

Matthias Beller · Xiao-Feng Wu

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Carbonylative Activation of C-X Bonds

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# Foreword

It is a great pleasure for me to write this foreword for a truly outstanding monograph dealing with transition metal catalyzed carbonylations for the efficient installment of a carbonyl group in a wide variety of organic molecules. The carbonyl group represents simply one of the most versatile functionalities in organic chemistry, and its presence in a large number of biomolecules, including those of many of the major pharmaceuticals and agrochemicals, further supports its high value and importance. Hence, methods for the synthesis of aldehydes, ketones, esters, amides and others, as well as derivatives thereof, are in constant demand.

Although the synthetic organic chemist is armed with an arsenal of synthetic methods for preparing compounds with carbonyl groups in various forms, there is a continued focus and pressure from industry and society to develop cleaner, more benign and more efficient protocols for the installment of this organic functionality. Traditional methods rely on the conversion of pre-existing functionalities to the desired carbonyl derivative, generally by the application of stoichiometric reagents. However, this approach leads to significant purification and waste disposal issues. In contrast, carbon monoxide and transition metal catalysis together represent a perfect combination for introducing carbonyl groups into various different sites in organic substrates. Transition metal catalysis has revolutionized the way synthetic chemists assemble organic molecules, and this diatomic gas is ideal as a C1-building block that is relatively inexpensive and sufficiently reactive even at low temperatures. Carbon monoxide is widely exploited in large-scale applications in industry for the transition metal catalyzed conversion of simple alkenes and alcohols to higher oxygenated and more valuable products. Yet its widespread use in industry for the synthesis of more complex molecules is still limited. Academia plays an important role in this respect for promoting this chemistry, and recent years have witnessed the efforts of organic and organometallic chemists to constantly discover and develop new synthetic protocols at an exceedingly rapid pace.

Matthias Beller and his team at the Leibniz Institute for Catalysis, The University of Rostock, Germany, is one of the most influential research groups dedicated to the development of new and applied transition metal catalyzed carbonylations. Their work has inspired many chemists, including our own research in this field, through the development and mechanistic understanding of new carbonylation

transformations. Hence, who would be more fitting to compile the complete literature in this field? This monograph by Matthias Beller and Xiao-Feng Wu is timely and welcome, and will undoubtedly inspire many chemists to the further development and application of carbonylation chemistry in academia and in industry.

Troels Skrydstrup  
Aarhus University

# Preface

Homogenous catalyst plays an important role in modern organic synthesis, especially now that more focus is being placed the development of sustainable chemistry. With the assistance of catalysis, many organic reactions can be carried out under much milder conditions and in a more selective manner. One branch of homogenous catalysts is carbonylation, which has significant industrial importance and is of academic interest. Several distinguishable advantages of carbonylation reactions are: (1) the carbon chain can be easily increased after the insertion of carbon monoxide; (2) carbonyl-containing compounds are important synthetic intermediates in organic synthesis, which hold imperative applications in advanced materials, dyes, pharmaceuticals, and so on; and (3) carbon monoxide as one of the most important C1 sources can be applied and incorporated into the parent molecules which give more complex compounds. As a result of these advantages, the field of carbonylation research has received much attention during the past decades and this attention is still increasing. When I joined Matthias Beller's group in 2009 and began to work on "Carbonylative Transformation of C–X Bonds," it was difficult for me to find a general textbook on this topic. As a new student with limited knowledge in coupling chemistry, it was even more difficult. Gradually I began to collect the literature on this topic, which was quite a time-consuming process. Even after I had finished my Ph.D. studies in 2012, we still could not find a general textbook available. In this context, and with Matthias's encouragement and support, we began to prepare a book on this topic by ourselves in order to fill the gap and provide a general overview for new researchers who wish to work in this area.

This book is divided into 12 chapters and organized according to the various nucleophiles. In [Chap. 1](#), we give a general introduction and compare and describe the advantages and differences between homogenous and heterogeneous catalysts. We then include a definition of carbonylation and describe mechanisms for different transition metals on carbonylation reactions together with their differences in activities. The following chapters are based on the different properties of nucleophiles applied, chapters are given. Water, alcohols, and amines as nucleophiles are described in [Chap. 2](#), as they go through the same reaction mechanism. [Chapter 3](#) focusses on reductive carbonylation, which give aldehydes as their product. All the reactions that include organometallic reagents as nucleophiles,

where ketones are the main product, are discussed in [Chap. 4](#). In [Chap. 5](#), we discuss the combination of carbon monoxide, alkynes, and organo-halides to give alkyneones as the terminal product, which is the so-called carbonylative Sonogashira reaction. In [Chap. 6](#), we focus on carbonylative C–H activation reactions. Carbonylative Heck reactions partly go through the Heck mechanism and give alkenones as the product; these results are mentioned in [Chap. 7](#). The carbonylative coupling of two different nucleophiles that need additional oxidants is called oxidative carbonylation and we summarize this in [Chap. 8](#). Furthermore, nitro as an interesting functional group can be reduced by CO to ureas, isocyanates, and related compounds. As an important sub-branch in carbonylation reactions, we discuss the reduction of C–NO<sub>2</sub> with CO in [Chap. 9](#). The applications of carbonylation reactions in total synthesis are presented in [Chap. 10](#). The *Taiji* among carbonylation, noncarbonylation, and decarbonylation is the difficulty in developing carbonylation reactions. A successful carbonylation reaction needs to suppress the noncarbonylation pathway and avoid the decarbonylation reaction. We discuss this topic in [Chap. 11](#) within the context of our own understanding. The book ends with our personal outlook on the field in [Chap. 12](#).

