

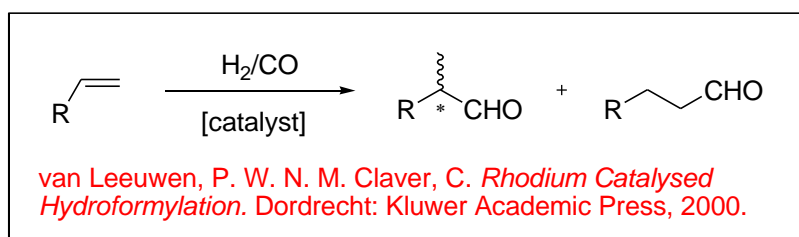
## Module 9 Carbonylation Reactions

### Lecture 31

Carbonylation of the unsaturated substrates using transition metal catalysis provides powerful tool to produce fine chemical intermediates. The asymmetric carbonylation is among the most challenging homogeneous process and their potential is yet to be made. The Rh-catalyzed hydroformylation of alkenes together with the Pd-catalyzed hydroxy and alkoxy carbonylation of alkenes are the most famous examples for the asymmetric carbonylation reactions. The important difference between these reactions is the Rh-catalyzed hydroformylation is of greater industrial interest than the palladium based carbonylation process.

#### 9.1 Hydroformylation Reaction

The conversion of alkenes to aldehydes is the largest volume homogeneous transition metal-catalyzed reaction. This process has been extensively explored and a number of methods and catalysts have been developed to control the regioselectivity in internal and terminal aldehydes (Scheme 1).

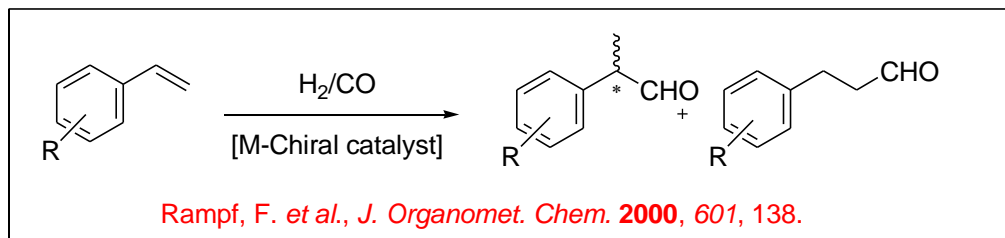


Scheme 1

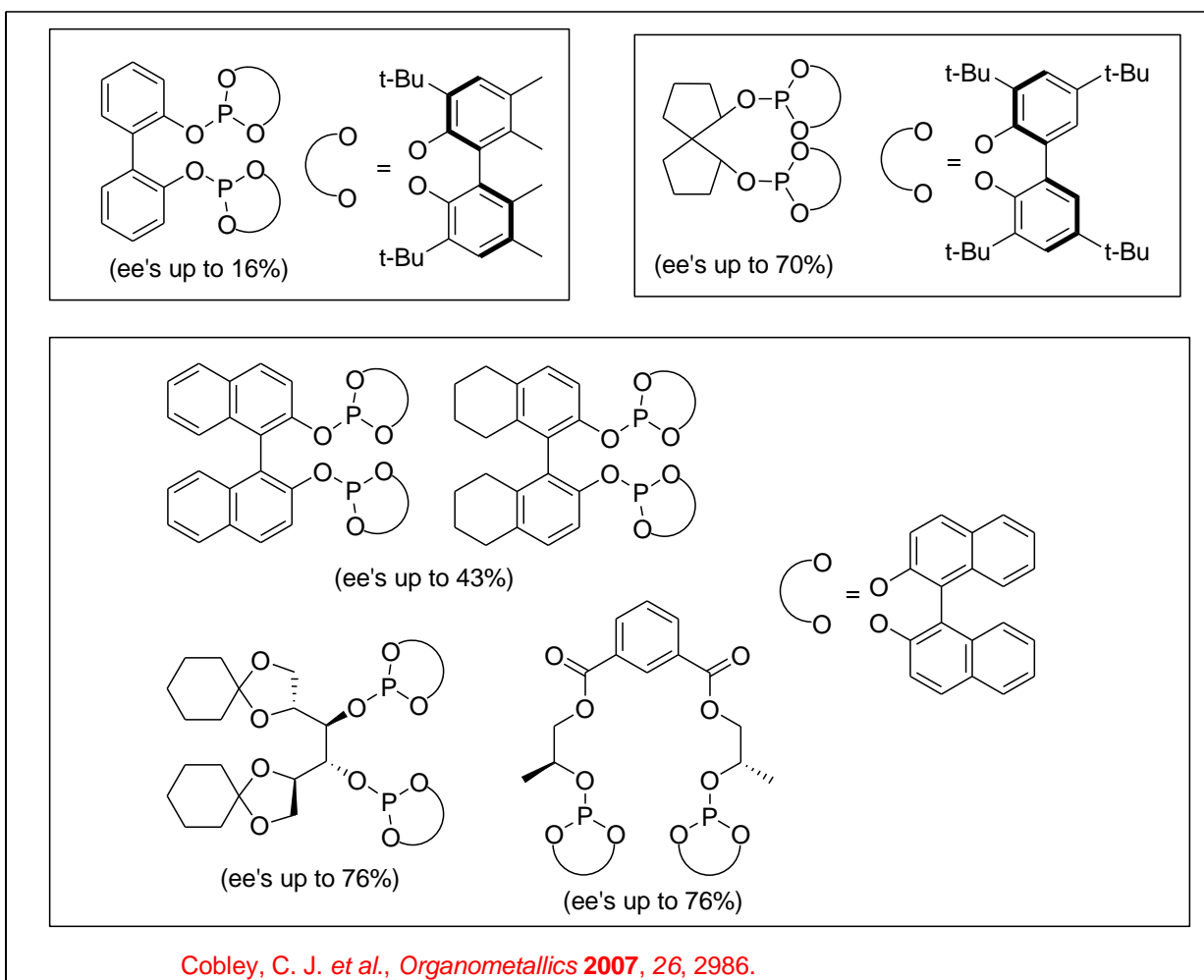
##### 9.1.1 Reaction of Vinyl Arenes

The asymmetric hydroformylation of vinyl arenes is an attractive route to afford optically active aldehydes, which are substrate precursors for the synthesis of high-value pharmaceuticals, agrochemicals, biodegradable polymers and liquid crystals (Scheme 2). Since the beginning of 1970, chiral Rh-diphosphine complexes have been used as catalysts for this transformation with moderate enantioselectivity (below 60%). From beginning of 1990, the use of bisphosphacyclic ligands, diphosphites and phosphine-phosphite, has emerged as alternative for this reaction. Scheme 3 summarizes some of the new diphosphite

ligands developed with biaryl, spiro, pyranoside, mannitol and macrocyclic backbones for the asymmetric hydroformylation of vinyl arenes with low to moderate success (ee's from 16% to 76%).

