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Transition Metal Catalyzed Carbonylation Reactions

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 alkynones 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_2 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

Contents

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.

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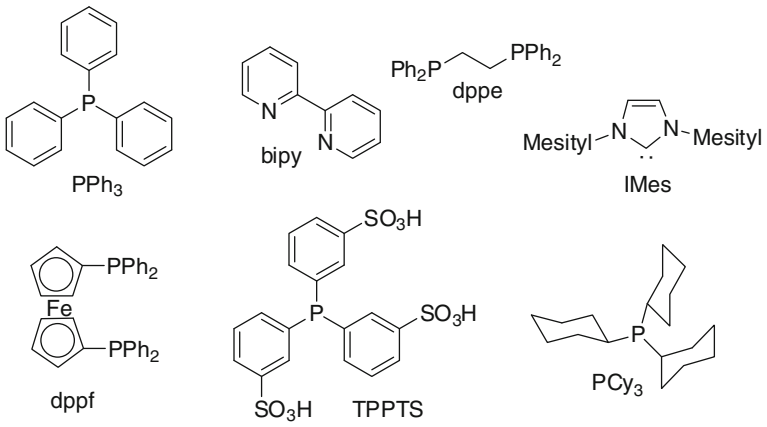
4. Due to the advancements in organometallic chemistry and organic ligand synthesis, nowadays a plethora of ligands [P-, N-, and recently C-ligands) is theoretically available (10,000–100,000). These ligands are extremely important in determining the activity, productivity and selectivity of a homogeneous 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.
5. 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.
6. 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.

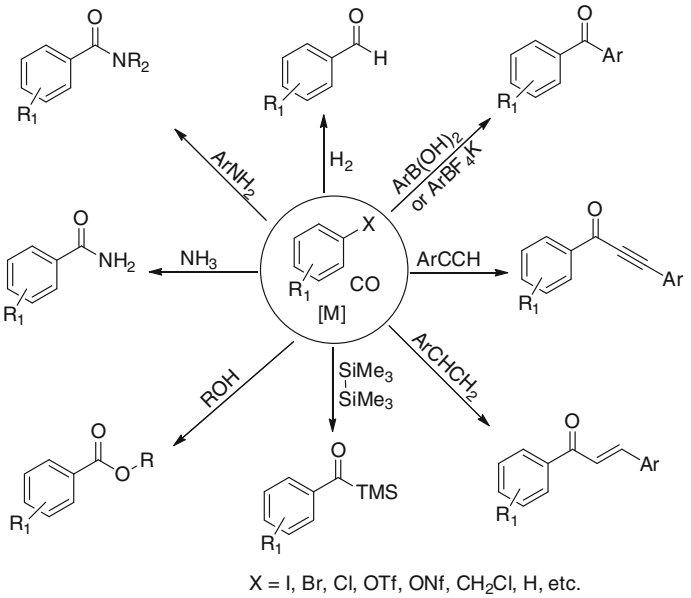
1.1 Definition of Carbonylation

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, $Mo(CO)_6$, $Co(CO)_6$, formic acid, aldehyde, etc. If the starting material is alcohols or amines, some additives for activation are needed, such as ^{t}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 hydrocarbonxylation 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.

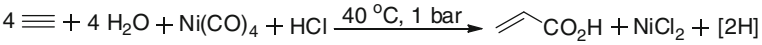
1.2.1 Nickel

Nickel can be used in one of three ways when carbonylating alkynes: stoichiometrically, stoichiometric-catalytically, and catalytically. When $Ni(CO)_4$ 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 $Ni(CO)_4$ 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	$Co_2(CO)_8$	$Ni(CO)_4$	PdX_2L_2	PtX_2L_2+SnX_2	RhX_3
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

$Ni(CO)_4$ 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 $NiBr_2$. 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 α-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 $Ni(CO)_4$ is used alone.

1.2.2 Cobalt

The $Co_2(CO)_8$ catalyzed hydrocarboxylation of linear α-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 alkanoic 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, $RhCl_3$ or $Rh(CO)_2Cl_2$ 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.

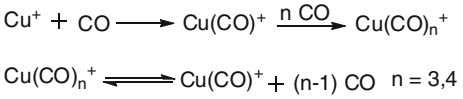
1.2.5 Copper

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

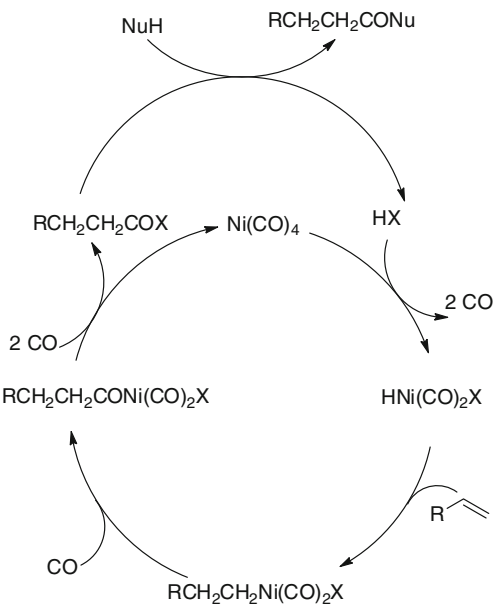
conditions. The discussion of the carbonylation mechanisms will conclude with the mechanism of the Rh-catalyzed carbonylation of methanol.

1.3.1 Nickel

The mechanism of the Ni catalyzed carbonylation is depicted in Scheme 1.5 [17]. $Ni(CO)_4$ 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 $Ni(CO)_4$, forming $HNi(CO_2)X$. 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 $Ni(CO)_4$. The former reacts with the nucleophile so that the product is set free and HX is regenerated.

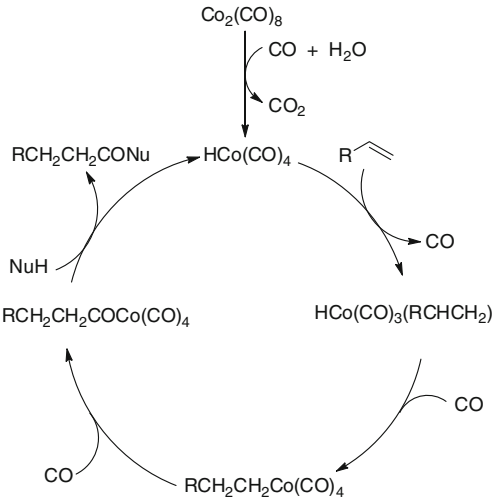
1.3.2 Cobalt

It is commonly assumed for cobalt catalyzed carbonylations that $Co_2(CO)_8$ reacts with hydrogen or a nucleophile (NuH) with an acidic proton to form the catalytically active species $HCo(CO)_4$ [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).

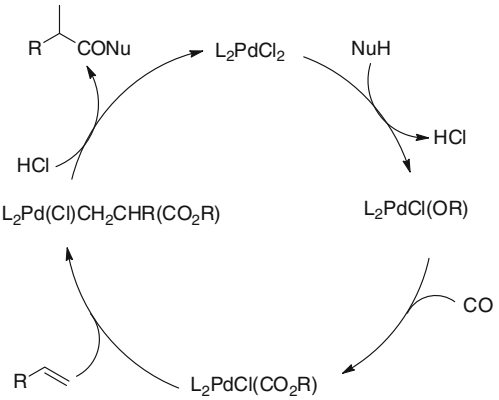
The subsequent coordination and insertion of CO into the metal-alkyl bond leads to a liable acyl complex. Finally, hydrolysis of the acyl complex with the nucleophile NuH gives off the corresponding carboxylic acid or carboxylic acid derivative and completes the catalytic cycle. Presumably, the acyl 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 $HPdCl(PPh_3)_2$ as the active species under acidic conditions. Evidence for this comes from the isolation of *trans*-Pd-(COPr)$Cl(PPh_3)_2$ from propene hydroformylation, [19] while $Pd(CO)(PPh_3)_3$ is inactive as a catalyst in the absence of HCl.

In the case of PdX_2L_2/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 Pd^{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

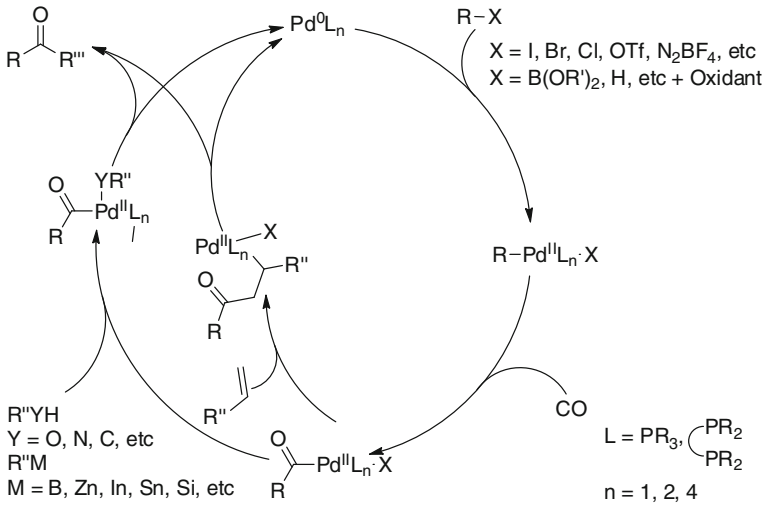


Scheme 1.7 Mechanism of the Pd-catalyzed carbonylations under neutral or basic conditions

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].

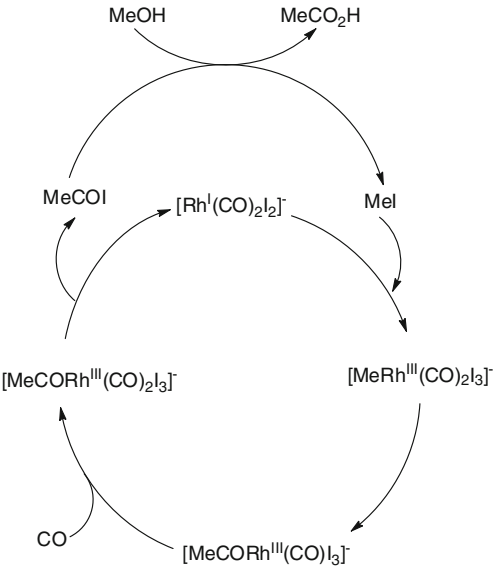
1.3.4 Rhodium

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 carbonyaltive 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 $[Rh^{I}(CO)_2I_2]^-$, 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 $[Rh^{I}(CO)_2I_2]^-$. 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, alkoxycarbonylation 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.

References

1. Herrmann, W.A.: N-Heterocyclic Carbenes: A new concept in organometallic catalysis. Angew. Chem. Int. Ed. **41**, 1290 (2002)
2. Hillier, A.C., Nolan, S.P.: Palladium/nucleophilic carbene catalysts for cross-coupling reactions.Plat. Met. Rev. **46**, 50 (2002)
3. Jacobsen, E.N., Pfaltz, A., Yamamoto, H. (eds.): Comprehensive asymmetric catalysis. Springer, Berlin (1999)
4. Falbe, J.: New syntheses with carbon monoxide, p. 243. Springer, Berlin (1980)
5. Beller, M., Tafesh, A. In: Cornils, B., Herrmann, W.A. (eds.) Wiley-VCH (eds.) Applied homogeneous catalysis with organometallic compounds. Chapter 2, p. 187. Wiley-VCH, Weinheim (1996)
6. Bertleff, W.: Ullmann′s encyclopedia of industrial chemistry, vol. A5, 5th edn, p. 217. VCH, Weinheim (1986)
7. Berrisford, D.J., Bolm, C., Sharpless, K.B.: Ligand-accelerated catalysis. Angew. Chem. Int. Ed. Engl. **34**, 1059 (1995)
8. Beller, M., Cornils, B., Frohning, C.D., Kohlpaintner, C.W.: Progress in hydroformylation and carbonylation. J. Mol. Catal. **104**, 17 (1995)
9. Colquhoun, H.M., Thompson, D.J., Twigg, M.V.: Carbonylation, direct synthesis of carbonyl compounds. Plenum Press, New York (1991)
10. Heck, R.F.: Palladium reagents in organic syntheses. Academic Press, New York (1985)
11. Röper, M.: CO activation by homogeneous catalysts.Stud. Surf. Sci. Catal. **64**, 381 (1991)
12. Souma, Y., Sano, H.: Carbonylation of alcohols, olefins, and saturated hydrocarbons by CO in the Ag(I)–H_2SO_4 system. Bull. Chem. Soc. Japan **47**, 1717 (1974)
13. Yoneda, N., Fukuhara, T.: Carboxylation reaction of diisobutene and 1-octene with carbon monoxide using a copper(I) carbonyl BF3-H_2O catalyst system. Chem. Lett. **3**, 607 (1974)
14. Souma, Y.: Carbonylation of dienes and diols in the presence of copper(I) carbonyl catalysts. Bull. Chem. Soc. Japan **49**, 3291 (1976)
15. Souma, Y., Sano, H.: Carbonylation of saturated hydrocarbons catalyzed by copper(I) carbonyl. J. Org. Chem. **38**, 3633 (1973)
16. Milstein, D.: Aspects of intermediacy of carbalkoxymetal complexes in carbon monoxide reactions. Acc. Chem. Res. **21**, 428 (1988)
17. Heck, R.F.: The Mechanism of the Allyl Halide Carboxylation Reaction Catalyzed by Nickel Carbonyl. J. Am. Chem. Soc. **85**, 2013 (1963)
18. Falbe, J.: New syntheses with carbon monoxide, p. 1. Springer, Berlin (1980)
19. Bardi, R., del Pra, A., Piazzesi, A.M., Toniolo, L.: Metals in organic syntheses. III. Highly regioselective propene hydrocarboxylation promoted by a PdCl2(PPh3)2–PPh3 catalyst precursor: trans-Pd(COPr-n)Cl(PPh3)2 as an active catalytic species. Inorg. Chim. Acta **35**, L345 (1979)
20. Wu, X.-F., Neumann, H., Beller, M.: Palladium-catalyzed carbonylative coupling reactions between Ar–X and carbon nucleophiles. Chem. Soc. Rev. **40**, 4986 (2011)
21. Forster, D.: On the mechanism of a rhodium-complex-catalyzed carbonylation of methanol to acetic acid. J. Am. Chem. Soc. **98**, 846 (1976)

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 hydroxycarbonyaltion, alkoxycarbonylation or aminocarbonylation, respectively. From a mechanism point of few, 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 alkoxycarbonylations and aminocarbonyaltions have also been applied on an industrial scale, such as the carbonylation of 1,2-xylyldichloride to give isochroman-3-one, aminocarbonylation of 2,5-dichloropyridine to give Lazabemide and so on. In this chapter, the hydroxycarbonyaltion, alkoxycarbonylation or aminocarbonylation of C–X bonds will be discussed. The C–X bonds here include C_{sp2}-X, C_{sp3}-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

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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^{TM} 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 $[Rh(CO)_2I_2]^-$ is the rate-determining step of the catalytic cycle. It was also observed that acetyl iodide readily adds to $[Rh(CO)_2I_2]^-$, 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].