We truly hope that this book can help researchers who are new to the field understand and gain an overview of carbonylation. We also hope that it will be a useful general reference book for more senior scientists.

Xiao-Feng Wu



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# Chapter 1

## Introduction

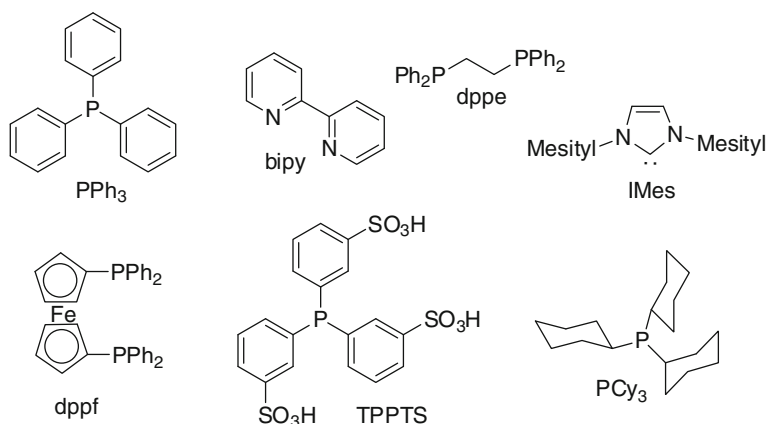
Transition metal catalysts dominate organic synthesis and the fine chemical industry. Specifically, there are numerous procedures in industrial and fine chemical companies that require transition metals as their key catalysts. Traditionally, transition metal catalysts can be divided into the categories of homogeneous catalysts and heterogeneous catalysts. When comparing homogeneous and heterogeneous catalysis, there are common characteristics as well as significant differences. Following is a summarization of the most important of them:

1. Homogeneous catalysts are most often the “pre-catalysts” and are characterized by the fact that the catalyst, starting materials and products stay within the same reaction phase. Homogeneous catalysts are molecularly defined in nature. This fact, combined with the possibility of synthesizing potential intermediates of a given catalytic cycle, allows for an easier understanding of the reaction mechanism. Based on this general mechanistic understanding, a more rational development of improved catalysts is possible.
2. Most often, homogeneous catalysis takes place under much milder reaction conditions compared to heterogeneous catalysis. Typically, reactions are performed between room temperature and 120 °C. Also, the reaction pressure is comparatively low; in general, reactions are run at atmospheric pressure. If gases or low boiling point starting materials are used, reactions are performed between 1 and 60 bar pressure. Nevertheless, high pressure processes are also known. Hence, the conversion of more complicated organic building blocks with different functional groups is preferably done with homogeneous catalysts. On the other hand, the temperature-based stability of heterogeneous catalysts is increased compared to their homogeneous counterparts such as heterogeneous catalysts catalyzed CH-activation processes, which need higher temperatures (>250 °C) in order to take place with significant rate.
3. It is important to note that most reactions using homogeneous catalysts are run in the liquid phase in a batch-wise mode. Especially in academic research laboratories, homogeneous catalysis is attributed to batch reactions using organic solvents. However, in large-scale industrial processes, e.g., carbonylation reactions, oxidations are performed in a continuous mode.

- Due to the advancements in organometallic chemistry and organic ligand synthesis, nowadays a plethora of ligands (P-, N-, and recently C-ligands) is theoretically available (10,000–100,000). These ligands are extremely important in determining the activity, productivity and selectivity of a homogeneous catalyst. In fact, “ligand-tailoring” constitutes an extremely powerful tool to control all kinds of selectivity in a given catalytic reaction and to influence catalyst stability and activity. A selection of important ligands for homogeneous catalysis is shown in Scheme 1.1. Apart from the well-known aryl and alkyl phosphines and amines, carbenes [1, 2] have also recently become more and more important. In addition, mixed ligand systems with two different chelating groups, as well as hemilabile ligands, find increasing interest.
- In asymmetric catalysis [3] the stereoselectivity of a given reaction is induced by a soluble chiral phosphine or amine ligand. Although in general not recognized, there is an interesting analogy of ligands for homogeneous catalysis and supports and modifiers used in heterogeneous catalysis.
- Importantly, the separation of the catalyst is straightforward, done in heterogeneous catalysis via filtration. In homogeneous catalysis, either the distillation of starting materials and products, chromatography, crystallization, or modern techniques of multiphasic catalysis have to be applied.

Due to the specific characteristics of homogeneous and heterogeneous catalysis, the application and use of these systems are most often performed in various chemistry communities. Although noteworthy efforts have been undertaken to bridge this gap, a lot of work still has to be done in order to make full use of the synergism of the two fields.