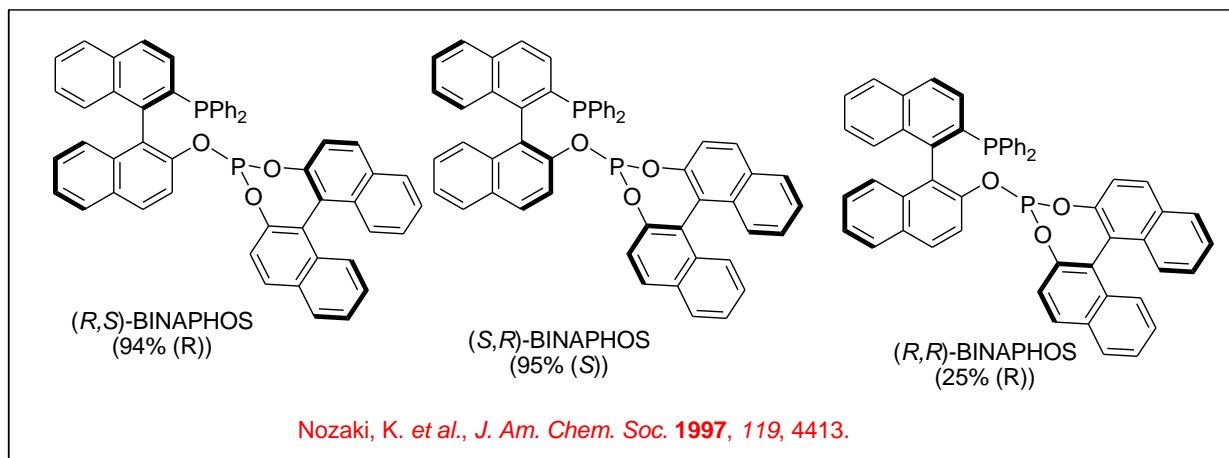


Scheme 2



Scheme 3. Diphosphite Ligands for Hydroformylation.

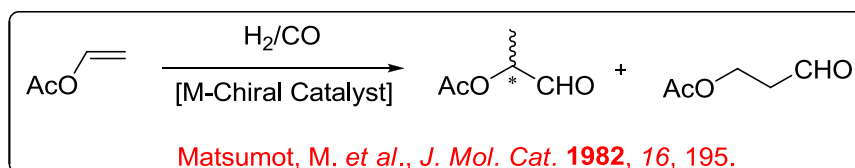
Scheme 4 summarizes some of successful phosphine-phosphite ligands for the asymmetric hydroformylation of vinyl arene. The enantioselectivity depends on the configuration of both the binaphthyl moieties. The best enantioselectivity is observed when the configurations of the two binaphthyl moieties are opposite.



Scheme 4. Rh-Catalyzed Asymmetric Hydroformylation of Styrene. Enantioselectivities obtained at 100 bar of syn gas and 60°C are shown in brackets.

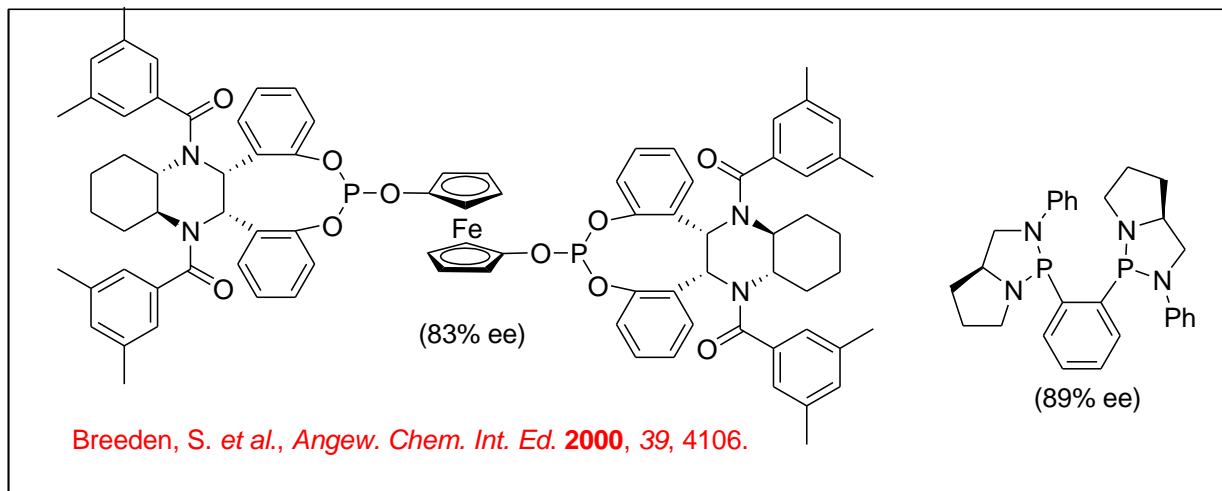
### 9.1.2 Reaction of Vinyl Acetate

The reaction of vinyl acetate is more challenging compared to that of vinylarenes. This process affords 2- and 3- acetoxy propanals with high selectivity (Scheme 5). Ethyl acetate and acetic acid are produced as by-products.



Scheme 5

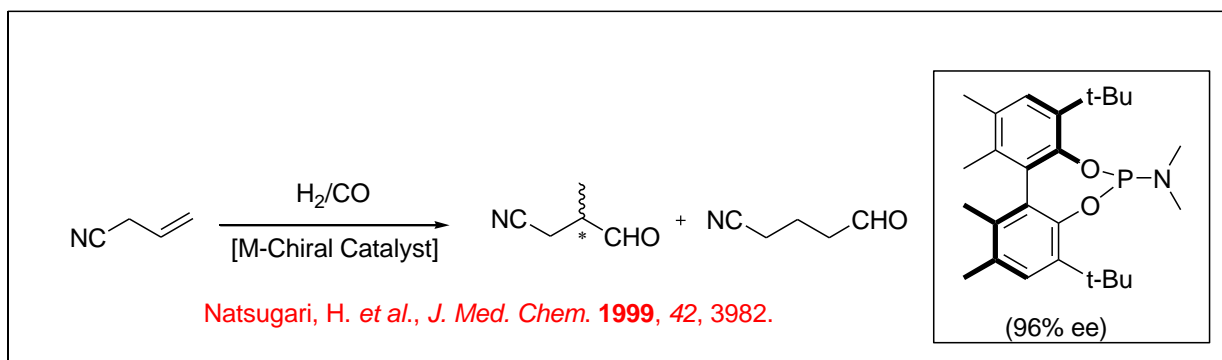
Scheme 6 illustrates some of the successful ligands for the Rh-catalyzed hydroformylation of vinyl acetate. The enantioselectivity of the reactions are shown in the brackets.



Scheme 6

### 9.1.3 Reaction of Allyl Cyanide

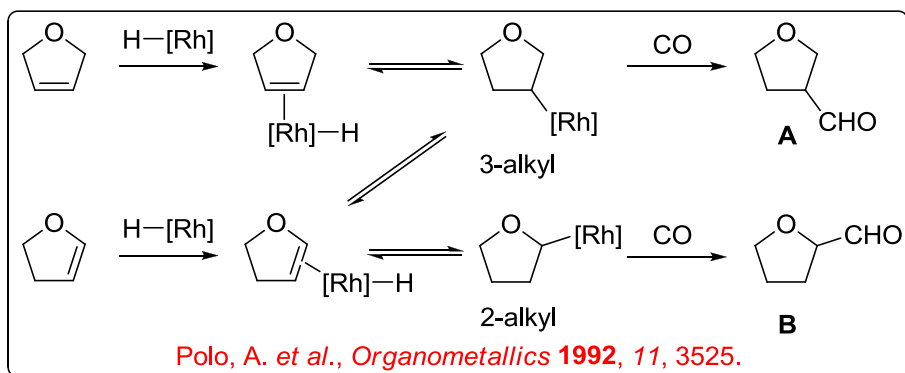
The asymmetric hydroformylation of allyl cyanide is of great interest because the iso-aldehyde derivative can be converted into 2-methyl-4-butanol, which is intermediate, for the asymmetric synthesis of tachikinin, a novel NK1 receptor agonist (Scheme 7). The reaction has been studied using diphosphite, phosphine-phosphite, bis-phosphacyclic and phosphoramidite ligands with up to 96% ee.