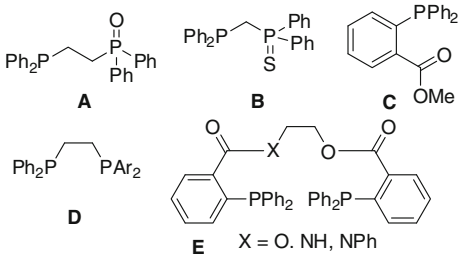
As we described above, the oxidative addition of methyl iodide to the $[Rh(CO)_2I_2]^-$ is the rate-determining step. Hence the activity of the Rh center can be improved by using strong electron donating ligands to increase its nucleophilicity, as the group of Cole-Hamilton reported the use of PEt_3 as ligand for the $[Rh(CO)_2I_2]^-$ system [21]. $[RhI(CO)(PEt_3)_2]$ showed higher activity for methanol carbonylation at 150 °C than the industry standard, $[Rh(CO)_2I_2]^-$, in the presence of high concentrations of water. $[RhI(CO)(PEt_3)_2]$ was degraded to $[Rh(CO)_2I_2]^-$ during the reaction. The reactivity differences between the 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 PEt_3 complexes. The degradation of $[RhI(CO)(PEt_3)_2]$ to $[Rh(CO)_2I_2]^-$ proceeds via $[RhHI_2(CO)–(PEt_3)_2]$ and $[RhI_3(CO)(PEt_3)_2]$, from which the reductive elimination of $[Et_3PI]^+$ leads to Et_3PO. In the presence excessive water, $[RhI_3(CO)(PEt_3)_2]$ formation is suppressed, but Et_3P is lost, albeit much more slowly and at higher temperatures, as $[Et_3PX]^+$ (X = Me or 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 °C and 34.5 bar of CO with *cis*-$RhCl(CO)_2Ph_2P(CH_2)_2P(O)Ph_2$ **A** as the catalyst [22]. Based on a mechanistic study, the ligand exhibited a hemi-labile behavior, as the P(O)-Rh coordination is weak and can be easily replaced by CO. This behavior was found to be more reluctant, if replacing $Ph_2P(CH_2)_2P(O)Ph_2$(A) with $Ph_2PCH_2P(O)Ph_2$ which produced a more stable five-member ring, while Baker's group found that with $Ph_2PCH_2P(S)Ph_2$ (B) as a ligand produced a reactivity 8 times higher than $[Rh(CO)_2I_2]^-$ under the classic Monsanto conditions [23]. Notably, neither $Ph_2PCH_2P(O)Ph_2$ nor $Ph_2PN(Ph)P(S)Ph_2$ have been shown to be particularly effective under the same conditions. In contrast to the $Ph_2P(CH_2)_2P(O)Ph_2$ system, no evidence for hemi-labile behavior was found for the $Ph_2PCH_2P(S)Ph_2$ 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 $Ph_2PCH_2P(S)Ph_2$ ligand. The strong electron donation, which accelerates oxidative additions, would normally be expected to inhibit CO insertion, but this is overcome by a steric effect of the $Ph_2PCH_2P(S)Ph_2$ ligand. Dilworth and colleagues show that phosphine-tholate and -thioether ligands ($Ph_2PCH_2CH_2SMe$, $Ph_2PC_6H_4$-2-SMe, $Ph_2PCH_2CH_2SH$, $Ph_2PC_6H_4$-2-SH) also displayed improved catalytic activity (4 times higher) compared with $[Rh(CO)_2I_2]^-$ [26] (Scheme 2.1).

Dutta's group reported using $PPh_2(C_6H_4$-2-$CO_2Me)$ (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 °C); both

Scheme 2.1 Ligands for Rh-catalyzed methanol carbonylation



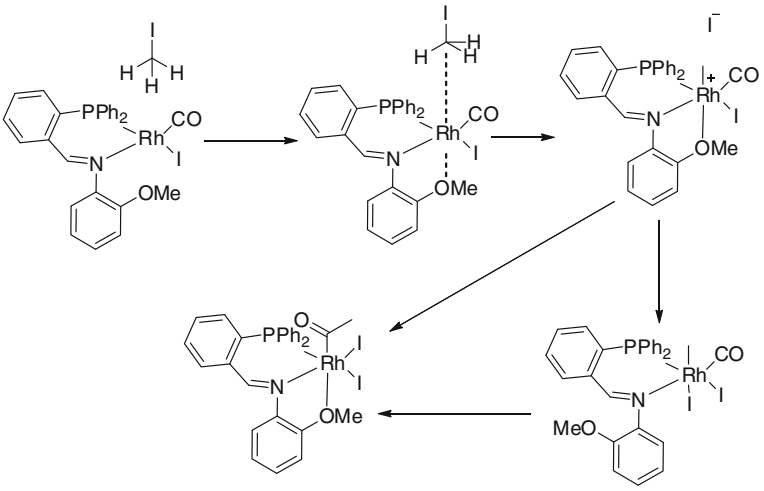
complexes were more active than the PPh_3 analogue and the non-phosphine promoted $[Rh(CO)_2I_2]^-$ system.

Pringle and colleagues tested a series of asymmetrical fluorinated diphosphine ligands, $Ph_2PCH_2CH_2PAr$ (D), for rhodium-catalyzed methanol carbonylation [28]. These ligands were designed to mimic the asymmetrical coordination characteristics of heterofunctional bidentate ligands such as (A) and (B) discussed above. The asymmetrical ligands produced catalysts with high selectivity to acetic acid and higher activity compared with a catalyst based on the symmetrical dppe ligand. However, the industrial $[Rh(CO)_2I_2]^-$ system produced better activity than all the catalysts tested here. In situ HPIR spectroscopy showed the absence of bands due to $[Rh(CO)_2I_2]^-$ and it was inferred that the diphosphine ligand remains coordinated with Rh during catalysis.

Süss-Fink and colleagues prepared some chelating ligands by the reaction of 2-diphenyl-phosphinobenzoic acid with appropriate diols or amino alcohols (E) and tested in the carbonylation of methanol [29, 30]. All the ligands produced enhanced activity compared with $[Rh(CO)_2I_2]^-$ under the classical conditions.

Haynes, Gonsalvi and their colleagues prepared and characterized a series of rhodium iodo carbonyl complexes containing bidentate iminophosphine ligands [31]. The steric and electronic properties of the *N*-aryl substituent of the iminophosphine determined the reactivity of these complexes toward MeI. Most importantly, the presence of an *o*-methoxy group can promote both oxidative addition and migratory CO insertion steps, which might be explained by the effect arising from an intramolecular interaction between the methoxy oxygen and the Rh center. Such an interaction can enhance the nucleophilicity of the Rh(I) reactant (by stabilization of the SN_2 transition state) as well as providing a driving force for migratory CO insertion. A direct evidence for an Rh-O interaction was provided by the X-ray crystal structure of the acetyl product. Migratory CO insertion can also be promoted by bulky ligands (as found in related systems), but there is an unexpected steric effect on MeI oxidative additions. The moderate acceleration of an MeI addition by more bulky ligands may arise from the hemilability of the iminophosphine (Scheme 2.2).

Recently, several publications on the mechanistic study of carbonylation of MeI with various ligands were published [32–37]. Rankin et al. have shown that the catalyst prepared in situ from 1,2-$(t Bu_2PCH_2)_2C_6H_4$ (DTBPMP) and $[RhCl(CO)_2]_2$ gave better results on the carbonylation of methanol compared with the Monsanto catalyst, at both 150 and 180 °C [32]. Detailed HPIR and HPNMR studies show, however, that the active species is not stable under the reaction conditions decomposing to the monoanion $[Rh(CO)_2I_2]^-$(Monsanto catalyst), which is a less efficient catalyst, and the quaternary phosphonium cation, $[(Me^tBu_2PCH_2)_2C_6H_4]^+_2$. The promoting effect from inorganic iodides may be responsible for the higher rate observed in the presence of DTBPMB at 180 °C. And decreasing the water concentration from 17 to 3 %w/w led to an extremely slow reaction. Clarke and colleagues systemically studied the properties of bidentate phosphines with Rh(I) in the carbonylation of methanol (Scheme 2.3) [33, 34]. They concluded that DPPX and BINAP are more efficient in all the tested C_4-diphosphines, and the



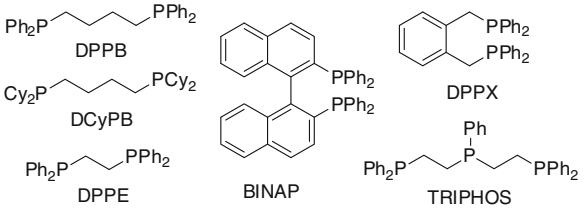
Scheme 2.2 Rh-iminophosphine catalyzed carbonylation of MeI

stability of Rh-acetyl species testing should be the first stage in further studies on the mechanism.

Haynes and associates carried out a mechanism study for Rh/Xantphos-catalyzed methanol carbonylation based on the combination of structural, spectroscopic, kinetic, and theoretical methods. The Rh(III) acetyl complex [Rh(Xantphos)-(COMe)I_2], as the catalyst resting state, was isolated and shown to adopt a nearly octahedral geometry with the Xantphos ligand coordinated in a "pincer" κ^3-P,O,P fashion, which differs from related acetyl complexes with *cis*-chelating diphosphines that adopt square-pyramidal structures.

In addition to the phosphine-based ligands, some nitrogen ligands and carbene ligands were also tested in the rhodium-catalyzed carbonylation of MeI or MeOH [38, 39]. For example, the faster oxidative addition of MeI was observed (10^3–10^4 times faster than $[Rh(CO)_2I_2]^-$), and more stable Rh(III) methyl complexes resulted from α-diimine ligands with low steric bulk (e.g., bpy). In comparison, inhibited oxidative addition but promoted methyl migration, as observed with more bulky α-diimine ligands containing *ortho*-alkyl groups on the *N*-aryl substituents. Steric effects were also found to be important for determining the reactivity of rhodium complexes containing *N*-heterocyclic carbene (NHC) ligands.

Scheme 2.3 Ligands tested with Rh(I)



In order to merge the advantages of homogeneous and heterogeneous catalysts, rhodium catalysts have also been immobilized. Several polymer-supported or ionic liquid-supported catalysts have been developed as well [40–42].

The iridium-catalyzed carbonylation of methanol known as the *Cativa*™ process was announced by BP Chemicals in 1996; it now operates on a number of plants worldwide [43–46]. The advantages of iridium catalysts are better stability because of stronger metal–ligand bonding, broad reaction conditions tolerability, and others.

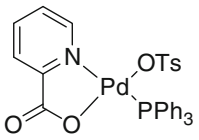
Cobalt in the same group with Rh and Ir was also explored in the carbonylation of methanol. The first report on this topic was in 1986, using $Co_2(CO)_8$ as the catalyst [47]. But the activity and selectivity of this system is low, and high temperatures and pressure (200 °C, 600 bar) were necessary. In 1999 Cole-Hamilton and colleagues found a high active cobalt catalyst based on the combination of $Cp^*Co(CO)_2$, PEt_3 and MeI [48]. The $[CoI(CO)_2(PEt_3)_2]$ was isolated from the final reaction solution. The activities and selectivities of this catalyst system are comparable to those of their rhodium-based analogues.

Palladium catalysts were prepared and tested in the carbonylation of alcohols as well [49, 50]. By using pyridine-2-carboxylato as a ligand and in the presence of LiI or LiCl as an additive, alcohols were carbonylated (Scheme 2.4). The combination of a Pd/CeO_2 catalyst for the in situ generation of CO, via methanol decomposition, with a copper mordenite methanol carbonylation catalyst was shown to be a successful strategy for the development of a methanol-only halide-free route to acetic acid by Hargreaves and colleagues [51]. There was a pronounced dependence upon the reactor bed configuration. A stacked bed, in which the Pd/CeO_2 decomposition catalyst was placed upstream of the Cu-MOR carbonylation catalyst, exhibited a much greater acetyls yield than the physical mixture of the two catalysts.