Remarkably, all industrial carbonylation reactions are done with homogeneous catalysts. Important examples include the production of aliphatic aldehydes and acetic acid. Despite enormous efforts, the leaching of volatile carbonyl clusters and



**Scheme 1.1** Typical ligands for homogeneous catalysis

complexes from heterogeneous catalysts prevent the technical use of this class of compounds. After a general introduction and comparison of homogeneous and heterogeneous catalysts, a definition of carbonylation and their mechanisms will be discussed.

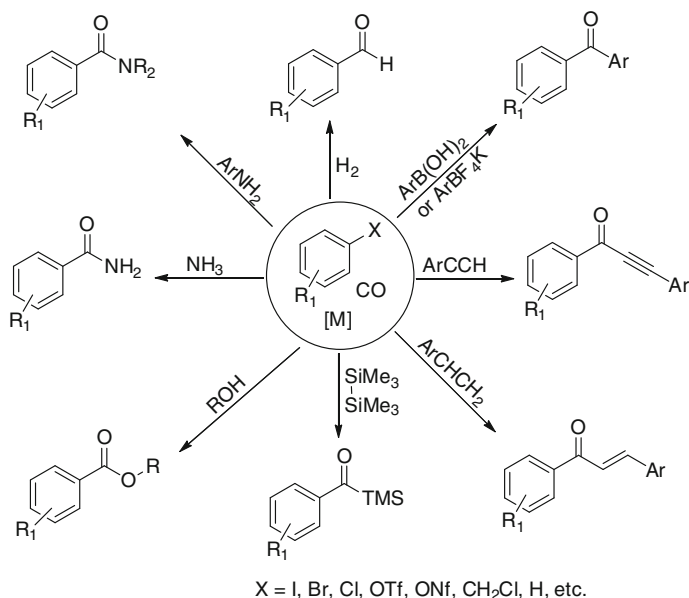
## 1.1 Definition of Carbonylation

The term carbonylation [4–6] is used for a large number of closely related reactions that all have in common the fact that a CO molecule is incorporated into a substrate either by the insertion of CO into an existing bond, e.g., C–X (X=Cl, Br, I), or by the addition of CO to unsaturated compounds, such as alkynes or alkenes in the presence of nucleophiles (NuH). The latter reaction is closely related to the hydroformylation reaction (oxo-synthesis) by which a formyl group and a hydrogen atom are attached to an olefinic double bond. Although hydroformylation is also a carbonylation, it is treated separately due to its industrial importance. The initial work in the field of carbonylations was done by W. Reppe at BASF in the 1930s and 1940s; he also coined the term “carbonylation” [4]. Since then, carbonylation reactions have gained great industrial importance. Today, after hydroformylation, alcohol carbonylation is the most significant industrial branch of carbonylation chemistry.

In Scheme 1.2, all of the types of carbonylations that are discussed in the book are depicted. Alcohols, amines, ethers, carboxylic acids and halides can be converted to acids, amides, esters, ketones, alkynones, alkenones, anhydrides and acid halides with the assistance of transition metal catalysts in the presence of a CO source. The CO sources used can be carbon monoxide gas, Mo(CO)<sub>6</sub>, Co(CO)<sub>6</sub>, formic acid, aldehyde, etc. If the starting material is alcohols or amines, some additives for activation are needed, such as <sup>t</sup>BuONO, TsCl, AcCl. If the substrate is (Hetero)ArH, additional oxidants will be necessary; this is a so-called oxidative carbonylation. If an unsaturated compound is to be carbonylated, a nucleophile NuH that carries an acidic hydrogen has to be present. In the case of insertion reactions, this is not necessary.

## 1.2 Catalysts

In the industrial importance of carbonylation in aliphatic carboxylic acid derivatives production, we are going to take the hydrocarboxylation of alkene as an example to discuss the activity differences of the catalysts. Effective catalysts for the hydrocarboxylation are the transition metals Ni, Co, Fe, Rh, Ru, Pd, Pt, and Ir. Under reaction conditions, the corresponding metal carbonyls or hydridocarbonyls are formed from various catalyst precursors which can be metal salts (halides preferred), complex salts, oxides, or, in some special cases, even fine metal



**Scheme 1.2** Transition metal catalyzed carbonylation reactions of C–X bonds

powders. In the case of metal halides, the nature of the anion plays an important role. The catalytic activity of these co-catalysts increases from chloride over bromide to iodide. Fluorides are inactive. From an industrial point of view, the most important catalysts are Ni and Co; these require extreme conditions, as can be seen in Table 1.1.

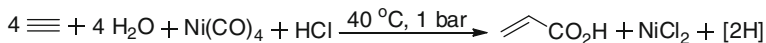
### 1.2.1 Nickel

Nickel can be used in one of three ways when carbonylating alkynes: stoichiometrically, stoichiometric-catalytically, and catalytically. When Ni(CO)<sub>4</sub> is used in stoichiometric amounts, the carbonylation requires only mild reaction conditions, as the former serves both as a CO source and catalyst (Scheme 1.3).