Scheme 7

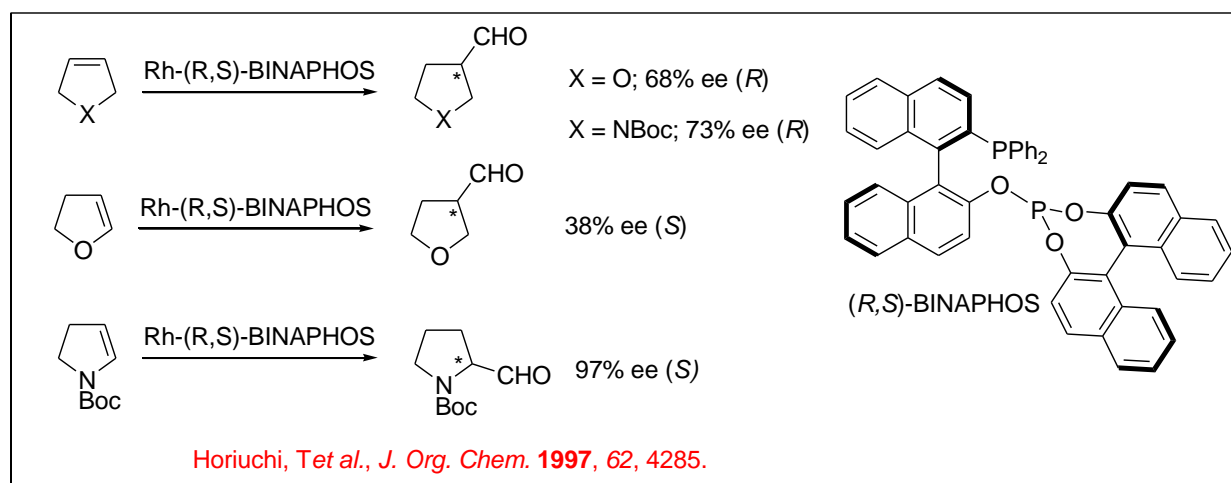
### 9.1.4 Reaction of Heterocyclic Alkenes

Few studies are focused on the hydroformylation of heterocyclic alkenes. For these substrates, the regioselectivity is of special interest because it is different from that of the acyclic alkenes. For example, the hydroformylation of 2,5-dihydrofuran can lead to the formation of both the tetrahydrofuran-3-carbaldehyde **A** (expected product) and tetrahydrofuran-2-carbaldehyde **B** (could be formed via an isomerization process). The regioselectivity is to be controlled by the modification of the ligands and reaction conditions.



Scheme 8

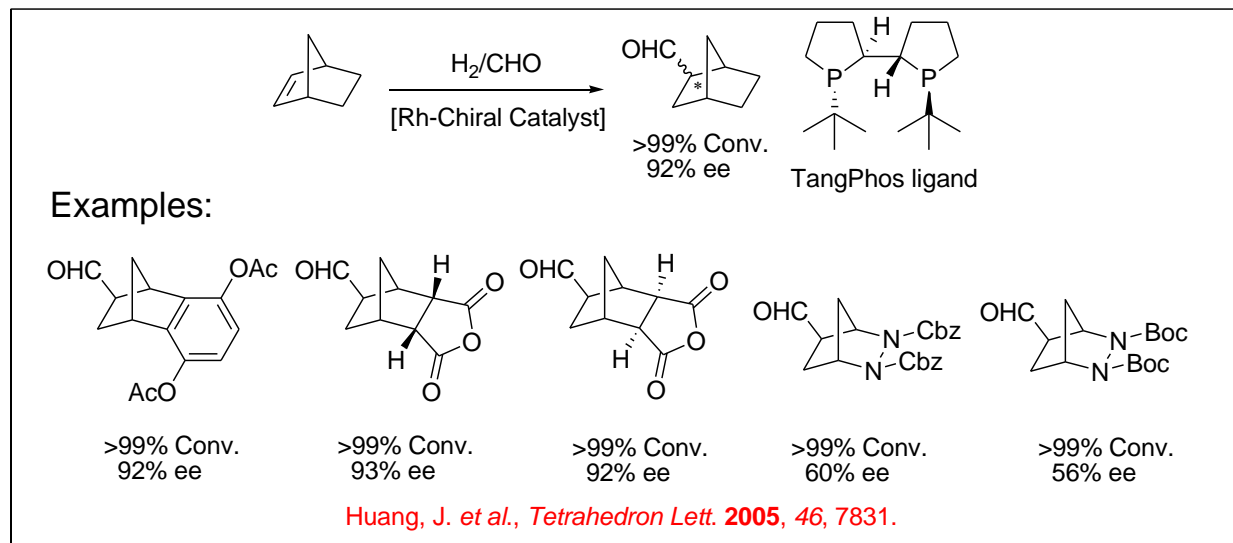
Scheme 9 summarizes the reaction of 2,5-dihydrofuran, 3-pyrroline derivative and 4,7-dihydro-1,3-dioxepin derivative using chiral Rh-complex bearing R,S-BINAPHOS. The optically active aldehydes are obtained as single products with enantioselectivities between 64-97%. In case of 2,5-dihydrofuran, up to 64% regioselectivity is observed for the formation of tetrahydrofuran-3-carbaldehyde **A**, while the reaction of 2,3-dihydrofuran led to the formation of a mixture of **A** and **B** (1:1) with an ee of 38% in **A**.



Scheme 9

### 9.1.5 Reaction of Bicyclic Alkenes

The asymmetric hydroformylation of bicyclic alkenes has received little attention. This reaction is interesting because of the following features: (i) the reaction can lead to the formation of three chiral centers upon one C-C bond formation; (ii) there is no regioselectivity problem; (iii) functional groups located opposite to the carbon-carbon double bond could be versatile. Scheme 10 summarizes some of the examples for the asymmetric hydroformylation of bicyclic alkenes employing Rh-TangPhos.



Scheme 10

### Problems

- How does the product formation differ from cyclic alkenes compared to that of acyclic alkenes?
- Write a mechanism for the Rh-catalyzed hydroformylation of alkenes.

### Reference

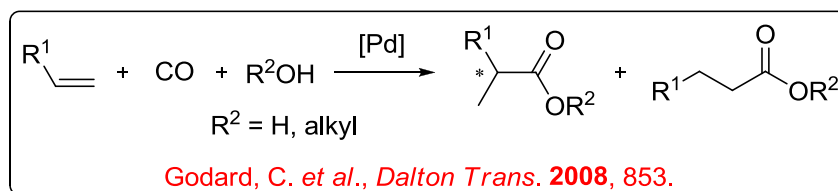
- I. Ojima, *Catalytic Asymmetric Synthesis*, 3<sup>rd</sup> ed., Wiley, New Jersey, 2010.