Compared with the carbonylation of methanol, the carbonylation of C_{sp3}-X is relatively easier. Based on the C–X bond energy, the rate of the oxidative addition of the organic halide to an electronically unsaturated metal complex decreases along the sequence: C–I > C–OTf ≥ C–Br ≫ C–Cl ≫ C–F. In addition to (hetero)aryl halides, alkenyl-X [52–56] and steroidal [57–62] derivatives have been successfully used as reagents in carbonylation reactions as well.

In addition to carboxylic acid derivatives, anhydrides and acid fluorides are also accessible straightforward via carbonylation reactions depending on the various nucleophiles used. For example, water (hydroxycarbonylation) will give carboxylic acid, alcohols (alkoxycarbonylation) will give esters, amines (aminocarbonylation) will give amides, and anhydrides and acid fluorides can be produced if

Scheme 2.4 Palladium catalyst for carbonylation of alcohols

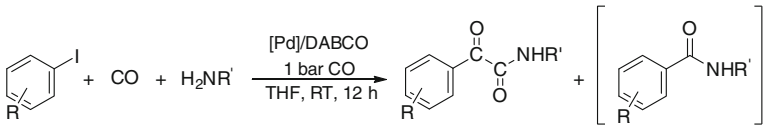


carboxylate salts or fluorides are used. One obvious advantage for carbonylation with respect to biologically active compound preparation is that a variety of carbonylation products can be easily prepared from the same aromatic substrate by simply changing the nucleophiles. Notably, such carbonylation reactions can be performed efficiently nowadays as the parallel pressure devices are commercially available.

Palladium-catalyzed double carbonylation as a more special carbonylation variant usually requires high CO pressures in order to compete with the corresponding monocarbonylation reactions. By introducing two molecules of carbon monoxide, α-keto acids, esters or amides are produced from their parent (hetero)aryl, alkenyl and alkyl halides [63–82]. Up until 2001, Uozumi and colleagues reported a procedure that significantly improved the existing protocols. They found 1,4-diaza-bicyclo[2.2.2]octane (DABCO) to be a superior base for the highly selective double carbonylation of aryl iodides with primary amines (Scheme 2.5) [83]. The desired α-keto amides were prepared under atmospheric pressure of CO at room temperature in the presence of a simple palladium-triphenylphosphine complex.

For intermolecular alkoxycarbonylation, [83–97] aminocarbonylation [98–102], and hydroxycarbonylation [103–107] reactions, (hetero)aromatic bromides and iodides are the most widely used starting materials at present. Heck and colleagues described the first palladium-catalyzed alkoxycarbonylation reaction in 1974 [108]. Carboxylic acid *n*-butyl esters were synthesized from aryl and vinyl iodides and bromides after they reacted with carbon monoxide (1 bar) in *n*-butanol at 100 °C. In the presence of 1.5 mol% of either $PdX_2(PPh_3)_2$ or the respective haloarylbis(triphenylphosphine)-palladium(II) complexes in the presence of a slight excess of tri-*n*-butylamine as a base, good yields of the corresponding esters were usually obtained. Notably, the reaction without added phosphine ligands was limited to aryl iodides. Since Heck's pioneering report, impressive improvements concerning solvents, bases, and catalyst systems, particularly ligands, have been made, all of which have significantly broadened the scope of the method.

Notable progress with regard to catalyst productivity was achieved by Beller's group. Several reaction parameters, such as temperature, carbon monoxide pressure, solvents, bases, various catalyst precursors and the ligand-to- palladium ratio were investigated in detail by taking palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone as the model system [109]. An almost quantitative yield of butyl ester was achieved at low pressure (5 bar CO) and 100 °C in the presence of only 0.3 mol% $Pd(PPh_3)_4$ and three equivalents of Et_3N in *n*-butanol.



Scheme 2.5 Palladium-catalyzed double carbonylation of aryl iodides

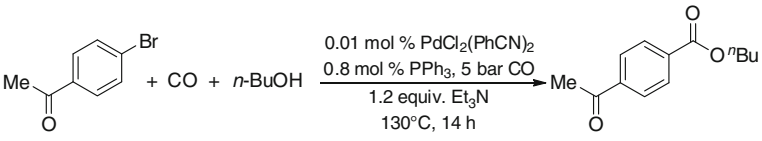
The optimization resulted in the highest turnover (TON up to 7,000) known until then for any alkoxycarbonylation of aryl halides (Scheme 2.6).

Ramesh et al. synthesized a cyclometallated dimeric palladium(II) catalyst with covalently bonded based on the concept that release slowly the highly active species from structurally more stable catalyst precursors [110]. By utilizing this dimeric oxime-type palladacycle as the catalyst, various aryl iodides were reacted with aliphatic alcohols and phenols in a highly selective manner and gave the corresponding esters in excellent yields. Based on these excellent yields, apparently no by-products were formed. Remarkably, the complex was stable even at high temperatures (120 °C) and under 10 bar of carbon monoxide.

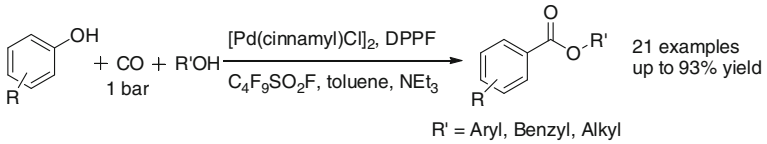
Other attempts include the use of a combined bimetallic ruthenium/palladium catalyst [111], and heterogeneous palladium complexes were also carried out in order to develop more efficient and practicable catalysts for alkoxycarbonylations of aromatic iodides [112, 113]. Advantageously, the latter catalyst systems could be effectively removed from the reaction mixture by a simple filtration process and they were reused several times with only a minor loss of activity.

Bromoanisoles and unprotected bromoanilines, as examples of more challenging substrates, were recently overcomed in methoxycarbonylation by Albaneze-Walker and colleagues [114]. Using 3 mol% of $PdCl_2$/*rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) at low pressure (4.5 bar CO, 100 °C), high yields (>91 %) were achieved, except for *p*-bromoaniline (50 %). More recently, Beller's group developed a general palladium-catalyzed carbonylation of aryl and heteroaryl bromides with phenols. The reaction proceeds smoothly in the presence of di-1-adamantyl-*n*-butylphosphine under 2 bar of CO in dioxane at 100 °C. Later on, the same group developed a one pot alkoxycarbonylation of phenols with alcohols and phenols via the in situ formation of ArONf. The reaction proceeds selectively to the desired benzoates in good yields (Scheme 2.7) [115, 116]. As phenols occur naturally and are ready available, applying phenols as electronphiles instead of aryl halides is an interesting topic. Additionally, in all the sulfonate compounds, ArONf is more stable than ArOTf and more active than ArOTs or ArOMs.

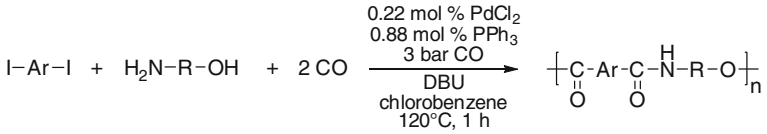
Carbonylation was applied in oligomerizations and polycondensations as well, even though most of the previous work focused on monocarbonylation reactions. Chaudhari and colleagues reported a palladium-catalyzed carbonylation-polycondensation reaction of aromatic diiodides and aminohydroxy compounds [117]. With their methodology, alternating polyesteramides were prepared in chlorobenzene with 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) as a base under 3 bar of carbon monoxide at 120 °C (Scheme 2.8).



Scheme 2.6 Palladium-catalyzed alkoxycarbonylation of aryl bromides



Scheme 2.7 Palladium-catalyzed carbonylation of phenols



Scheme 2.8 Palladium-catalyzed polycondensations

With the same reaction as that of alkoxycarbonylation, the first palladium-catalyzed amidation reaction of aryl-X compounds was again developed by Heck and his group. They demonstrated that by carbonylation reactions, secondary and tertiary amides are conveniently produced [118]. More specifically, (hetero)aryl bromides and vinyl iodides were reacted with primary or secondary amines under atmospheric CO pressure at 60–100 °C in the presence of 1.5 mol% $PdX_2(PPh_3)_2$. Stoichiometric amounts of a tertiary amine were required to neutralize the formed acid if weakly basic amines were used as nucleophiles.

Aminocarbonylations of aryl iodides in the absence of carbon monoxide[1] and a base were realized in 2002 by a combination of phosphoryl chloride with *N,N*-dimethylformamide (DMF) [120]. With the assistance of 2.5 mol% $Pd_2(dba)_3$, good to high yields of amides were obtained in toluene at 120 °C (Scheme 2.9). The generated Vilsmeier reagent was suggested to be essential for the reaction to take place.

Cunico and Maity published another example of palladium-catalyzed CO-free carbonylation of aryl halides [121]. Depending on the substrate, 2 mol% of either $Pd(PPh_3)_4$ or $Pd(P^tBu_3)_2$ was used to catalyze the reaction of heteroaryl and aryl bromides with *N,N*-dimethyl-carbamoyl(trimethyl)silane (Scheme 2.10). Tertiary amides were prepared in good yields by direct carbamoylation under their conditions. Remarkably, chlorobenzene, 1-chloro-4-methoxybenzene, and iodobenzene gave the desired products in 74, 78, and 60 % yields, respectively.

Skrydstrup's group developed a two-reaction tubes technology for the CO free carbonyaltion reactions.[2] They use 9-methylfluorene-9-carbonyl chloride as a CO precursor; CO gas been released in the presence of a palladium catalyst and transferred to another tube for carbonylation reactions. Various carbonylation reactions have been adopted by this technology.

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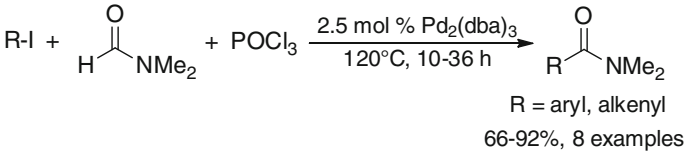
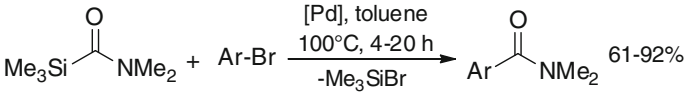
[1] For a review of carbonylation reactions using carbon monoxide equivalents, see [119].

[2] For selected examples, see [122–124].



Scheme 2.9 Palladium-catalyzed aminocarbonylation without CO



Scheme 2.10 Palladium-catalyzed aminocarbonylation of aryl bromides

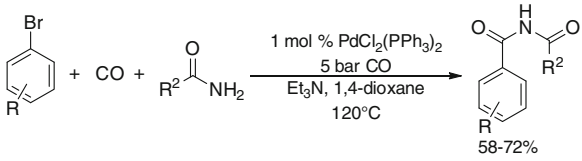
More recently, a solid-phase palladium-catalyzed aminocarbonylation of aryl bromides or iodides utilizing molybdenumhexacarbonyl ($Mo(CO)_6$) as the carbon monoxide source was presented [125]. Compared to previous carbonylations with metal carbonyl compounds, these reactions proceeded under mild conditions without the presence of microwave irradiation.

The scope of aminocarbonylations was extended by the works from various groups. For example, Skoda-Földes and Kollár studied the carbonylation reactions of ferrocene derivatives in the presence of $Pd(OAc)_2/PPh_3$ [126–128]. Ferrocene amides and novel ferrocene α-ketoamides were synthesized in good yields based on palladium-catalyzed aminocarbonylation or double carbonylation of iodoferrocene at 40–50 bar of CO. The double-carbonylated products were favored at 40–60 °C and amides were produced almost exclusively at 100 °C, as the selectivity of the reaction with less sterically hindered secondary amines is highly dependent on the reaction temperature. Analogous aminocarbonylation reactions of 1,1′-diiodoferrocene led to 1′-iodo-ferrocenecarboxamides and 1′-iodo-ferroceneglyoxylic amide-type products.

Moreover, Schnyder and Indolese proved that the carbonylation of aryl bromides with primary amides or sulfonamides can lead to asymmetrical aroyl acyl imides. When the reactions were carried out under mild conditions, Et_3N was found to be the best base and the desired products were produced in 58–72 % yields (Scheme 2.11) [129].

Beller and colleagues reported the aminocarbonylation of non-protected bromoindoles for the first time. The substrates were converted directly into the

Scheme 2.11 Palladium-catalyzed aminocarbonylation with amides

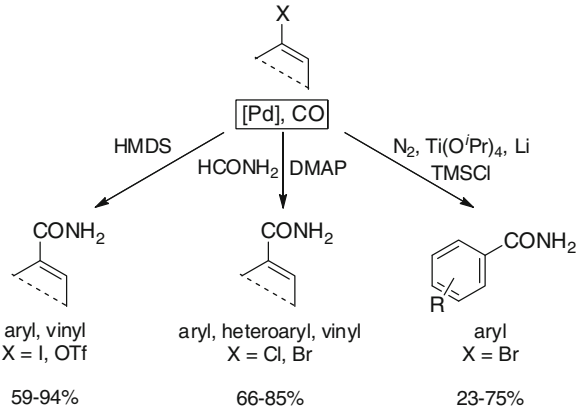


corresponding indole carboxylic amides via palladium-catalyzed carbonylation [130]. At 25 bar of CO and 130 °C, the use of $PdCl_2(PhCN)_2$/1,1′-bis(diphenylphosphino)ferrocene (dppf) and Et_3N was found to be optimal for high yields (>90 %) for the reaction of indoles with piperazine and morpholine derivatives, *n*-butylamine, and ethanol. Remarkably, the free carboxylic acid was also directly accessible in a 67 % yield. Moreover, under the optimized reaction conditions, potentially bioactive amphetamine analogs were obtained in high yields.