The nickel salt can be recovered and processed, but due to its high cost and the toxicity of Ni(CO)<sub>4</sub> this method has no industrial application. In the stoichiometric-catalytic process, mild conditions can also be applied and smaller amounts of

**Table 1.1** Conditions for hydrocarboxylations with various catalysts

Catalyst	Co <sub>2</sub> (CO) <sub>8</sub>	Ni(CO) <sub>4</sub>	PdX <sub>2</sub> L <sub>2</sub>	PtX <sub>2</sub> L <sub>2</sub> +SnX <sub>2</sub>	RhX <sub>3</sub>
Temperature (°C)	150–200	200–320	70–120	80–100	100–130
Pressure (bar)	130–200	150–300	1–150	1–200	1–100



**Scheme 1.3** Stoichiometric carbonylation of acetylene

$\text{Ni(CO)}_4$  are used, but this process has not found a commercial application either. The catalytic processes are run below 100 bar and above 250 °C. The catalyst precursors are nickel salts such as  $\text{NiBr}_2$ . Nickel catalysts are very suitable for the carbonylation of alkynes, whereas for olefins, Co, Rh, Pd, Pt, and Ru are equally good, if not better. Characteristic of nickel catalysts in the hydrocarboxylation of  $\alpha$ -olefins is that as a main product (60–70 %) the branched carboxylic acid is formed. With internal olefins, branched products are formed exclusively. It has also been shown that carbonylations in the presence of triphenylphosphine can be run under milder conditions than when  $\text{Ni(CO)}_4$  is used alone.

### 1.2.2 Cobalt

The  $\text{Co}_2(\text{CO})_8$  catalyzed hydrocarboxylation of linear  $\alpha$ -olefins usually gives 50–60 % linear carboxylic acids, the total carboxylic acid yield being 80–90 %. Typical conditions are 150–200 °C, 150–250 bar. A special feature of cobalt catalysts is that if internal olefins are used predominantly, the linear products are formed. This effect is very similar to what is observed in Co-catalyzed hydroformylation. In the case of Co catalysts, the addition of hydrogen (5–10 vol %) is beneficial and accelerates the reaction, although one has to be cautious not to hydroformylate the substrate. In the presence of 3–8 mol equiv. pyridine as a ligand, the phenomenon of ligand-accelerated catalysis [7] is observed with higher activity and improved selectivity for the Co-catalyst. The cobalt carbonyl/pyridine catalyst system is applied industrially for the synthesis of higher alkanolic acids, e.g., the hydrocarboxylation of isomers of undecene yields dodecanoic acid with approximately 80 % selectivity. The cobalt catalyst can be recovered upon distilling the products of the reaction.

### 1.2.3 Rhodium

The most widely used catalysts for the carbonylation of alcohols are rhodium or cobalt, the former possessing the advantage that the reaction can ensue under milder conditions. In the Rh catalyzed carbonylation of methanol, the acetic acid selectivity is 99 % at low CO pressure—as low as 1 bar. Several companies have been working on the Rh catalyzed hydrocarboxylation of alkenes,  $\text{RhCl}_3$  or  $\text{Rh(CO)}_2\text{Cl}_2$  often used as a catalyst.

### 1.2.4 Platinum and Palladium

More recently, other catalysts, such as Pd, Pt, Rh, and Ru, have found widespread use due to their better performance under milder conditions [8–11]. Platinum catalysts are superior with regard to regioselectivity, especially with tin compounds as co-catalysts. However, the rates remain quite low even under high pressure. As in hydroformylation, the catalysts may be ligand-modified or not. Co and Ni are usually used in an unmodified manner, whereas ligands are used with Pd and Pt. Complex Pd(II)-compounds of the formula  $L_mPdX_n$  ( $L$  = phosphine, nitril, amine, olefin;  $X$  = anion of an acid;  $m + n = 3$  or  $4$ ) like  $(Ph_3P)_2PdCl_2$  catalyze after the addition of HCl or HBr the reaction of olefins with alcohols at 35–100 °C and 300–700 bar. Due to the mild conditions, substrates such as butadiene and styrene can be converted, which polymerize or isomerize under conditions of the unmodified catalysts Ni and Co. Conversions with water are also possible if the temperature is increased another 50 °C. The regioselectivity of hydroesterification of alkyl acrylates or aromatic olefins catalyzed by  $L_mPdX_n$  can be largely controlled by variation of the ligands. Triphenylphosphine promotes preferential carboxylation to the branched isomer, whereas with bidentate phosphine, the linear product is produced overwhelmingly.

### 1.2.5 Copper

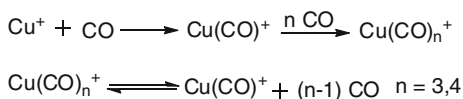
Copper(I) carbonyl catalyzes the hydroesterification of olefins and alcohols under very mild conditions (25 °C, 1 bar) in strong acids [12–15].

The branched products predominate in the reaction product. The reaction is a modified Reppe-Koch conversion. The copper carbonyl ion functions as a CO supplier, transporting the CO from the gas phase to the  $H_2SO_4$  solution (Scheme 1.4).