## Lecture 32: Asymmetric Alkoxy carbonylation and Related Reactions

### 9.2.1 Reaction of Vinylarenes

From academic and industrial standpoint, the Pd-catalyzed asymmetric hydroxy- and alkoxy carbonylation reactions are attractive processes. However, they are less successful compared to the Rh-catalyzed hydroformylation reactions. This is because of the difficulty in getting simultaneously both high regio- and enantioselectivities.

The alkoxy carbonylation of vinylarenes is an important process and the resulting products (2-arylpropanoic acids and derivatives) serve as substrate precursors for nonsteroidal anti-inflammatory drugs, particularly ibuprofen and naproxen (Scheme 1).

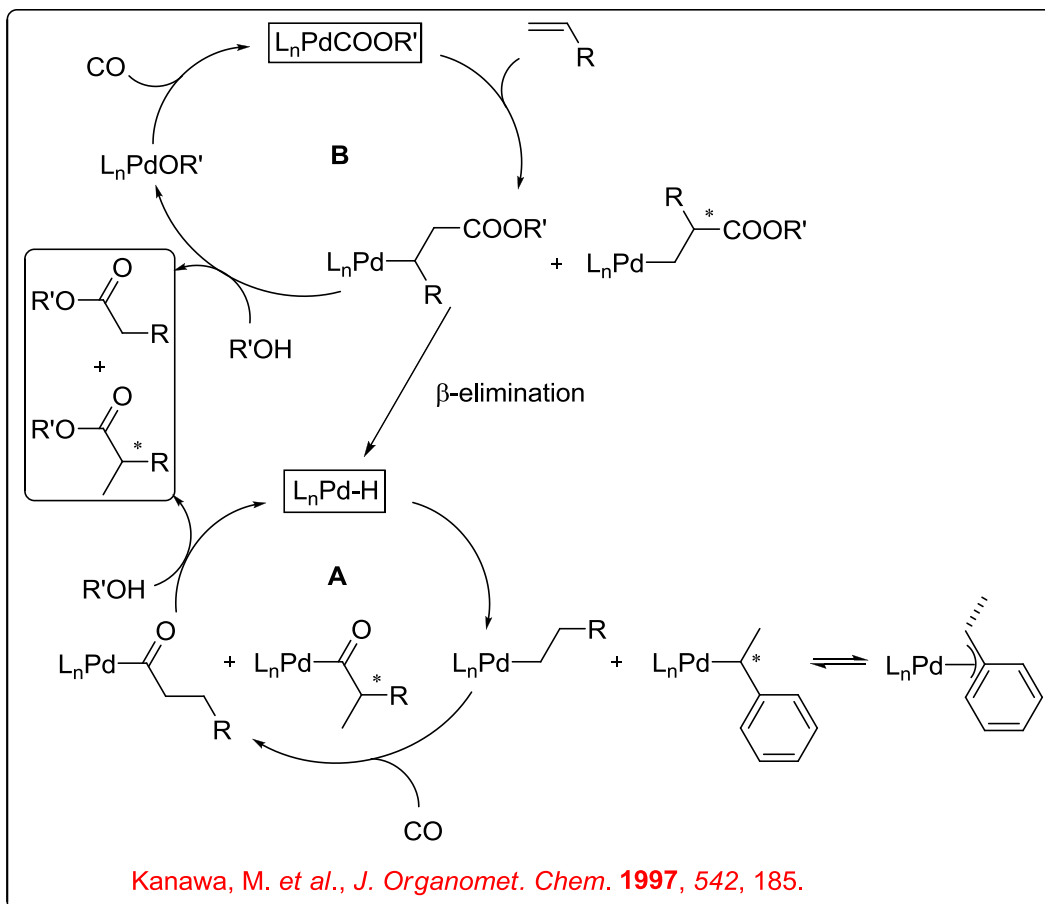


Scheme 1

The coexistence of two catalytic cycles has been suggested for the alkoxy carbonylation reaction (Scheme 2). In the hydrido-palladium complex cycle A, the insertion of the alkene to the Pd-H bond can give alkyl palladium complex that could react with CO via coordination and migratory insertion to yield Pd-acyl complex. Alcoholysis of the Pd-acyl complex can regenerate the Pd-H species and yield the ester. In the alkoxy carbonyl cycle B, the alkene inserts into the palladium-carbon bond of alkoxy carbonyl-palladium complex and the resulting product on alcoholysis gives an alkoxy-palladium complex and the ester. The alkoxy-palladium complex then reacts with CO via coordination and migratory insertion to regenerate the alkoxy carbonyl-palladium complex. The formation of the Pd-H species may also take place from the complexes formed in the catalytic cycle B via  $\beta$ -elimination of an



unsaturated ester after the alkene insertion. In case of vinylarene, the branched alkyl intermediate could be stabilized through the formation of  $\eta^5$ -benzyllic



Scheme 2

In case of asymmetric synthesis, the regioselectivity of these reactions is of critical importance due to the branched products only contain the chiral center. Figure 1 summarizes the some of the diphosphine ligands used for the palladium catalyzed hydroxy- and alkoxyacylation of vinylarenes. Although the enantioselectivity is found to be moderate to good (up to 98%), in most of the methods, the regioselectivity is found to be low.

Bidentate pyridine-phosphine ligands have also been studied for palladium catalyzed asymmetric ethoxycarbonylation of styrene (Figure 2). The regioselectivity of branched products is to be good but the enantioselectivity is found to be low ( $l/b = \text{linear/branched}$ ).

Figure 3 summarizes the selective monodentate ligands studied for the palladium catalyzed asymmetric methoxycarbonylation of vinylarenes. The ligand **18** is found to be effective for the hydroxycarbonylation of 2-vinyl-6-methoxynaphthalene under 1 atm of a mixture of CO and O<sub>2</sub> in the presence of PdCl<sub>2</sub>-CuCl<sub>2</sub> at room temperature affording the target product with 91% ee and 100% regioselectivity.