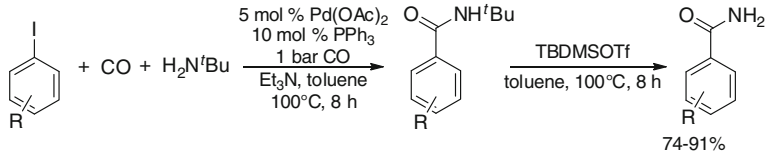
As the importance of primary amides, Morera and Ortar used hexamethyldisilazane (HMDS) as a source of ammonia in the carbonylation of aryl iodides and triflates to primary amides (Scheme 2.12) [131]. The desired products were isolated in high yields after hydrolysis. In addition, Indolese et al. reported the efficient aminocarbonylation of aryl bromides with formamide at 5 bar of carbon monoxide. Here, using 4-(dimethylamino)pyridine (DMAP) as a base was the key factor for success [132]. Primary benzamides were also prepared from aryl bromides using CO and a titanium-nitrogen complex in conjunction with NaO^tBu [133].

Additionally, primary amides and ketoamides were synthesized in good yields via a more traditional carbonylation-deprotection sequence in the presence of $Pd(OAc)_2/2PPh_3$ (Scheme 2.13) [134]. Initially, aryl iodides were reacted with *tert*-butylamine under 1 bar of CO. When the reaction proceeded at 60 °C, ketoamides resulting from double carbonylation were mainly produced, whereas formation of the amides was favored at 100 °C. The desired primary amides were produced after heating the previous isolated products with one equivalent of *tert*-butyldimethylsilyl triflate (TBDMSOTf) in toluene at 100 °C.

Remarkably, Beller's group developed several novel methodologies for the primary amides synthesis [135–139]. In the presence of palladium catalysts, aryl halides, phenyl triflates, benzyl chlorides and even phenols were transformed into the corresponding primary amides in good to excellent yields. Ammonia gas was used directly as an amine source and also as a base. These were the primary reports on using NH_3 and CO for primary amides synthesis (Scheme 2.14).

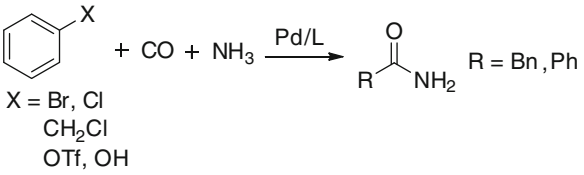


Scheme 2.12 Palladium-catalyzed carbonylative synthesis of primary amides



Scheme 2.13 Carbonylative synthesis of primary amides from aryl iodides

Scheme 2.14 Procedures for carbonylative synthesis of primary amides

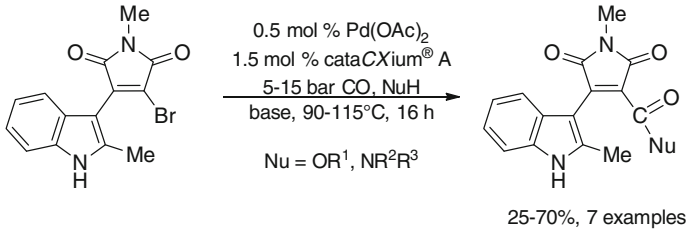


By using $Pd(OAc)_2$ and commercially available di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) as the catalyst system, various aromatic and heteroaromatic esters, amides, and acids were prepared from the corresponding bromoarenes in Beller's group [140]. Compared to most known carbonylation protocols, excellent yields can be achieved at relatively low catalyst loadings (<0.5 mol% Pd) and carbon monoxide pressure (5 bar). Most recently, this catalyst system was applied to synthesize novel potentially bioactive 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides from 3-bromo-indolylmaleimide (Scheme 2.15) [141].

Cacchi and colleagues published a novel CO-free protocol utilizing an acetic anhydride/lithium formate combination as a condensed source of carbon monoxide for the hydroxycarbonylation of aryl and vinyl halides or triflates [142]. The transformations tolerated a wide range of functional groups, including ether, ketone, ester, and nitro groups. In 2006, the combination of acetic anhydride/lithium formate was adapted for the palladium-catalyzed hydroxycarbonylation of aryl bromides (Scheme 2.16) [143]. Using 3–5 mol% $Pd(OAc)_2$ and dppf (Pd/P = 1), the reaction of bromoarenes with acetic anhydride and lithium formate proceeded smoothly in DMF at 120 °C and provided carboxylic acids in good yields. In addition, terephthalic acid was prepared from 1,4-dibromobenzene in a 75 % yield under the standard conditions without further optimization.

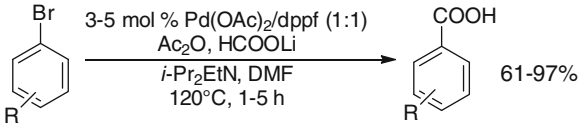
Successively, carbon aerogels doped palladium nanoparticles as a recoverable catalyst was applied in the hydroxycarbonylation of aryl iodides by Cacchi and colleagues [144]. Using DMF as a solvent at 100 °C with acetic anhydride/lithium formate along with lithium chloride and DiPEA (*N,N*-diisopropylethylamine) as a base, high to excellent yields can be achieved. The catalyst can be reused up to 12 times without any appreciable loss of activity in the case study of *p*-iodotoluene.

In palladium-catalyzed carbonylations, aryl triflates are used regularly as substrates [145–151], while arene diazonium salts [152–156] and diaryl iodonium salts [157–162] are less commonly applied.



Scheme 2.15 Carbonylative functionalize of 3-bromo-indolylmaleimide

Scheme 2.16 Palladium-catalyzed hydroxycarbonylation of aryl bromides

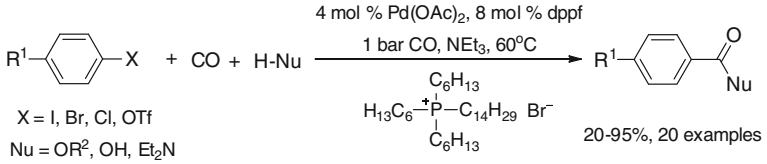


Tanaka and his associates demonstrated for the first time how to use non-volatile ionic liquids (ILs) as solvents in palladium-catalyzed carbonylations [163]. In the case of alkoxycarbonylation of bromobenzene, higher yields were obtained when 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] was used as the reaction medium compared with standard conditions. And the selectivity for the monocarbonylation of iodobenzene with *i*-PrOH or Et_2NH was significantly enhanced by [bmim][BF_4]. After separation of the products, the solvent-catalyst system was easily recycled and exhibited catalytic activity up to seven times. Since then the replacement of traditional solvents with quaternary ammonium halides, imidazolium- or pyridinium-derived ILs has gained increasing importance [164–173]. Recently, the phosphonium salt IL trihexyl(tetradecyl)phosphonium bromide has proven to be an effective reaction medium for various carbonylation reactions of aryl and vinyl bromides or iodides under mild conditions (Scheme 2.17) [174].

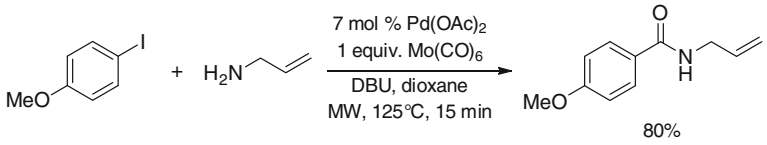
Larhed and colleagues developed the use of microwave irradiation in palladium-catalyzed carbonylations of aryl-X compounds [175–186]. Typically, these reactions were conducted in sealed vessels using microwave irradiation and either $Mo(CO)_6$ or formic acid derivatives as CO sources. Alternatively, alkoxy- and hydroxycarbonylations of aryl iodides with gaseous carbon monoxide have been performed by using pre-pressurized reaction vessels in conjunction with microwave heating [187–189].

More recently, a microwave-promoted palladium-catalyzed aminocarbonylation of (hetero)aryl halides (X = I, Br, Cl) using $Mo(CO)_6$ and allylamine as a nucleophile was also described [190, 191]. Remarkably, no side products resulting from the competing Heck reaction were detected. Importantly, this was the achievement that aminocarbonylation was realized on a larger laboratory scale (25 mmol) starting from 4-iodoanisole (Scheme 2.18).

Taking the advantages of (hetero)aryl chlorides into consideration, they have also been explored in carbonylation reactions as substrates. As early as 1989,



Scheme 2.17 Palladium-catalyzed carbonylation of ArX

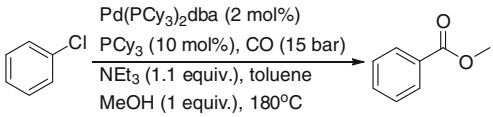


Scheme 2.18 $Mo(CO)_6$-mediated carbonylation of aryl iodides

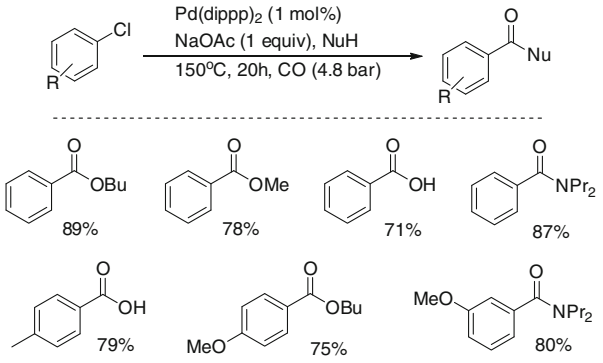
Osborn and colleagues reported the catalytic carbonylation of chlorobenzene and dichloromethane [192]. By using $[Pd(PCy_3)_2(dba)]$ as a catalyst in the presence of additional PCy_3, chlorobenzene was catalytically carbonylated at 180 °C in toluene under 15 bar of CO using NEt_3 as a base (Scheme 2.19). In their report, instead of PCy_3, P*i*Pr$_3$ can be used as an effective ligand for the activation of DCM at 25 °C to give ketene as well, but not $P(CH_2Ph)_3$, PPh_2Cy and PPh_3. In the case of chlorobenzene, Pd^0 complexes with P*t*Bu$_3$, P*t*Bu$_2$Ph, PPh_2Cy and P(*m*-tol)$_3$ are non-active at all. Here it is also interesting to point out that chlorobenzene can react with $[Pd(PCy_3)_2(dba)]$ to give a phenylpalldium complex at 60 °C, and a benzoylpalladium complex be prepared from a phenylpalladium complex at room temperature under 30 bar of CO (the reverse transformation can be easily realized at 60 °C under argon). But the catalytic alkoxycarbonylation of chlorobenzene must be carried out at 180 °C.

Meanwhile, Milstein's group succeeded with a breakthrough type of work on the carbonylation of aryl chlorides with his dippp (1,3-bis(di-isopropylphosphino)propane) ligand [193, 194]. In their studies, aryl chlorides were transformed into esters, amides, acids and aldehydes in good yields under relatively mild conditions (Scheme 2.20). Under the best conditions, the reactivity of ligands is decreasing as dippp>dippb>dippe ⋙ dppp>dppe. In the case of the formylation of aryl chlorides, the reaction is specific to the dippp ligand. Their mechanistic study had shown the importance of chelate stability, ligand basicity, concentration of the active 14e species and the effect of the P-Pd-P angle on its reactivity [195, 196]. The reactivity toward the oxidative addition of chlorobenzene follows the $Pd(dippp)_2$>$Pd(P^iPr_2^nBu)_3$≫$Pd(dippe)_2$≫$Pd(dppp)_2$ trend. This catalyst system was applied in the synthesis of polyamides from aromatic dichlorides, diamines and CO [197].

In 2001 Beller's team developed another efficient phosphine ligand for the carbonylative transformation of aryl chlorides [198, 199]. With the assistance of a



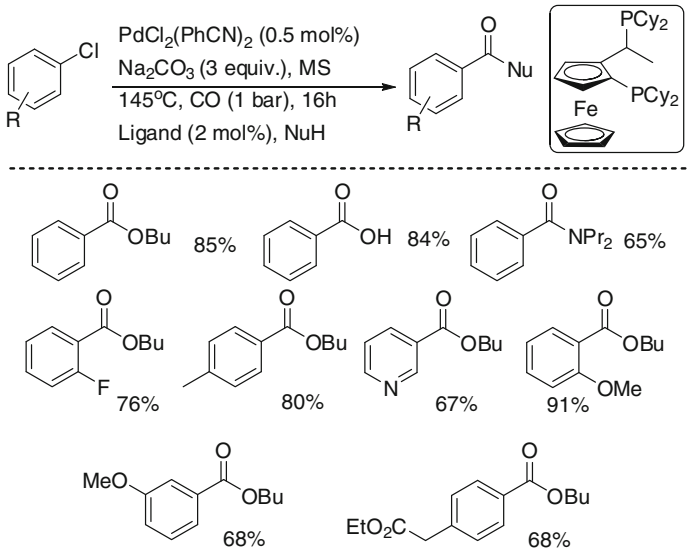
Scheme 2.19 [$Pd(PCy_3)_2(dba)$]-catalyzed carbonylation of chlorobenzene



Scheme 2.20 $Pd(dippp)_2$-catalyzed carbonylation of aryl chlorides

1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicycloheyxlphosphine ligand, both activated and non-activated aryl chlorides were carbonylated under mild reaction conditions and given the corresponding products in good yields (Scheme 2.21). Compared with previous methodologies, the advantages of this procedure are the fact that the ligand used is air stable and commercially available. Later on, the same group did a comprehensive study in the alkoxycarbonylation of various *N*-heteroaryl chlorides [200]. Studies of the butoxycarbonylation of 2- and 3-chloropyridine revealed the importance of selecting both the right phosphine ligand and ligand concentration in order to obtain efficient conversion and selectivity. Among the various ligands tested, 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenyl-phosphino) ferrocene (dppf) led to the most efficient palladium catalyst systems for the conversion of 2- and 4-chloropyridines and similar heteroaryl chlorides. The best catalytic systems for the alkoxycarbonylation of less activated substrates, such as 3-chloropyridines, were found to be those containing 1,4-bis(dicyclohexylphosphino)butane. Good to excellent yields of a number of *N*-heterocyclic carboxylic acid esters were obtained by applying the appropriate ligand in the right concentration at low catalyst loadings (0.005–0.5 mol% Pd). For the first time, catalyst turnover numbers (TON) of up to 13,000 were obtained for the carbonylation of a (hetero)aryl chloride.