## 1.3 Reaction Mechanisms

For Ni, Co, and Pd, three possible mechanisms had been envisaged for the carbonylation of unsaturated compounds [16]. In the following, these mechanisms are discussed with olefins as substrates but are also valid for alkynes. The latter are more reactive, therefore giving higher rates and not isomerizing under reaction

**Scheme 1.4** Cu(I)–CO complexes active in Cu(I)-catalyzed carbonylations





conditions. The discussion of the carbonylation mechanisms will conclude with the mechanism of the Rh-catalyzed carbonylation of methanol.

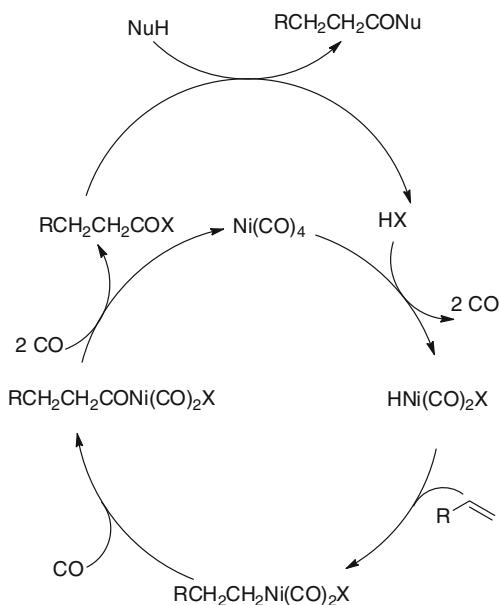
### 1.3.1 Nickel

The mechanism of the Ni catalyzed carbonylation is depicted in Scheme 1.5 [17].  $\text{Ni}(\text{CO})_4$  is formed from various Ni precursors by a reductive reaction with CO. The halide ions are important since they are the source of HX that can be oxidatively added to  $\text{Ni}(\text{CO})_4$ , forming  $\text{HNi}(\text{CO})_2\text{X}$ . The latter reacts with olefin in an *anti*-Markovnikov way, giving the linear alkyl-Ni species. The insertion of CO into the alkyl-Ni bond forms the acyl-Ni complex that decomposes under reductive elimination into the corresponding acid halide and  $\text{Ni}(\text{CO})_4$ . The former reacts with the nucleophile so that the product is set free and HX is regenerated.

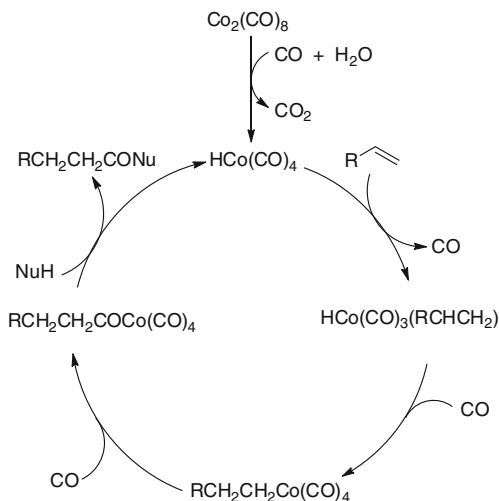
### 1.3.2 Cobalt

It is commonly assumed for cobalt catalyzed carbonylations that  $\text{Co}_2(\text{CO})_8$  reacts with hydrogen or a nucleophile (NuH) with an acidic proton to form the catalytically active species  $\text{HCo}(\text{CO})_4$  [18]. After replacement of one CO ligand by the

**Scheme 1.5** Mechanism of Ni catalyzed carbonylations



**Scheme 1.6** Mechanism of the CO catalyzed carbonylation



olefin, which can occur either by an associative or dissociative mechanism, olefin insertion into the Co–H bond takes place (Scheme 1.6).

The subsequent coordination and insertion of CO into the metal-alkyl bond leads to a liable acyl complex. Finally, hydrolysis of the acyl complex with the nucleophile NuH gives off the corresponding carboxylic acid or carboxylic acid derivative and completes the catalytic cycle. Presumably, the acyl cleavage takes place by a nucleophilic attack on the carbonyl carbon of the acyl group.

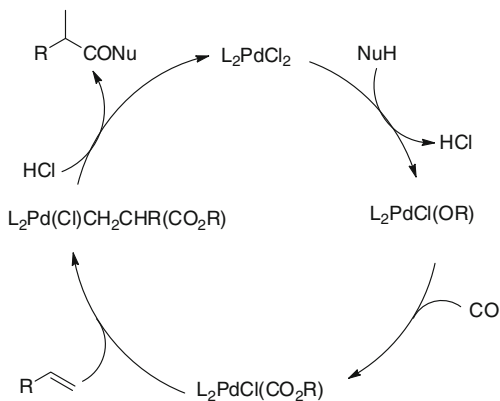
### 1.3.3 Palladium

In the case of Pd-catalyzed carbonylations, there is support for the involvement of  $\text{HPdCl}(\text{PPh}_3)_2$  as the active species under acidic conditions. Evidence for this comes from the isolation of *trans*-Pd-(COPr)Cl( $\text{PPh}_3$ )<sub>2</sub> from propene hydroformylation, [19] while  $\text{Pd}(\text{CO})(\text{PPh}_3)_3$  is inactive as a catalyst in the absence of HCl.