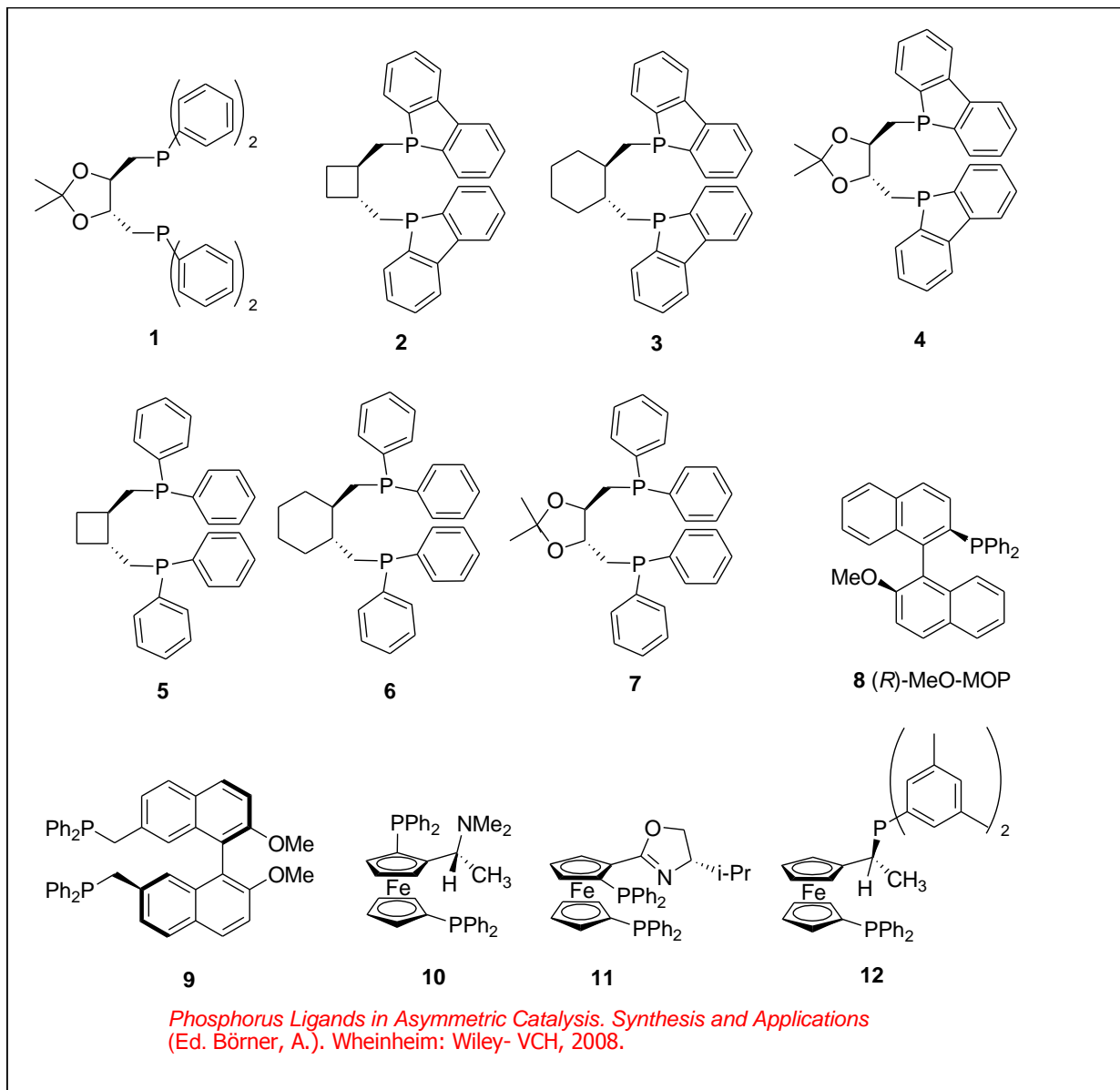


Figure 1. Diphosphine Ligands used in the Asymmetric Hydroxy- and Alkoxy-carbonylation of Vinylarenes.

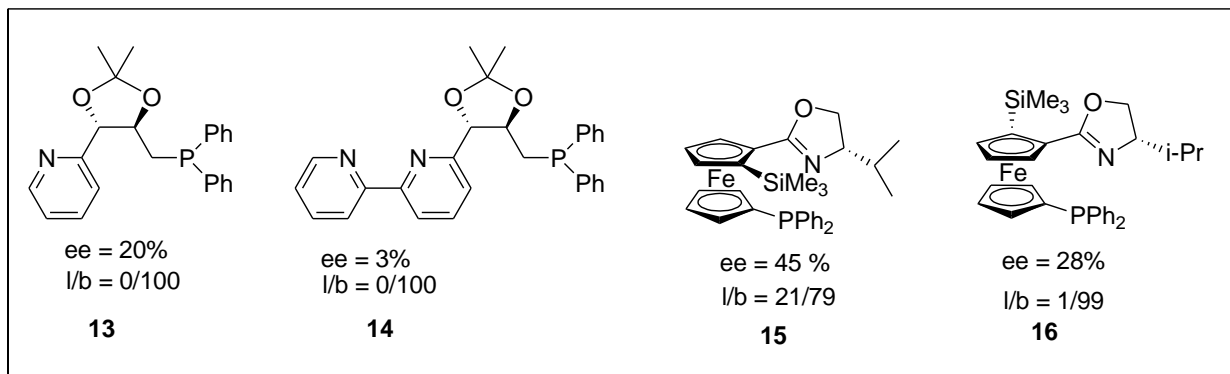


Figure 2. P-N Ligands used for Alkoxycarbonylation Reactions.

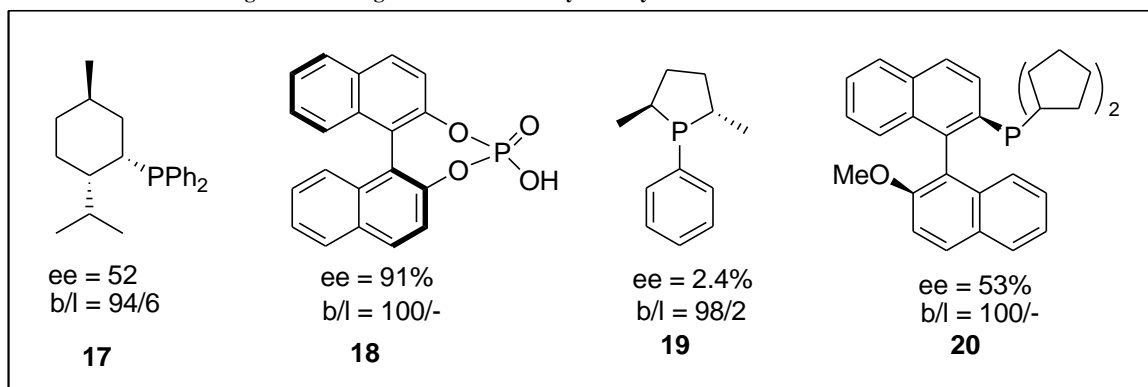
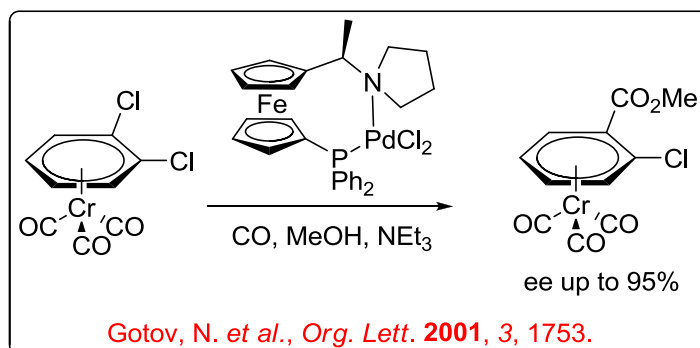


Figure 3. Monodentate Phosphine Ligands used for methoxycarbonylation of vinylarenes.