Recently, another type of Josiphos ligand was discovered to be an efficient ligand for palladium-catalyted carbonylation of aryl sulfonates [201]. The catalyst

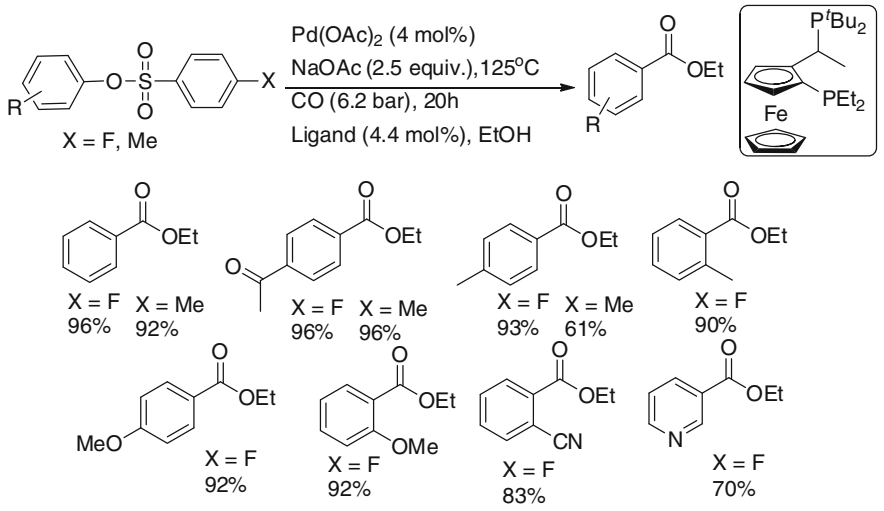


Scheme 2.21 Pd-Josiphos-catalyzed carbonylation of aryl chlorides

system is effective for the carbonylation of aryl *p*-fluorobenzenesulfonates and -tosylates with a general functional group tolerance under less severe reaction conditions. Both electron-rich and electron-poor arenesulfonates were carbonylated and gave the corresponding esters in good to excellent yields (Scheme 2.22).This method provides an alternative route to making aryl carboxylic acid derivatives from readily available and air-stable starting materials and therefore is useful in an industrial manufacturing process. As the authors indicated, the catalyst was also found to be effective for the carbonylation of aryl chlorides.

In 2008, Buchwald and colleagues developed an efficient procedure for the carbonylation of aryl chlorides, aryl tosylates and aryl mesylates [202–204]. Under their reaction conditions, carboxylic acid derivatives were prepared in good yields (Scheme 2.23). The advantages of this procedure are: (1) 1,3-bis(dicyclohexylphosphino)propane bis(tetrafluoroborate) as the ligand used is stable and easily available; and (2) the reactions were carried out in a reaction tube under 1 bar of CO, avoid the using of autoclave.

A catalyst system based on palladium-1,2-bis-(di-*tert*-butylphosphinomethyl)benzene (BDTBPMB) was reported by Cole-Hamilton and colleagues, showing good activity for the methoxycarbonylation of strongly activated aryl chlorides, like 4-chloromethylbenzoate or 4-chlorocyanobenzene (Scheme 2.24) [205]. Selective carbonylation of aromatic chlorides to carboxylic acid esters is catalyzed by Pd/BDTBPMB complexes in alcohols in the presence of base, when the aromatic ring is very electron poor. For less activated aromatic rings, such as that in 4-chloroacetophenone, selective carbonylation can only be achieved by using alcohols of low nucleophilicity, such as 2,2,2-trifluoroethanol. More nucleophilic

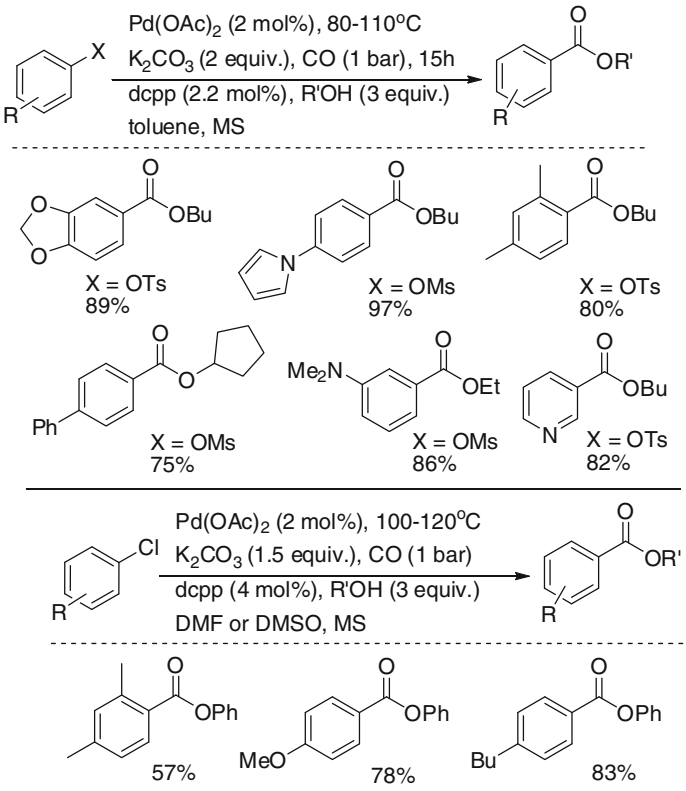


Scheme 2.22 Pd-Josiphos-catalyzed carbonylation of aryl arenesulfonates

alcohols give many side products arising from nucleophilic aromatic substitution, reductive dehalogenation and an unusual transformation of the methylketone into a methyl ester. Labelling studies show that this reaction formally occurs by displacement of the methyl group by methoxide. Nitro and cyano groups on the ring also undergo severe side reactions.

In addition to the ligands-tuned carbonylative activation of aryl chlorides, several other catalyst systems were developed, based on the use of a nanopartical, biphasic system and Lewis acids as well.

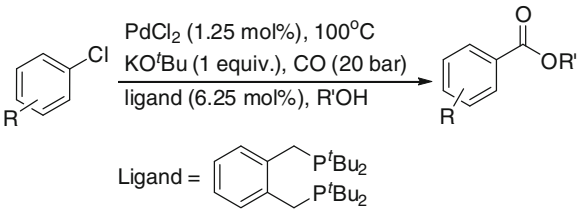
Pd/C was found to act as an effective catalyst for the carbonylation of aryl chlorides as 200 °C [206]. It was found that both activated and non-activated aryl chlorides were transformed into the corresponding methyl esters [CO (3 bar), AcONa, MeOH], and the addition of $K_2Cr_2O_7$ can enhance the catalytic activity. The role of $K_2Cr_2O_7$ is very likely to reoxidize large particles of metallic palladium into a highly dispersed palladium(II) species that can be reduced again under CO into an active zerovalent palladium complex. Alper and Grushin found that bis(tricyclohexylphosphine)palladium dichloride is an active catalyst for the carbonylation of chloroarenes to carboxylic acids under biphasic conditions [207]. The reactions were carried out in an aqueous solution of KOH under 1 bar of CO at 100 °C; both activated and non-activated aryl chlorides were carbonylated in good yields. In 1997 the combination of $PdCl_2(PCy_3)_2$-K_2CO_3 aqueous solution-triethylamine [CO (5 bar), 180 °C] was a highly selective procedure for the hydrocarbonylation of chlorobenzene [208]. 4-Chlorobenzophenone and/or benzoyl chloride can be synthesized by $PdCl_2$ in the presence of Lewis acids ($AlCl_3$ or $GaCl_3$) from chlorobenzene under 10 bar of CO at 120 °C [209]. In the absence of $PdCl_2$, 4-chlorobenzaldehyde was produced as the product of the Gattermann-



Scheme 2.23 $Pd(OAc)_2$-DCPP-catalyzed carbonylation of ArCl and ArOTs

Koch reaction, which is promoted by $AlCl_3$ [210]. Activated aryl chlorides can also give the corresponding carbonylated products in low to moderate yields in ionic liquids using Pd-benzothiazole carbine as a catalyst under atmospheric pressure of CO at 140 °C [211].

Perry's group developed a palladium-catalyzed aminocarbonylation of activated aryl chlorides under low CO pressure and in the presence of iodide salt (KI, NaI) [212]. Moderate to excellent yields of amides were prepared from activated



Scheme 2.24 $PdCl_2$-BDTBPMB-catalyzed carbonylation of activated ArCl

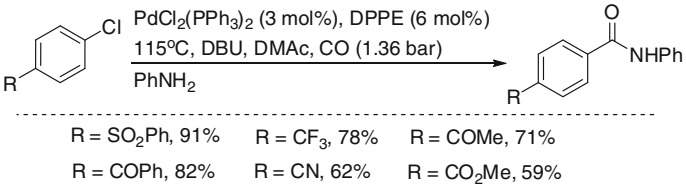
chlorides; electron-rich aryl chlorides were not effectively amidated, even after adding iodide (Scheme 2.25).

Besides the electron-withdrawing substituent activated aryl chlorides, heteroaryl chlorides are another family of activated chlorides that also holds interesting biological activities. Under this background, there are many procedures that have been developed for the carbonylative transformation of heteroaryl chlorides. In general, the reaction conditions for these methodologies are much milder.

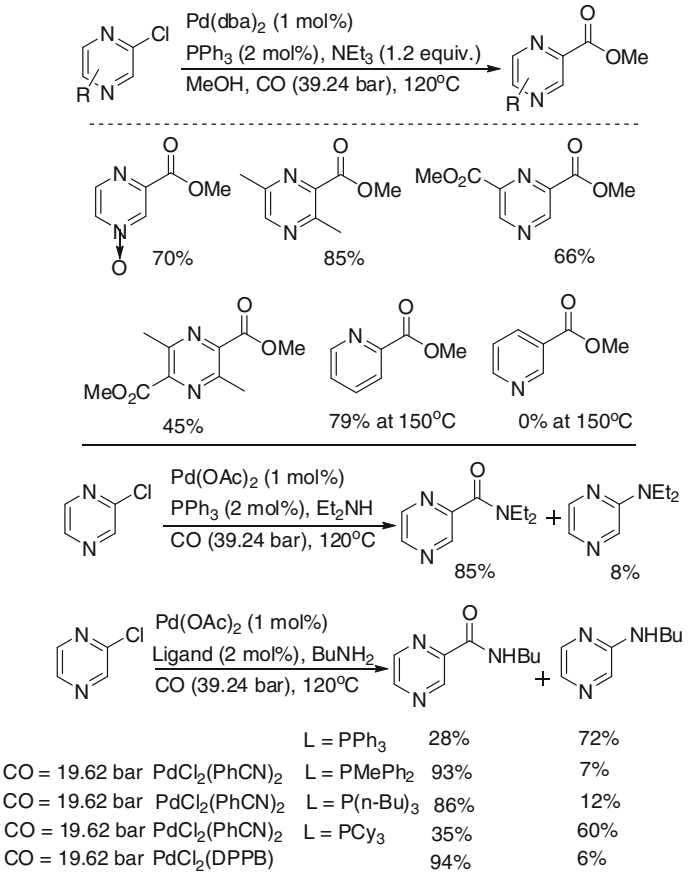
In 1984 Head and colleagues reported a palladium-catalyzed carbonylative synthesis of heterocyclic esters from the corresponding halides [213]. The main substrates are heterocyclic bromides; one example of heterocyclic chloride was also described. Using $PdCl_2(PPh_3)_2$ as a catalyst under 7.9 bar of CO at 100 °C in ethanol with NEt_3 as the base, 5-chloroethylnicotinate was produced from 3,5-dichloropyridine.

Palladium-catalyzed carbonylation of chloroquinolines and chloropyridines were developed as well [214, 215]. 3-substituted 2-chloroquinolines were carbonylated with MeOH under the assistant of $Pd(OAc)_2$ (2 mol%), DPPP (4 mol%), NaOAc (1 equiv.), CO (100 bar), in DMF at 140 °C for 2 days. Good to excellent yields of esters were isolated. In comparison, 4,7-dichloroquinone was selectively carbonylated at 4-position using 2 mol% of $PdCl_2(PPh_3)_2$, 10 mol% of PPh_3, in methanol with NEt_3 as a base, under 50 bar of CO at 150 °C for one hour. Good yields of the corresponding aldehyde, ester and amide were produced with excellent selectivity. Under the same reaction conditions, 2,6-dichloropyridine was converted to dimethyl diester in 90 % yield, while 2,3-, 2,5-dichloropyridines gave mainly monoesters at 2-position. 2,7-Dichloro-1,8-naphthyridine and 2,9-dichloro-1,10-phenanthroline were transferred into dibutyl 1,8-naphthyridine-2,7-dicarboxylate and dibutyl 1,10-phenanthroline-2,9-dicarboxylate with 40–60 % yields [216, 217]. The reactions were carried out with $PdCl_2(PPh_3)_2$ (2 mol%) as a catalyst, under 1 bar of CO at 120 °C.