In the case of  $\text{PdX}_2\text{L}_2/\text{SnX}_2$  catalyst systems, olefins seem to be a hydrogen source for the formation of the active Pd–H species. Under neutral or basic conditions, another mechanism involving a carbalkoxy complex may take place (Scheme 1.7) [19]. It is proposed that the reaction of an alcohol with a  $\text{Pd}^{\text{II}}$ -species forms a likely alkoxy complex. The coordination and insertion of CO into to the Pd–O bond gives an alkyl complex that reacts with HX to yield predominantly the branched carboxylic acid as a product.

In the case of a palladium-catalyzed carbonylative activation of C–X bonds, a general reaction mechanism is shown in Scheme 1.8. Normally this type of reaction starts from Pd(0) and is followed by the oxidative additional step and the coordination and insertion of CO to form the acylpalladium complex as the key

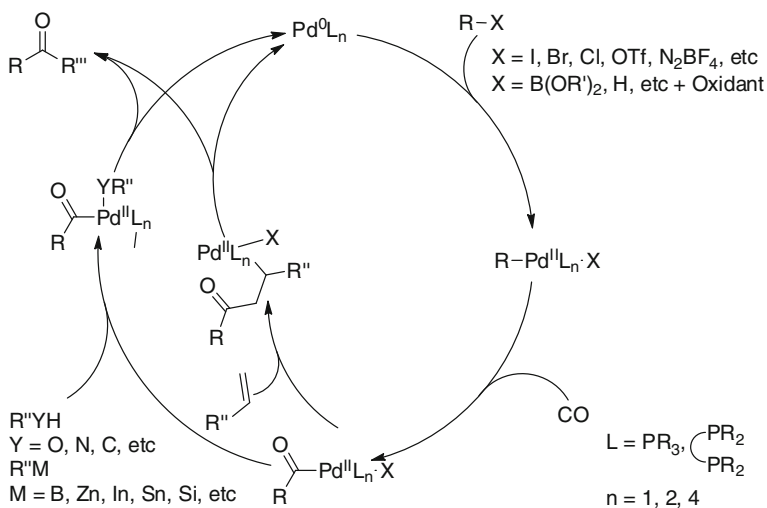
**Scheme 1.7** Mechanism of the Pd-catalyzed carbonylations under neutral or basic conditions



intermediate. Afterwards, either by nucleophilic attack, transmetalation or coordination of alkene, the terminal product can be eliminated after reductive elimination, meanwhile giving Pd(0) for the next catalytic cycle [20].

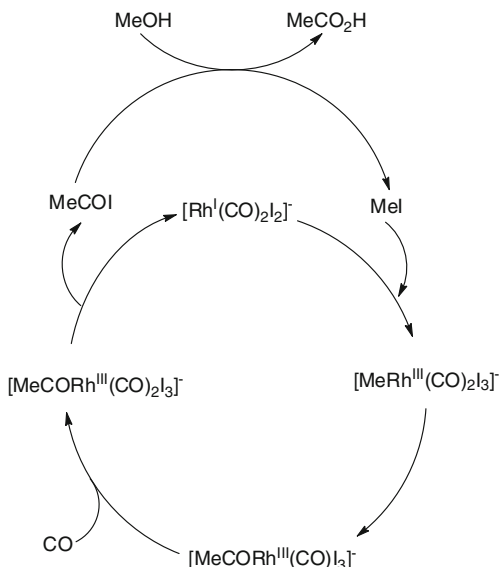
### 1.3.4 Rhodium

Found in the Rh-catalyzed carbonylation of methanol,  $[Rh^I(CO)_2I_2]^-$  is the catalytically active species [21]. It can be easily formed from various Rh compounds. The mechanism of Scheme 1.9 is in agreement with the independence of the



**Scheme 1.8** General mechanism for Pd-catalyzed carbonylative coupling reactions

**Scheme 1.9** Rh-catalyzed carbonylation of methanol



overall reaction rate on the methanol concentration and CO pressure. The reaction of the acyl complex occurs readily at 1 bar CO. The rate-determining step is the oxidative addition of methyl iodide to  $[\text{Rh}^{\text{I}}(\text{CO})_2\text{I}_2]^-$ , explaining the independence of the reaction rate on the CO pressure. After the oxidative addition, CO insertion into the alkyl-Rh bond takes place, giving a quadratic pyramidal complex. CO uptake gives an 18- electron complex that decomposes under the reductive elimination of acetic acid iodide into  $[\text{Rh}^{\text{I}}(\text{CO})_2\text{I}_2]^-$ . In a second half-cycle, the iodide reacts with methanol-producing acetic acid and methyl iodide.

In this chapter, the activities of various transition metal catalysts and their carbonylation reaction mechanisms have been compared and discussed. As mentioned earlier, carbonylation reactions have received impressive attention over the last decades and several procedures have been commercialized. As homogeneous catalysts, the advantages and disadvantages are all obvious, but there is still a need for efforts to combine the advantages of homogeneous and heterogeneous catalysts.

