.5–10.5
Acetylenic, $\text{RC}\equiv\text{CH}$	2.5–3.1	Alcohol hydroxyl, $\text{ROH}$	0.5–6.0 <sup>a</sup>
Alkyl iodide, $\text{RCH}_2\text{I}$	3.1–3.3	Amino, $\text{R}^9\text{NH}_2$	1.0–5.0 <sup>a</sup>
Ether, $\text{ROCH}_2\text{R}$	3.3–3.9	Phenolic, $\text{ArOH}$	4.5–7.7 <sup>a</sup>
Alcohol, $\text{HOCH}_2\text{R}$	3.3–4.0	Carboxylic, $\text{RCOH}$    O	10–13 <sup>a</sup>

<sup>a</sup>The chemical shifts of these protons vary in different solvents and with temperature and concentration.