Takeuchi's group did a comprehensive study on the palladium-catalyzed carbonylation of *N*-heteroaryl chlorides [218]. Carbonylation of chloropyrazines in methanol or amines gave the corresponding esters or amides in good to excellent yields (Scheme 2.26). In the methoxylcarbonylation of 2-chloropyrazine, PPh_3 and DPPE gave excellent yields of ester while tri-n-butylphosphine or tricyclohexylphosphine was not effective. With 1 mol% of $Pd(dba)_2$, 2 mol% of PPh_3, at 120 °C under 39.24 bar of CO, chloropyrazines were easily carbonylated, including *N*-



Scheme 2.25 $PdCl_2(PPh_3)_2$-DPPE-catalyzed carbonylation of activated ArCl

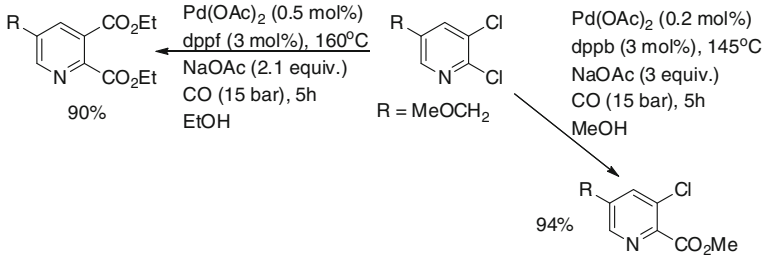


Scheme 2.26 Palladium-catalyzed carbonylation of 2-chloropyrizines

oxide. The reactivity of substrates increases in the order as: 2-chloropyrazine>2-chloropyridine≫3-chloropyridine. In the aminocarbonylation of 2-chloropyrizine, tri-n-butylphosphine was effective. High carbon monoxide pressure decreased the selectivity to the amides.

Bessard and colleagues developed a procedure for the selective mono- or di-carbonylation of 2,3-dichloropyridines (Scheme 2.27) [219, 220]. The choice of base and ligand plays a crucial role in the carbonylation. When Na_2CO_3 was used as a base, the major reaction pathway was substitution at the 2-position, giving a methoxy substituted product. Recently, some other catalytic systems have been established for the carbonylation of 2-chloropyridines [221–223]. DPPP and Binap were used as ligands for the alkoxycarbonylation of 2-chloropyridines; the corresponding esters were prepared in good to excellent yields.

Moreover, several other CO sources were discovered and applied in the carbonylation of aryl chlorides. Jenner and Taleb developed a palladium-catalyzed



Scheme 2.27 Palladium-catalyzed carbonylation of 2,3-dichloropyridine

carbonylation of aryl chlorides using methyl formate as a CO source, and benzoic acids were produced in good yields under aqueous conditions at 160 °C [224]. $PdCl_2(PCy_3)_2$ was found to be the only efficient catalyst. $Ru_3(CO)_{12}$ and ammonium formate improved the yield and selectivity.

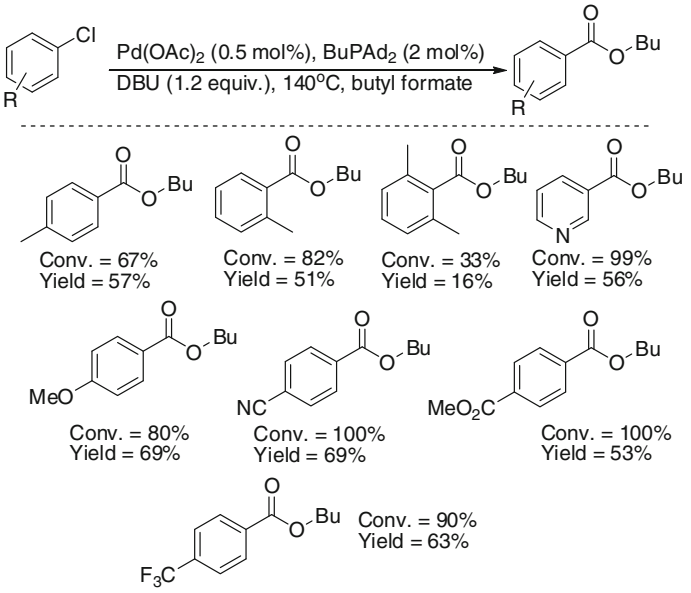
More recently, an improved protocol for palladium-catalyzed alkoxycarbonylation of aryl chlorides with alkyl formates was developed by Beller and colleagues [225]. In the presence of palladium(II) acetate/*n*-butylbis(1-adamantyl)phosphine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, for the first time non-activated chloroarenes could be conveniently carbonylated in good yields (Scheme 2.28). In this report, it has been shown that the catalyst system presented does not need the presence of ruthenium co-catalysts.

Larhed's group developed the microwave-promoted aminocarbonylation of aryl chlorides using $Mo(CO)_6$ as a solid carbon monoxide source [226–228]. This procedure offers aryl chlorides that rapidly transformed into a variety of benzamides (Scheme 2.29). Noteworthy features of this microwave method include the use of commercially available $[(t\text{-Bu})_3P]HBF_4$ to activate the strong Ar–Cl bond; impressive results with sluggish aniline and *tert*-butylamine reactants; air tolerance; short reaction times; and the use of $Mo(CO)_6$ as a solid carbon monoxide source.

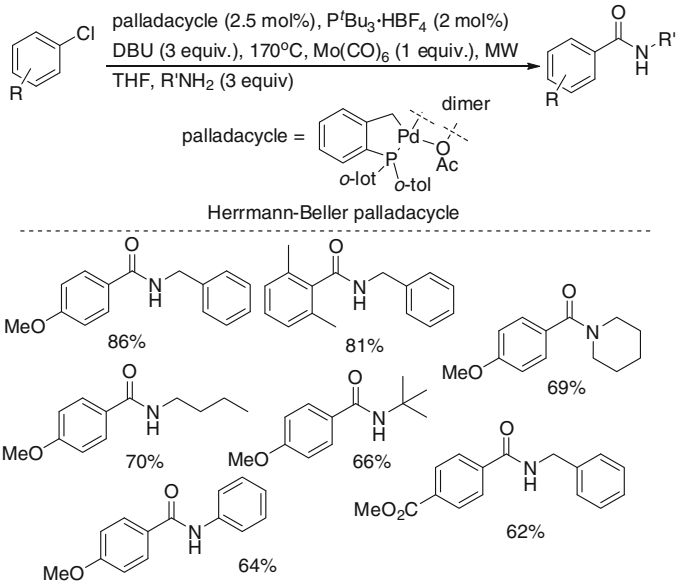
In addition to intermolecular carbonylations, there are intramolecular reactions that allow for the synthesis of various heterocycles. As a prime example, the intramolecular alkoxy- or aminocarbonylation (cyclocarbonylation) of hydroxyl- or amino-substituted aryl/vinyl halides enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, etc. [229].

The application of palladium-catalyzed carbonylation reactions in the synthesis of four-membered lactones was first reported by Stille and Cowell in 1980 [230]. They used $PdCl_2(PPh_3)_2$ as a catalyst and the lactones were synthesized in high yields under mild conditions (1–4 bar of CO; 25–60 °C) from the corresponding halo-substituted alcohols (Scheme 2.30a). Not only four-membered rings, but also five- and six-membered lactones can be achieved. Later on, Qing and Jiang modified this methodology for the preparation of trifluoromethyl-substituted four- and five-membered lactones (Scheme 2.30b) [231].

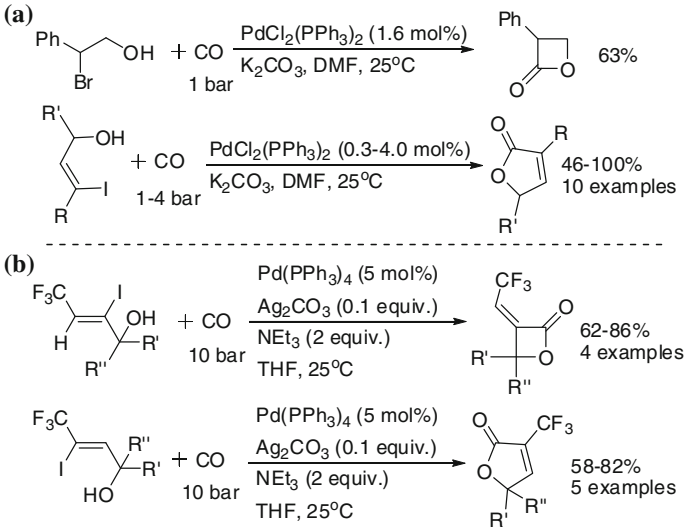
Shibasaki and colleagues reported the asymmetric synthesis of α-methylene lactones starting from prochiral alkenyl halides in 1991 [232]. In the presence of



Scheme 2.28 $Pd(OAc)_2$/$BuPAd_2$-catalyzed carbonylation of aryl chlorides



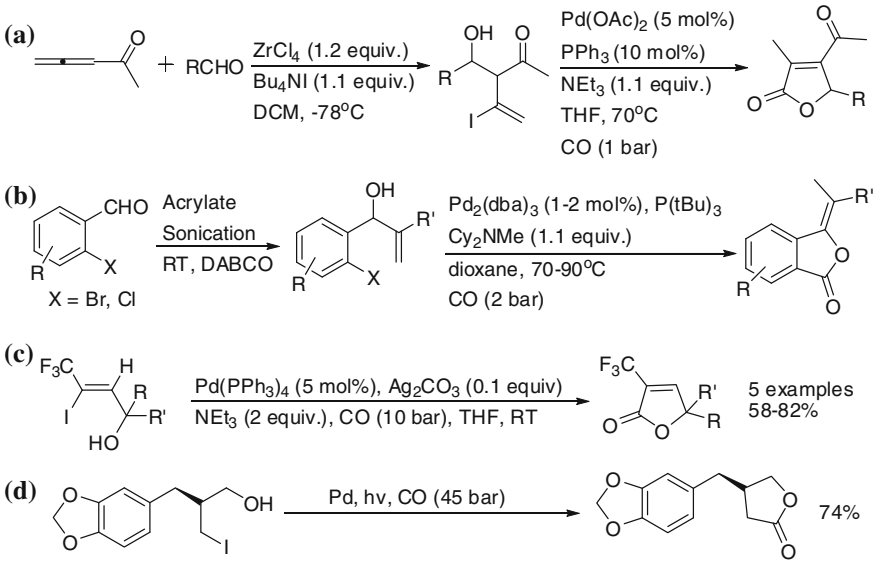
Scheme 2.29 Palladacycle-catalyzed carbonylation of aryl chlorides



Scheme 2.30 Palladium-catalyzed carbonylative syntheses of lactones

5 mol% of $Pd(OAc)_2$ and chiral ligands [(*S*,*S*)-chiraphos], under 1 bar of CO, the reaction was completed in one hour at 80 °C in DMSO with K_2CO_3 as the base. In 1994, Negishi's group reported on the palladium-catalyzed cyclic carbometalation-carbonylation, as well as the carbonylative cyclization of 1-iodo-2-alkenylbenzenes, 1-iodo-substituted 1,4-, 1,5-, and 1,6-dienes, and 5-iodo-1,5-dienes [233–235]. Moderate yields of five- or six-membered heterocycles were achieved under CO pressure. 3-Iodohomoallylic alcohols were synthesized from 3,4-pentadien-2-one, tetra-n-butyl ammonium iodide, and aldehydes in the presence of $ZrCl_4$ as a catalyst in good yields. These 3-iodohomoallylic alcohols can be further transformed into α,β-unsaturated γ-lactones by palladium-catalyzed cyclocarbonylation (Scheme 2.31a) [236]. Similarly, allylic alcohols could also be produced from aldehydes and acrylate via a Baylis–Hillman reaction. Following the same idea, 3-alkenyl phthalides were produced in good yields from the Baylis–Hillman adducts (Scheme 2.31b) [237]. With respect to the increasing importance of trifluoromethyl-substituted compounds, Qing and Jiang's report on the cyclocarbonylation of 3-iodo-3-trifluoromethyl allylic alcohols is noteworthy [238]. Several 3-trifluoromethyl-2(5*H*)-furanones were isolated in good yields (Scheme 2.31c). Interestingly, Ryu and colleagues reported the influence of light on the carbonylation of alkyl iodides [239, 240]. The reaction proceeds by a radical pathway (Scheme 2.31d). In the same report, carboxylic acid esters, α-keto amides were also synthesized from the corresponding alkyl iodides under the same reaction conditions. More recently, this group described the Pd/light-induced carbonylation of alkenes to esters and lactones.