### 9.2.1 Reaction of Other Substrate

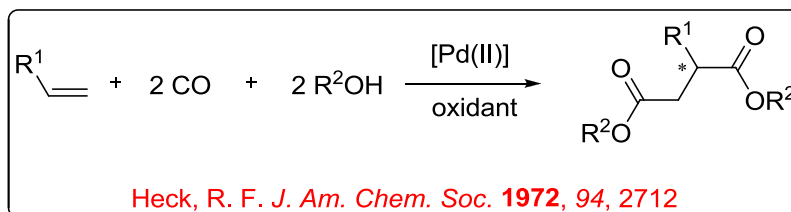
The methoxycarbonylation of 1,2-dichlorobenzene- $\text{Cr}(\text{CO})_3$  has been studied using palladium complex bearing chiral ferrocenyl (*R,S*)-PPF-pyrrolidine system to introduce planar chirality in  $\square$ -complexes (Scheme 3). The reaction provides up to 95% ee in the presence 1 atm of CO at 60 °C in the presence of triethylamine.



Scheme 3

### 9.2.3 Bis-Alkoxy carbonylation of Vinylarenes

Optically active butanedioic acid derivatives are important class compounds that can be used as intermediates for the synthesis of pharmaceuticals and building blocks for the construction of inhibitors. Palladium-catalyzed bis-alkoxy carbonylation of alkenes provides effective methods for the construction of these compounds. In 1970, Heck reported the first example of the



Scheme 4

reaction and its asymmetric version appeared after nearly 20 years. Figure 4 summarizes some of the ligands employed for the bis-alkoxy carbonylation reactions. Chiral bidentate phosphine, P-N and S,N-ligands have been screened and high enantioselectivity (92%) is reported in the bis-methoxycarbonylation of styrene with moderate chemoselectivity (50%) employing **21** as the ligand. In case of propene, 60% ee is observed as the highest enantioselectivity with poor chemoselectivity and conversion (13% and 23%, respectively), while the reaction of 4-methyl-1-pentene afforded good chemoselectivity (79%) but with lower enantioselectivity (14% ee).

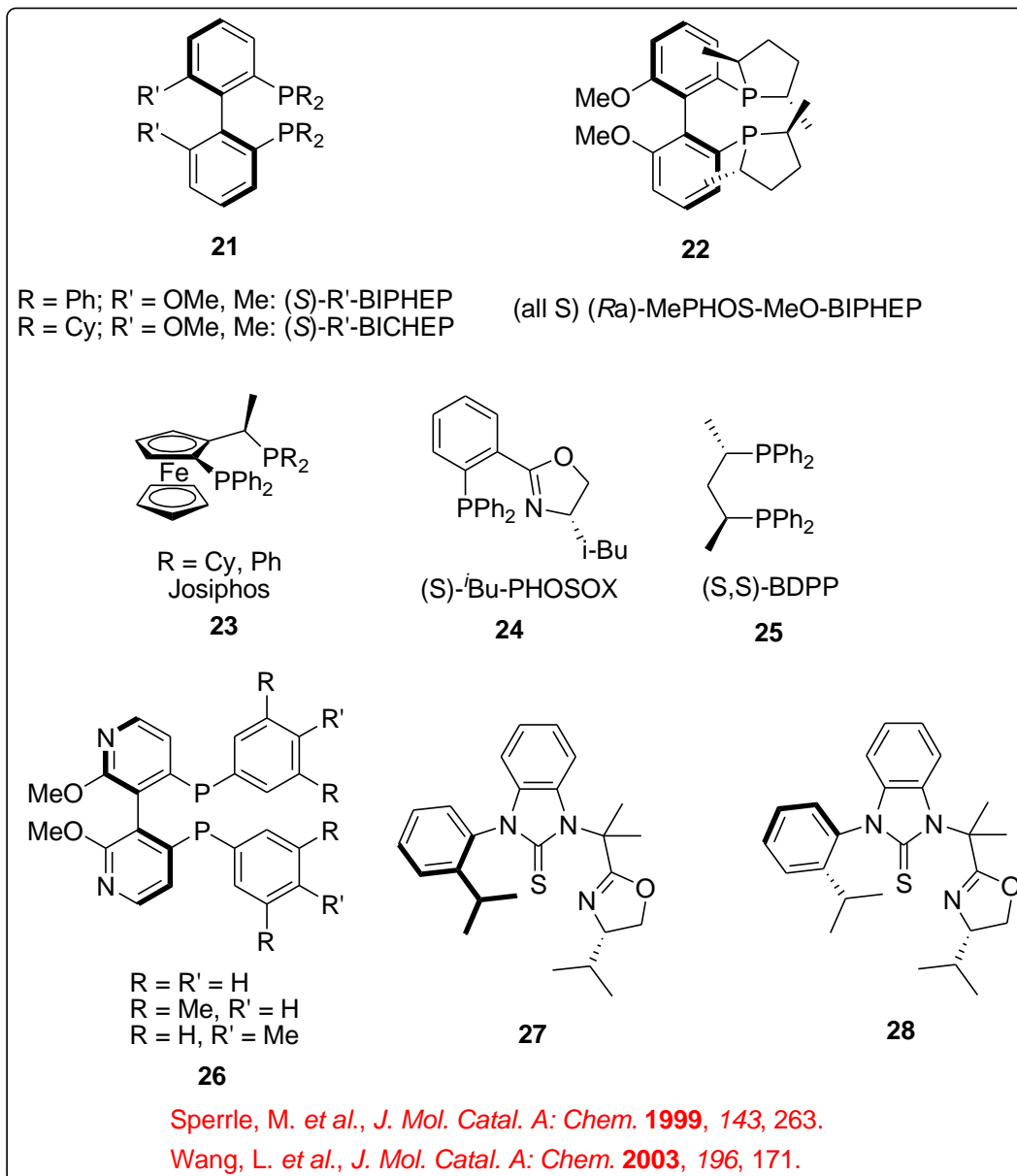


Figure 4. Ligands used in Asymmetric Bis-alkoxycarbonylation of Alkenes.

**Problems**

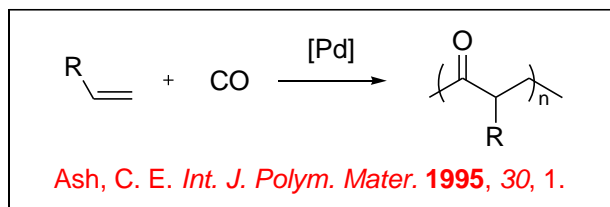
- C. What is the major difference between the Rh-catalyzed hydroformylation and the Pd-catalyzed hydroxy- and alkoxy-carbonylation reactions?
- D. What is the role of benzoquinone in the palladium-catalyzed bis-alkoxy-carbonylation of alkenes?

**Reference**

2. I. Ojima, *Catalytic Asymmetric Synthesis*, 3<sup>rd</sup> ed., Wiley, New Jersey, 2010.

## Lecture 33: Co- and Terpolymerization of Alkenes with Carbon Monoxide

The catalytic copolymerization of alkenes with carbon monoxide to afford polyketones is of the industrial interest (Scheme 1). Polyketones represent low-cost thermoplastics whose synthesis, properties and applications are thus the object of intense fundamental and applied research. The properties of polyketones can be modified by changing the nature or number of monomers, which makes them superior to polyalkenes, polyamides and polyacetals.