In the following ten chapters we will look at the details of the transitional metal-catalyzed carbonylative activation of C–X bonds. Depending on the nucleophiles used, their reactions' mechanisms are different and have their own term as well. For example, alkoxy carbonylation refers to using alcohols as nucleophiles, aminocarbonylation means using amines as nucleophiles, and so on. Each type of reaction will be discussed separately and end with a personal prediction.

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## Chapter 2

# Hydroxy-, Alkoxy- and Aminocarbonylations of C–X Bonds

As defined in [Chap. 1](#), transition metal catalyzed carbonylative activation of C–X bonds with nucleophiles such as water, alcohols or amines are called hydroxycarbonylation, alkoxy-carbonylation or aminocarbonylation, respectively. From a mechanism point of view, the catalytic cycles for these reactions end with the nucleophilic attack of nucleophiles with an acylpalladium complex and produce carboxylic acids, esters, and amides as their terminal products. As the importance of carboxylic acid derivatives, transition metal catalyzed hydroxyl, alkoxy- and aminocarbonylation reactions are important transformations in organic synthesis. Like the methanol carbonylation, this comprises more than 60 % of the world acetic acid production [1]. Several palladium-catalyzed alkoxy-carbonylations and aminocarbonylations have also been applied on an industrial scale, such as the carbonylation of 1,2-dichloroethane to give isochroman-3-one, aminocarbonylation of 2,5-dichloropyridine to give Lazabemide and so on. In this chapter, the hydroxycarbonylation, alkoxy-carbonylation or aminocarbonylation of C–X bonds will be discussed. The C–X bonds here include  $C_{sp^2}\text{-X}$ ,  $C_{sp^3}\text{-X}$ , and also in situ-generated C–X bonds.

We will begin with the carbonylation of MeI which in situ is generated from MeOH for acetic acid production because of its industrial importance. Acetic acid is an important chemical commodity with a wide range of applications in organic chemistry. In organic synthesis, acetic acid is mainly used as a raw material for vinyl acetate monomers and acetic anhydride synthesis, as well as a solvent for producing terephthalic acid from xylene via the oxidation process. In 1998 the world's capacity of acetic acid production was approximately 7.8 million tons, of which more than 50 % were produced by BP-Amoco and Celanese.

The first commercialized homogeneous methanol carbonylation route to acetic acid was established at BASF in 1955, using a homogeneous Ni catalyst. In 1960 BASF developed an improved process; it used an iodide-promoted CO catalyst and operated at an elevated temperature (230 °C) and pressure (600 bar) [2]. In 1970, Monsanto commercialized an improved homogeneous methanol carbonylation process using a methyl-iodide-promoted Rh catalyst [3–5]. This process operated at much milder conditions (180–220 °C, 30–40 bar) than the BASF process and performed much better [6]. Celanese and Daicel further improved the Monsanto

process during the 1980s by adding a lithium or sodium iodide as a promoter to enable the operation in a reduced water environment that can reduce the by-product formation via the water gas shift reaction, and improving raw materials consumption and reducing downstream separation costs [7, 8]. The general reaction mechanism for the Rh-catalyzed process, shown in Scheme 1.9, with Ni [9, 10] and Ir [11–13] being less expensive homogeneous metal catalysts than Rh; they have also been investigated in the carbonylation of methanol. The Ir-based process, called the Cativa™ process, was commercialized by BP Chemicals in 1996; it allows operating at reactor water levels comparable to those of the improved Celanese process.

Inherent in the homogeneous system, however, are drawbacks relating to catalyst solubility limitations and the loss of expensive Rh metal due to precipitation in the separation sections. Therefore, immobilization of the Rh complex on a support has been the topic of significant research as its heterogeneous catalyst properties. Moreover, Chiyoda and UOP have jointly developed a heterogeneous Rh catalyst system for the methanol carbonylation process to produce acetic acid [14–16].

Rhodium-catalyzed carbonylation of methanol is known as the Monsanto process, which has been studied extensively. From the reaction mechanism aspect, the study of kinetics has proved that the oxidative addition of methyl iodide to the  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  is the rate-determining step of the catalytic cycle. It was also observed that acetyl iodide readily adds to  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$ , indicating that the acetyl iodide must be scavenged by hydrolysis in order to drive the overall catalytic reaction forward. An alternative to sequential reductive elimination and the hydrolysis of acetyl iodide is the nucleophilic attack of water on the Rh acetyl complex and the production of acetic acid. The relative importance of these two alternative pathways has not yet been fully determined, although the catalytic mechanism is normally depicted as proceeding via the reductive elimination of acetyl iodide from the rhodium center. The addition of iodide salts, especially lithium iodide, can realize the reaction run at lower water concentrations; thus, by-product formation via the water gas shift reaction is reduced, subsequently improving raw materials consumption and reducing downstream separation. In addition to the experimental studies of the catalytic mechanism, theoretical studies have also been carried out to understand the reaction mechanism [17–20].