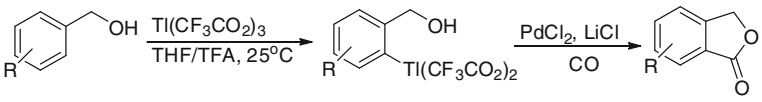
Larock and Fellows reported on the thallation-carbonylation of benzyl alcohols in 1982 [241]. Thallium (III) trifluoroacetate was used for the ortho-thallation of



Scheme 2.31 Palladium-catalyzed cyclocarbonylations

arenes, which are subsequently carbonylated with 10 mol% of $PdCl_2$, 2 equivalents of LiCl, and MgO in either methanol or THF under 1 bar of CO. Moderate yields of phthalides were obtained (Scheme 2.32).

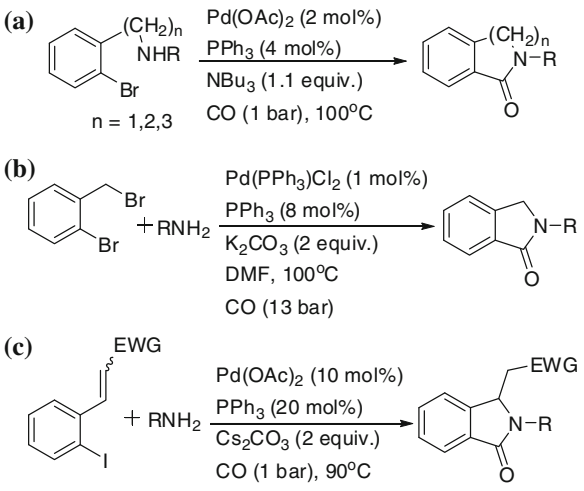
In 1978 Ban and colleagues reported on the palladium-catalyzed carbonylation of *o*-bromoaminoalkylbenzenes [242–245]. Five-, six-, and even seven-membered benzolactams were prepared in good yields in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 under atmospheric pressure of CO (Scheme 2.33a). A similar sequential reaction was also developed by Grigg and colleagues [246]. Here, starting from 2-halobenzylamines, ethyl glyoxalates and aryl boronic acids, the in situ-generated carbinolamines/imines reacted with CO to give isoindolones. Following this concept, Shim developed a palladium-catalyzed coupling of *o*-bromobenzyl bromides with primary amines. Initially, *o*-bromobenzyl amines are formed, which react later on, via palladium-catalyzed aminocarbonylation in DMF. The final products were obtained in fair to moderate yields (Scheme 2.33b) [247]. The latter reaction was improved by Grigg's group [248–250], as well as in further studies by other groups [251, 252]. Applying in situ-generated palladium nanoparticles, this three-component reaction proceeded even at room temperature



Scheme 2.32 Thallation-carbonylation of arenes

under 1 bar of CO and gave the desired products in good yields. Recently, the same group also described a novel palladium-catalyzed carbonylative synthesis of isoindolin-1-ones [253]. This three-component cascade process involved the carbonylation of substituted aryl iodides to generate the respective acyl palladium species, which reacted with a primary aliphatic/aromatic amine, amide or sulfonamide followed by an intramolecular conjugate addition to afford 3-substituted isoindolin-1-ones in good yields (Scheme 2.33c).

Moreover, Shim and colleagues described the cyclocarbonylation of 2-(2-bromophenyl)-2-oxazolines by a palladium-nickel catalyst [254]. Under 3 bar of CO and in the presence of the bimetallic catalyst, the corresponding isoindolinones were produced in high yields (Scheme 2.34a). Later on, they synthesized similar products by palladium-catalyzed coupling of 2-iodobenzoyl chloride with imines [255]. In the presence of $Pd(PPh_3)_2Cl_2/PPh_3$ as the catalyst system and NEt_3 as base, the corresponding isoindolinones were formed in moderate yields (Scheme 2.34b). More complex isoindolinones were produced by the same group through a palladium-catalyzed carbonylative coupling of 2-bromobenzaldehydes with aminoalcohols or diamines [256, 257]. These multi-step reactions provided the corresponding isoindolinones in good isolated yields (Scheme 2.34c). The reactions of diamines were carried out under lower temperatures and with lower catalyst loading. In addition to that, the palladium-catalyzed coupling of 2-bromobenzaldehydes and 2-bromocyclohex-1-enecarbaldehydes with primary amines has also been developed (Scheme 2.34d) [258, 259]. Interestingly, no base was needed in these reactions. With respect to the mechanism, the reaction began with the formation of an imine by condensation of the aldehyde and the primary amine. The oxidative addition of the carbon-bromide bond of the imine to the active palladium(0) catalyst produces the arylpalladium(II) complex. After the coordination of carbon monoxide with the metal center and subsequent insertion into the C–Pd bond, an aroylpalladium(II) intermediate is formed. Then, an

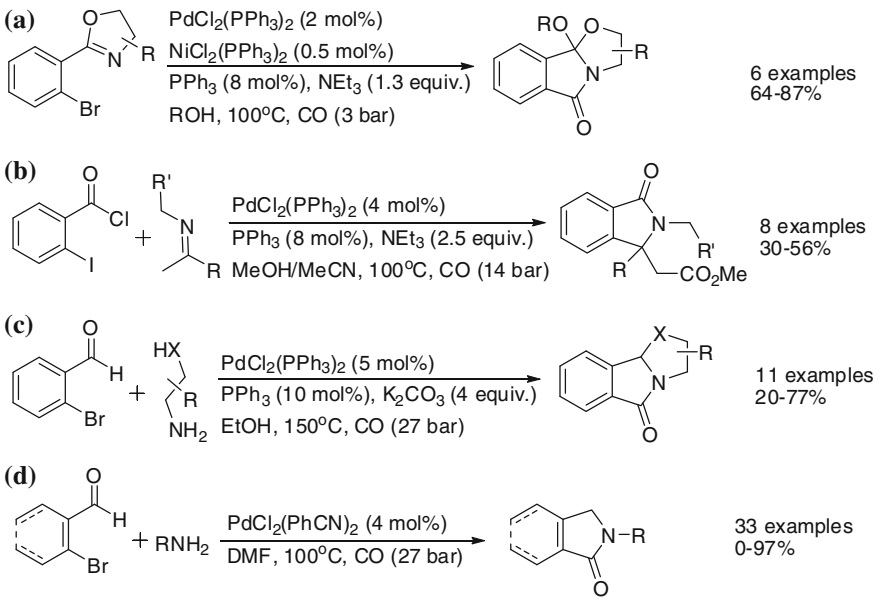


Scheme 2.33 Palladium-catalyzed carbonylative synthesis of isoindolin-1-ones

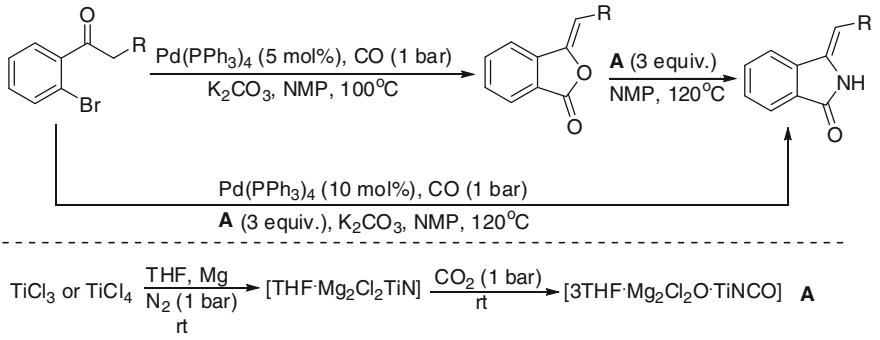
intramolecular acylpalladation to the imine gives the alkylpalladium(II) intermediate. Subsequent hydrogenolysis with molecular hydrogen leads to the isoindolin-1-one. It is assumed that hydrogen is produced by the reaction of CO with H2O generated in the initial condensation stage.

Mori and Shibasaki's group described the use of a special titanium-isocyanate complex for a novel one-step synthesis of isoindolinones and quinazolinones starting from *o*-halophenyl alkyl ketones [260]. As shown in Scheme 2.35, this reaction proceeds through the oxidative addition of the enol lactone, generated by palladium-catalyzed carbonylation of *o*-halophenyl alkyl ketones, to the titanium-isocyanate complex **A**.

In addition to isoindolinones, several methods for the preparation of phthalimides have been developed in the last two decades. In 1991, Perry's group reported on the carbonylative coupling of *o*-dihaloarenes with primary amines to phthalimides [261]. As shown in Scheme 2.36a, using $PdCl_2$ as a catalyst and DBU as a base, phthalimides were produced in good yields in DMAc. The group also succeeded in applying similar reaction conditions for the carbonylative synthesis of 2-arylbenzoxazoles and 2-arylbenzimidazoles [262–264]. Here, aryl halides were coupled with *o*-fluoroanilines and *o*-phenylenediamines to give 2-arylbenzoxazoles and 2-arylbenzimidazoles, respectively. More recently, Alper extended this methodology to 1,2-dibromobenzenes. The substrates were successfully transformed by using phosphonium salt-based ionic liquids as their solvent under 1 bar of CO [265]. This process showed a broad tolerance for



Scheme 2.34 Palladium-catalyzed carbonylative synthesis towards isoindolin-1-ones



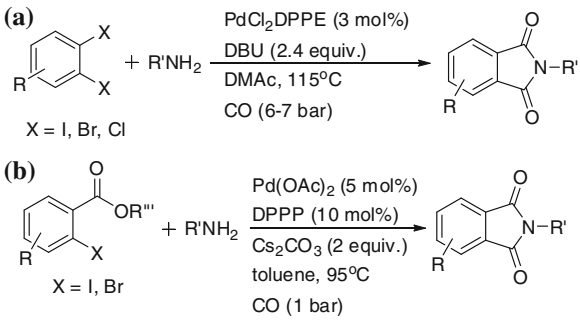
Scheme 2.35 Palladium-catalyzed carbonylative synthesis of isoindolin-1-ones

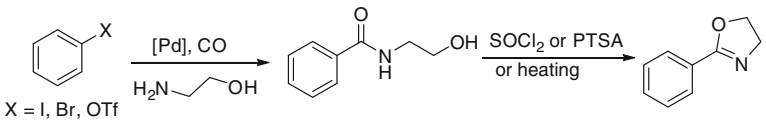
functional groups and excellent yields of products were obtained. The recyclability of the catalytic system was also investigated. Larock's group developed the straightforward carbonylation of *o*-halobenzoates and primary amines to phthalimides [266]. This method gave the corresponding products in good yields, and tolerated various functional groups (Scheme 2.36b). Later on, Queirz and his team showed that it is also possible to perform similar reactions under CO-free conditions by using $Mo(CO)_6$ as a CO source [267].

Meyers and colleagues described the palladium-catalyzed carbonylative synthesis of oxazolines as early as 1992 [268]. Aryl or enol triflates made from the corresponding ketones and phenols, and also aryl halides, were used as starting materials and coupled with amino alcohols to give chiral α,β-unsaturated or aryl oxazolines in good yields. Later on, Perry's group performed systematic studies on this one-pot, two-step process for the preparation of oxazolines (Scheme 2.37) [269, 270].

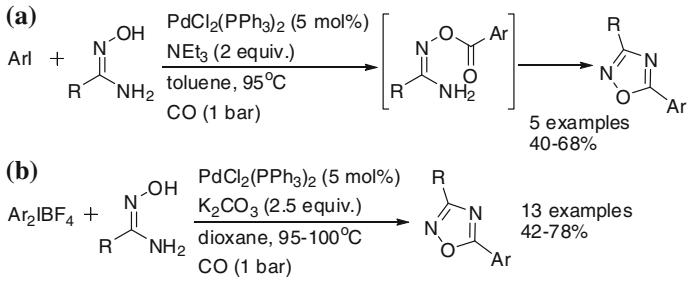
Young and DeVita developed a novel procedure for the synthesis of oxadiazoles (Scheme 2.38a) [271]. Various oxadiazoles were prepared in moderate yields from aryl iodides and amidoximes under 1 bar of CO in a one-pot manner. Both electron-withdrawing and electron-donating substituents were tolerated.

Scheme 2.36 Palladium-catalyzed carbonylative syntheses of phthalimides





Scheme 2.37 Palladium-catalyzed carbonylative syntheses of oxazolines



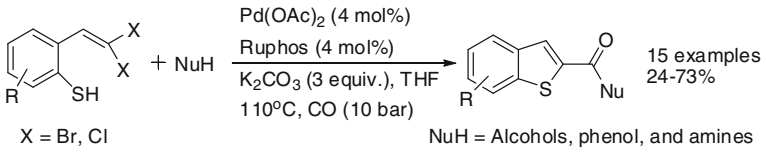
Scheme 2.38 Palladium-catalyzed carbonylative syntheses of oxadiazoles

Afterwards, Chen and Zhou described a similar reaction with diaryliodonium salts as starting materials (Scheme 2.38b) [272].

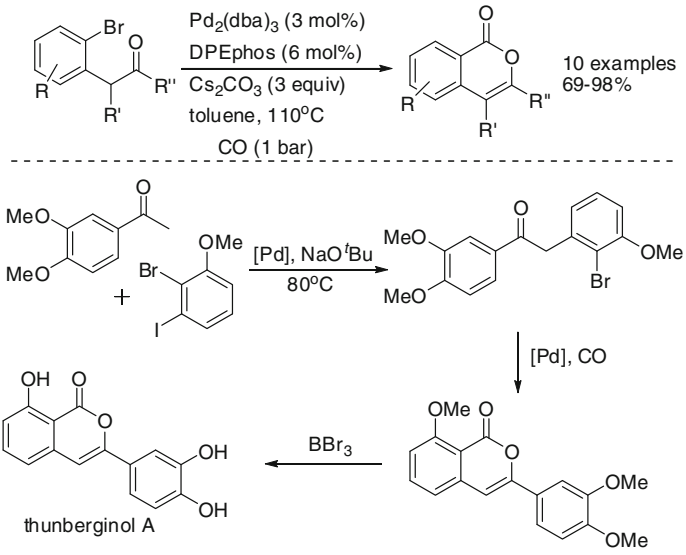
A facile and selective palladium-catalyzed carbonylative domino synthesis of benzothiophenes was developed by Alper and Zeng in 2011 [273]. 2-Carbonylbenzo[*b*]thiophene derivatives were produced from 2-*gem*-dihalovinylthiophenols in 24–73 % yields (Scheme 2.39). This protocol involved an intramolecular C–S coupling/intermolecular carbonylation cascade sequence and allowed for access to various highly functionalized benzo[*b*]thiophenes.