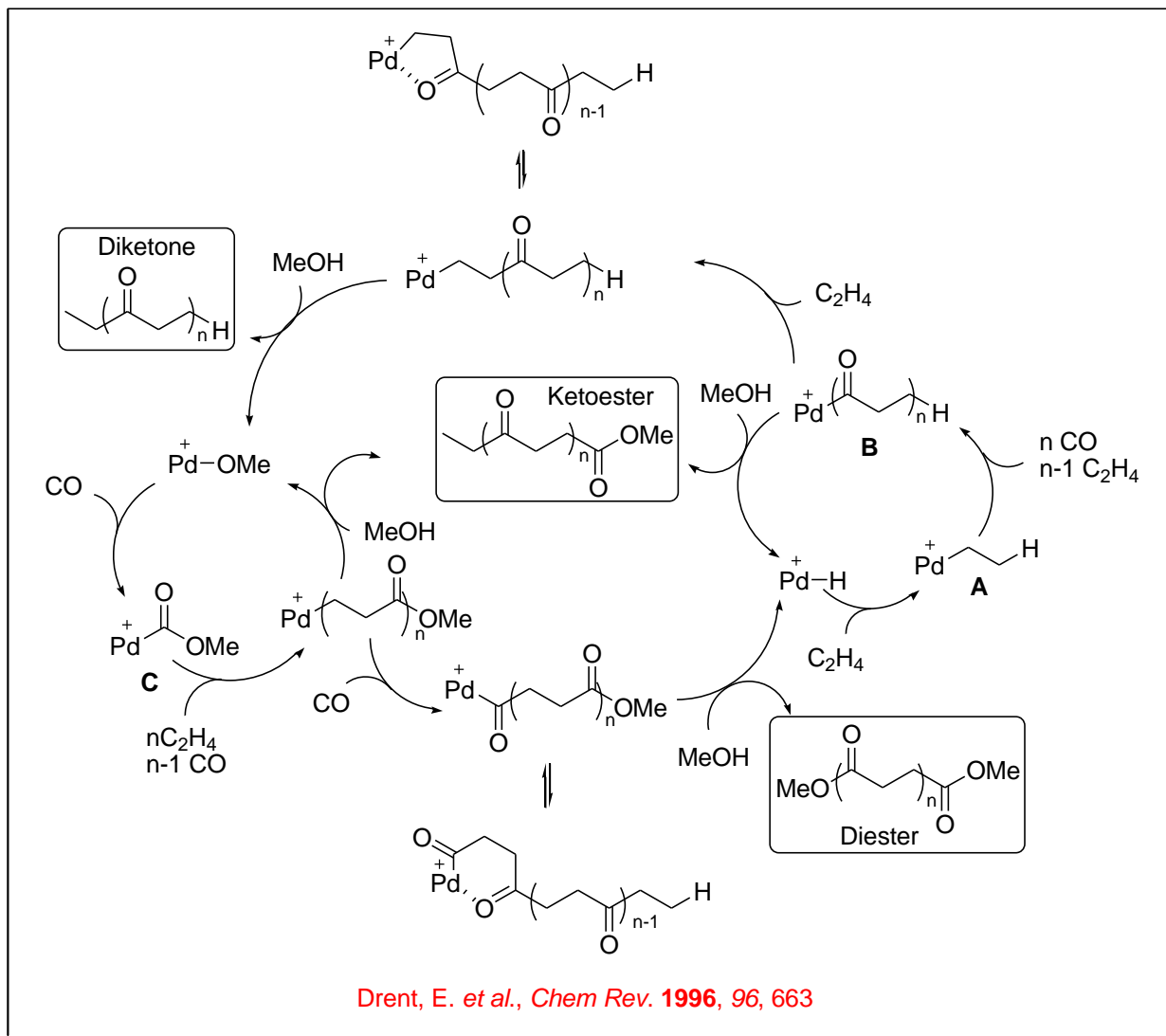


Scheme 1

The reaction involves two competing catalytic cycles (Scheme 2). One of the cycles initiates via a Pd-H species, in which, rapid insertion with ethylene with Pd-H leads to the formation of Pd-alkyl species **A** that reacts with CO to give Pd-acyl complex **B**. The latter irreversibly can insert with second ethylene molecule. Thus, the chain propagation occurs through alternating ethylene and CO insertions. Depending on the termination path, the catalytic cycle gives diketones or ketoesters. For example, methanolysis can lead to the formation of ketoester, while protonolysis can give diketones. While the second catalytic cycle initiates via a Pd-OMe species, in which, CO reacts with the Pd-OMe species to form a Pd-carbomethoxy complex **C**. By this cycle ketoester is also produced along with copolymer diester that is produced via methanolysis of a Pd-acyl complex. Thus, the methanolysis is the main terminating step of the reaction and the ethylene insertion is the rate determining step of the reaction.



With respect to the CO/vinylarene copolymerization, the main features of the catalytic cycle are comparable to that of the CO/ethylene copolymerization. In particular, the chain propagation step is similar, although, the termination and initiation steps will depend on the nature of the alkenes.



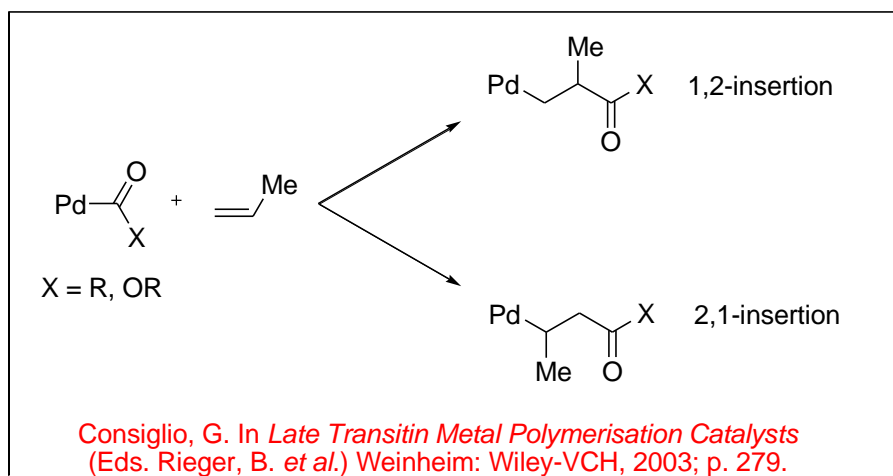
Scheme 2

### 9.3.1 Asymmetric Copolymerization of CO with Aliphatic Alkenes

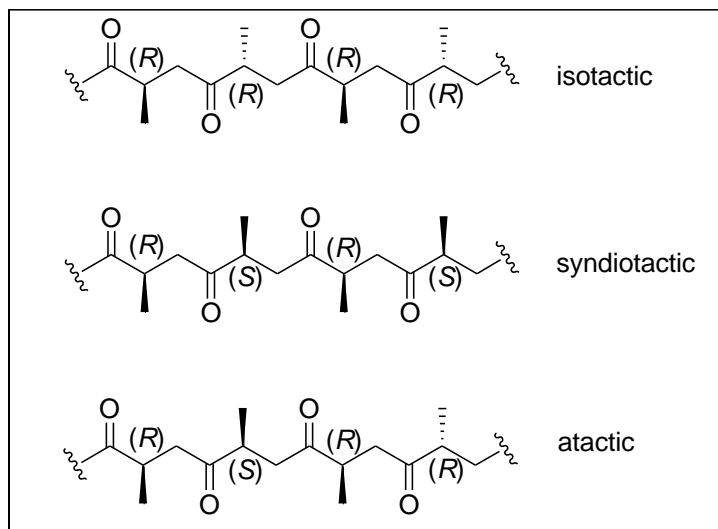
Unlike the reaction with ethylene, the CO/propene copolymerization can afford stereoregular copolymers. The mode of insertion of the propene into the Pd-acyl or Pd-carbomethoxy bond in a 1,2 or 2,1-fashion governs the regiochemistry (Scheme 3). The stereochemistry of the reaction can lead to the formation of isotactic, syndiotactic or atactic structure (Scheme 4).