As we described above, the oxidative addition of methyl iodide to the  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  is the rate-determining step. Hence the activity of the Rh center can be improved by using strong electron donating ligands to increase its nucleophilicity, as the group of Cole-Hamilton reported the use of  $\text{PEt}_3$  as ligand for the  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  system [21].  $[\text{RhI}(\text{CO})(\text{PEt}_3)_2]$  showed higher activity for methanol carbonylation at 150 °C than the industry standard,  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$ , in the presence of high concentrations of water.  $[\text{RhI}(\text{CO})(\text{PEt}_3)_2]$  was degraded to  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  during the reaction. The reactivity differences between the  $\text{PEt}_3$  complexes and the anionic complexes were further illustrated by detailed NMR and IR studies, such as the rate of the oxidation addition of MeI to the rhodium(I) center that is increased by a factor of 57 times at 25 °C while the insertion of CO into the Rh–C

band is slowed by a factor of 38 times for the  $\text{PEt}_3$  complexes. The degradation of  $[\text{Rh}(\text{CO})(\text{PEt}_3)_2]$  to  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  proceeds via  $[\text{RhHI}_2(\text{CO})-(\text{PEt}_3)_2]$  and  $[\text{RhI}_3(\text{CO})(\text{PEt}_3)_2]$ , from which the reductive elimination of  $[\text{Et}_3\text{PI}]^+$  leads to  $\text{Et}_3\text{PO}$ . In the presence excessive water,  $[\text{RhI}_3(\text{CO})(\text{PEt}_3)_2]$  formation is suppressed, but  $\text{Et}_3\text{P}$  is lost, albeit much more slowly and at higher temperatures, as  $[\text{Et}_3\text{PX}]^+$  ( $\text{X} = \text{Me}$  or  $\text{H}$ ). The relatively harsh reaction conditions used are responsible for the phosphine ligand dissociation and degradation.

Wegman and colleagues reported the carbonylation of methanol at  $80^\circ\text{C}$  and 34.5 bar of  $\text{CO}$  with *cis*- $\text{RhCl}(\text{CO})_2\text{Ph}_2\text{P}(\text{CH}_2)_2\text{P}(\text{O})\text{Ph}_2$  **A** as the catalyst [22]. Based on a mechanistic study, the ligand exhibited a hemi-labile behavior, as the  $\text{P}(\text{O})\text{-Rh}$  coordination is weak and can be easily replaced by  $\text{CO}$ . This behavior was found to be more reluctant, if replacing  $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{P}(\text{O})\text{Ph}_2$  (**A**) with  $\text{Ph}_2\text{PCH}_2\text{P}(\text{O})\text{Ph}_2$  which produced a more stable five-member ring, while Baker's group found that with  $\text{Ph}_2\text{PCH}_2\text{P}(\text{S})\text{Ph}_2$  (**B**) as a ligand produced a reactivity 8 times higher than  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  under the classic Monsanto conditions [23]. Notably, neither  $\text{Ph}_2\text{PCH}_2\text{P}(\text{O})\text{Ph}_2$  nor  $\text{Ph}_2\text{PN}(\text{Ph})\text{P}(\text{S})\text{Ph}_2$  have been shown to be particularly effective under the same conditions. In contrast to the  $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{P}(\text{O})\text{Ph}_2$  system, no evidence for hemi-labile behavior was found for the  $\text{Ph}_2\text{PCH}_2\text{P}(\text{S})\text{Ph}_2$  ligand. A detailed study on these ligands was carried out by Haynes and colleagues [24, 25] they found that the electronic and steric effects of ligands can combine to produce rather surprising and dramatic effects on the rates of key steps in catalytic cycles. The effects of two successive steps (oxidative addition and migratory insertion steps) on the carbonylation process were quantified and understood by combining kinetic and crystallographic studies. Surprisingly, both oxidative addition and migratory insertion steps can be promoted by the  $\text{Ph}_2\text{PCH}_2\text{P}(\text{S})\text{Ph}_2$  ligand. The strong electron donation, which accelerates oxidative additions, would normally be expected to inhibit  $\text{CO}$  insertion, but this is overcome by a steric effect of the  $\text{Ph}_2\text{PCH}_2\text{P}(\text{S})\text{Ph}_2$  ligand. Dilworth and colleagues show that phosphine-thiolate and -thioether ligands ( $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{SMe}$ ,  $\text{Ph}_2\text{PC}_6\text{H}_4\text{-2-SMe}$ ,  $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{SH}$ ,  $\text{Ph}_2\text{PC}_6\text{H}_4\text{-2-SH}$ ) also displayed improved catalytic activity (4 times higher) compared with  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  [26] (Scheme 2.1).

Dutta's group reported using  $\text{PPh}_2(\text{C}_6\text{H}_4\text{-2-CO}_2\text{Me})$  (**C**) as a ligand for the carbonylation of methanol [27]. The prepared complexes with one ligand and two ligands were tested as catalysts for methanol carbonylation (at  $135^\circ\text{C}$ ); both

**Scheme 2.1** Ligands for Rh-catalyzed methanol carbonylation