The best results are obtained utilizing catalyst containing bidentate phosphine ligands. The steric and electronic properties of the ligands control the activity of the catalyst and selectivity of the products. Scheme 5 summarizes some of the active ligands for the CO/propene copolymerization process that provide highly regio- and stereoselective co-polymers.

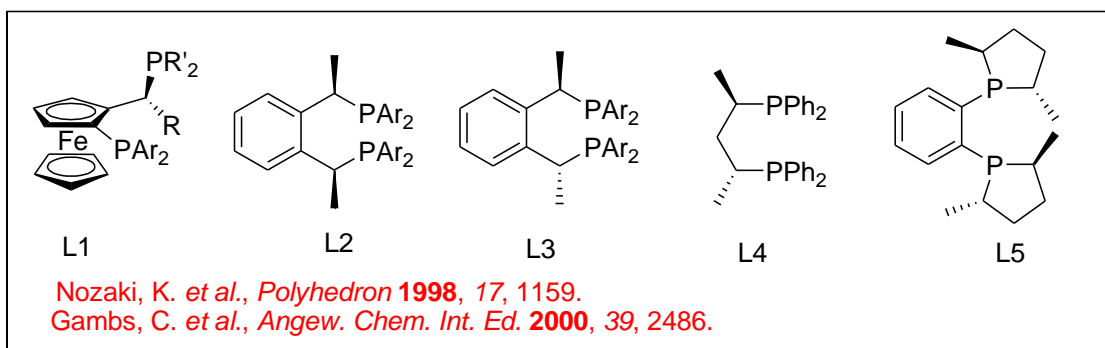
These catalysts are also effective for the copolymerization of CO with higher aliphatic 1-alkenes but slightly lower activity is observed compared to that with the reaction of propene. However, the regio- and stereoselectivities are found to be similar to that of propene reaction.



Scheme 3



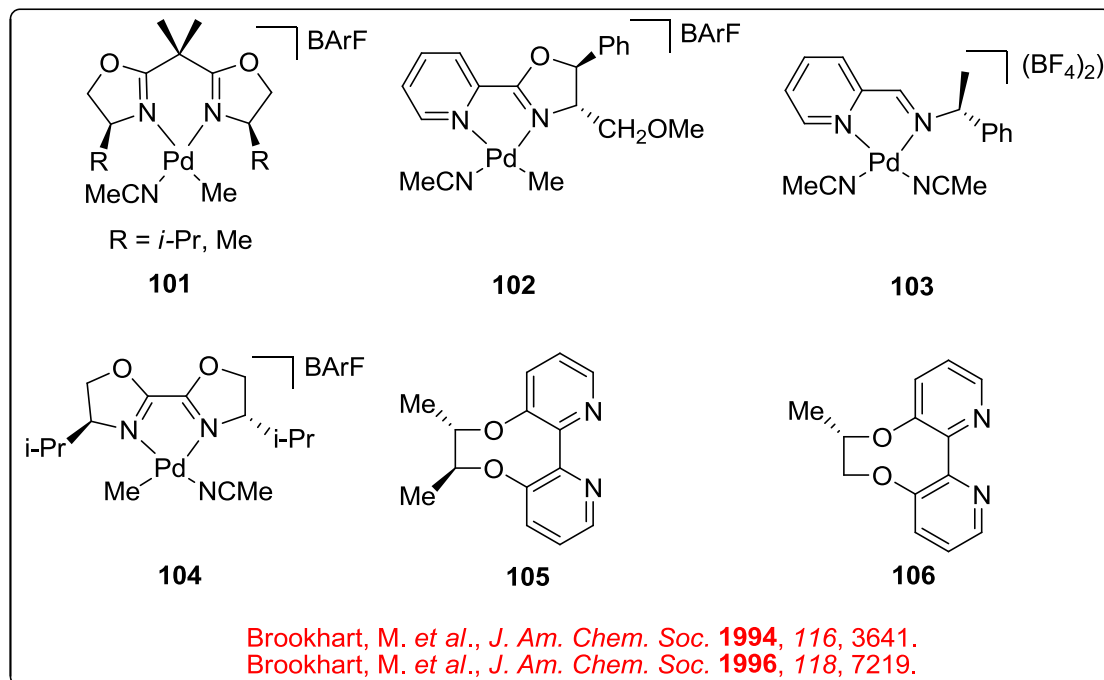
Scheme 4



Scheme 5. Examples of Chiral ligands used in CO/Propene Copolymerization

### 9.3.2 Asymmetric Copolymerization of CO with Vinylarenes

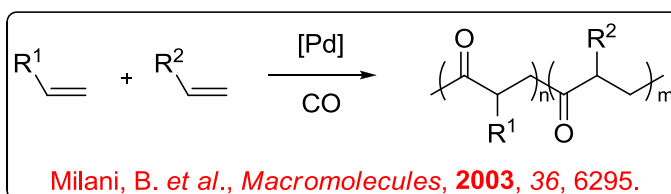
Unlike the CO/propene polymerization process that employs phosphine based ligands, the copolymerization of styrene with CO is generally found to be successful with dinitrogen ligands. Scheme 6 summarizes some of the successful dinitrogen based chiral ligands and chiral Pd-complexes for the CO/styrene copolymerization process.



Scheme 6. Ligands and Catalysts used in Pd-Catalyzed CO/Styrene Copolymerization

### 9.3.3 Asymmetric CO/Alkenes Terpolymerization

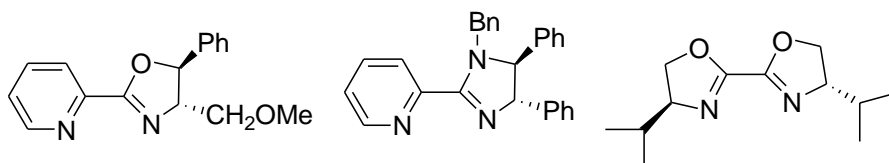
The CO/alkene copolymer is packed in orderly that makes highly crystalline and very fragile. One of the ways to somewhat disturb the orderly crystal packing in the copolymer is the introduction two different kinds of alkenes so that they can have two types of units: CO/alkene<sub>1</sub> and CO/alkene<sub>2</sub> (Scheme 7). Both chiral phosphines and chiral diamine ligands are found to be effective for these reactions.



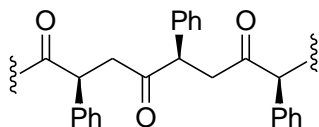
Scheme 7

#### Problems

A. Propose synthetic routes for the preparation of the following chiral ligands.



B. How will you prepare the following syndiotactic copolymer.



#### Reference

I. Ojima, *Catalytic Asymmetric Synthesis*, 3<sup>rd</sup> ed., Wiley, New Jersey, 2010.