In 2004, Willis's group demonstrated that in situ-generated enolates can be used as intramolecular nucleophiles in palladium-catalyzed aryl-carbonylation reactions to give the corresponding isocoumarins [274]. At 1 bar of CO, good yields were achieved with both cyclic and acyclic ketones as substrates. Later on, they also used this methodology in a concise synthesis of the natural product thunberginol A (Scheme 2.40).

Recently, Beller's group developed several novel procedures for palladium-catalyzed carbonylative synthesis heterocycles with alkoxycarbonylation or aminocarbonylation as the key step (Scheme 2.41) [275–279]. Starting from the



Scheme 2.39 Palladium-catalyzed carbonylative synthesis of benzothiophenes

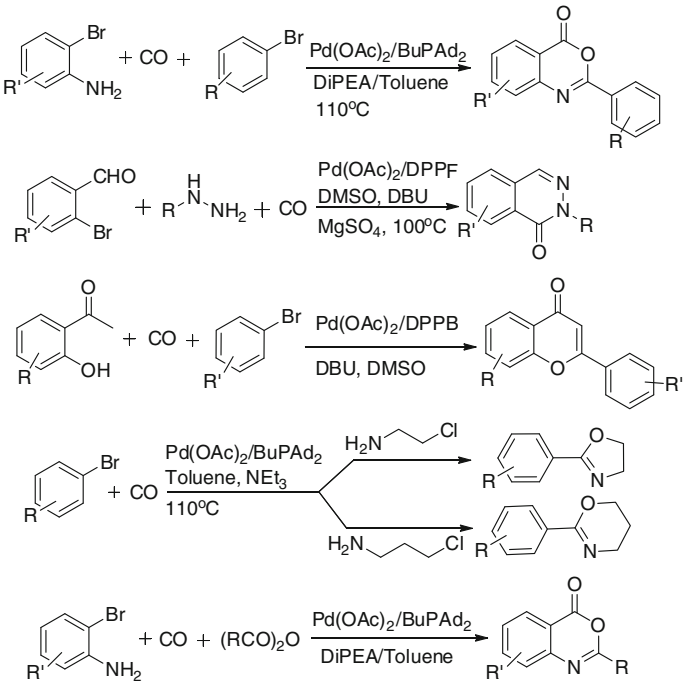


Scheme 2.40 Palladium-catalyzed carbonylative synthesis of isocumarins

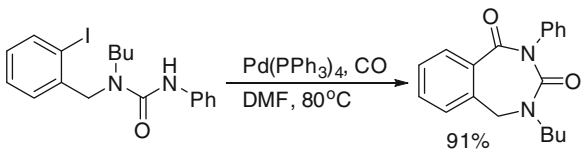
corresponding substrates in the presence of a palladium catalyst under CO pressure, the desired products were produced in good yields.

While most of the carbonylative cyclizations focused on the formation of five- and six-membered rings, there are also a few examples known for the preparation of larger rings. For example, in 1999 the palladium-catalyzed synthesis of a 2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepine-1,3-dione derivative was reported by Bocelli et al. [280]. Using 1-butyl-1(*o*-iodobenzyl)-3-phenylurea as a starting material at 80 °C under CO pressure, 91 % of the desired product was isolated (Scheme 2.42).

Alper and Lu developed a more general and efficient method for the synthesis of oxygen, nitrogen, or sulphur containing medium ring-fused heterocycles with recyclable palladium-complexed dendrimers on silica as catalysts [281–283]. Their process tolerates a wide array of functional groups, including halide, ether, nitrile, ketone, and ester. The dendritic catalysts showed high activity affording the heterocycles' excellent yields (Scheme 2.43). Importantly, these catalysts were easily recovered by simple air filtration and could be reused up to the eight cycles with only a slight loss of activity. Recently, the same researchers used PdI_2 and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane (Cytop 292) as an in situ-formed palladium complex for the intramolecular carbonylation of substituted 2-(2-iodophenoxy)anilines [284]. A series of substituted dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones were prepared in good yields under mild reaction conditions. This type of aminocarbonylation was also applied in the synthesis of C-14 labelled heterocycles [285].



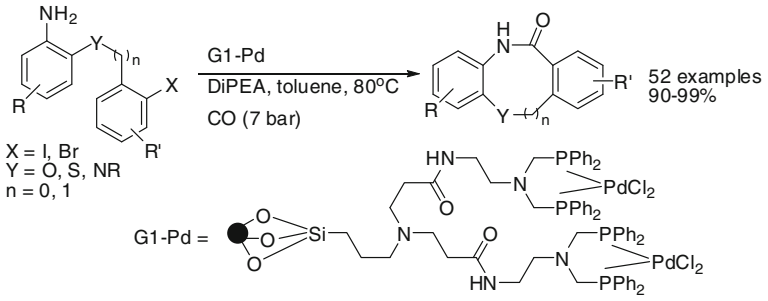
Scheme 2.41 Carbonylative syntheses of heterocycles



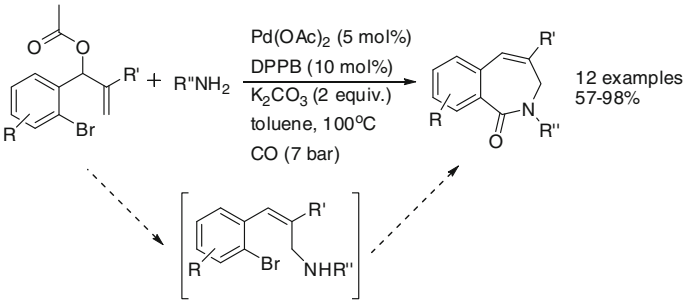
Scheme 2.42 Palladium-catalyzed carbonylative synthesis of benzodiazepinedione

More recently, Alper and colleagues described a convenient protocol for the synthesis of substituted benzazepine derivatives (Scheme 2.44) [286]. This protocol is based on the sequential palladium-catalyzed allylic amination and a subsequent intramolecular carbonylation reaction. The substrates were obtained by a Baylis–Hillman reaction.

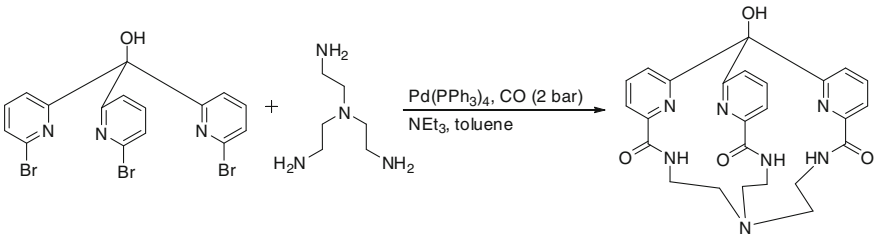
Larock and Cho developed a palladium-catalyzed intramolecular cyclocarbonylation of hydroxyl-substituted 3-iodofurans leading to the corresponding lactone-containing furans [287]. The 3-iodofurans are readily prepared by iodocyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various diols. Meanwhile, a neat one-pot synthesis of a cryptand was developed by using a palladium-catalyzed carbonylation reaction (Scheme 2.45) [288]. Finally, the Takahashi and Doi group also elegantly applied carbonylations for the preparation of macrosphelide and related macrolactams [289–291].



Scheme 2.43 Palladium-catalyzed carbonylative synthesis of benzodiazepinediones



Scheme 2.44 Palladium-catalyzed carbonylative syntheses of seven-membered lactams

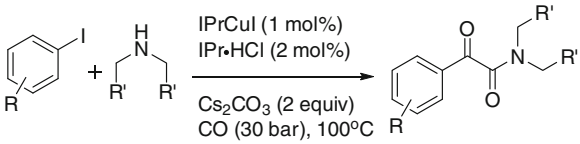


Scheme 2.45 Palladium-catalyzed carbonylative synthesis of H_3L

Copper as cheap metal was also applied in carbonylation reactions. In 2009 Xia and colleagues described a general and efficient copper-catalyzed double aminocarbonylation of aryl iodides (Scheme 2.46) [292]. Using an NHC–Cu catalyst, aryl iodides were double carbonylated with amines in good yields (72–93 %).

In 1990 Alper and Lee reported on a cobalt-catalyzed carbonylation of aryl iodides and alkyl iodides [293, 294]. In the presence of cobalt chloride or acetate, potassium cyanide, base, and PEG-400, carboxylic acids were produced from the corresponding iodo compounds. Lewis acids, such as boron trifluoride etherate

Scheme 2.46 Copper-catalyzed double carbonylation of aryl iodides



with $FeCl_2$ as promoters, were needed. Later on they found that $Co_2(CO)_8$ can effectively transform benzyl chlorides and bromides to the corresponding acid products in an aqueous system. η^1-Benzyl-, η^3-Benzyl, and (η^1-phenylacetyl)cobalt carbonyls were investigated as intermediates of this process.

In 1970 Hashimoto published a report on the reaction of potassium hexacyanodinickelate with organic halides in aqueous solutions [295]. Benzyl bromides were transformed into dibenzyl ketones in the presence of CO in a water–acetone solution. If the reaction was carried out in a water–methanol solution, *trans*-β-bromostyrene was transformed into methyl *trans*-cinnamat. Surprisingly, cinnamaldehyde was also formed in a 10 % yield (Scheme 2.47). The reaction of nickel carbonyl [$Ni(CO)_4$] with organic halides was studied by Bauld in 1963 [296]. Aryl iodides were reacted with $Ni(CO)_4$ in methanol and produced the corresponding methyl benzoate in good yields. If the reaction was carried out in THF, arils were formed. The reaction of allyl halides with $Ni(CO)_4$ in the presence of MgO will produce but-3-enylsuccinic acid [297].

Alper and his team developed nickel cyanide-catalyzed carbonylation of aryl iodides and allyl halides in an aqueous solution under the assistant of phase transfer reagent [298, 299]. Carboxylic acid derivates were produced in good yields. In the case of carbonylation of allyl halides, the catalytically active species [$Ni(CO)_3CN^-$] was isolated and characterized (Table 2.1). Mechanistic studies based on experimental and DFT calculation were also carried out by various groups [300, 301].

Yamane and Ren established an efficient molybdenum-mediated carbamoylation of aryl halides [302, 303]. The procedure is simple and requires only a slight excess of carbon monoxide in the form of $Mo(CO)_6$. This reaction provides a method for the synthesis of a variety of amides. Primary amides are also prepared in the reaction with aqueous ammonia (Scheme 2.48). Roberts and colleagues reported a similar reaction with microwave irradiation.

Scheme 2.47 Nickel mediated carbonylation reactions

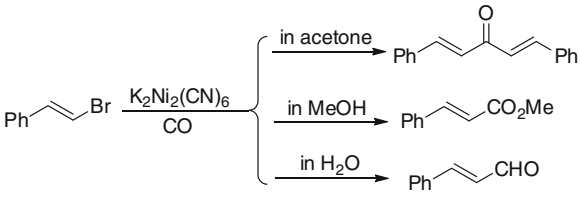


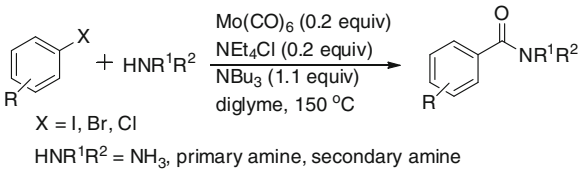
Table 2.1 Nickel-catalyzed carbonylation of organo halides

$R \times \longrightarrow [5N\,NaOH, solvent\,PTC]Ni(CN)_2 4H_2O(10\ mol\ \%\ )RCO_2H$

Substrate	Product	Isolated yield (%)
C_6H_5I	$C_6H_5CO_2H$	80[a]
$4\text{-}CH_3C_6H_4I$	$4\text{-}CH_3C_6H_4CO_2H$	65[a]
$3\text{-}CH_3C_6H_4I$	$3\text{-}CH_3C_6H_4CO_2H$	45[a]
$2\text{-}CH_3C_6H_4I$	$2\text{-}CH_3C_6H_4CO_2H$	80[a]
$4\text{-}ClC_6H_4I$	$4\text{-}ClC_6H_4CO_2H$	60[a]
$4\text{-}CH_3OC_6H_4I$	$4\text{-}CH_3OC_6H_4CO_2H$	40[a]
$2\text{-}HOCH_2C_6H_4I$	$2\text{-}HOCH_2C_6H_4CO_2H$	60[a]
$1\text{-}C_{10}H_7I$	$1\text{-}C_{10}H_7CO_2H$	60[a]
$PhCHCHCH_2Br$	$PhCHCHCH_2CO_2H$	67[b]
$PhCHCHCH_2Cl$	$PhCHCHCH_2CO_2H$	84[b]

[a] in toluene, $C_{16}H_{33}N(CH_3)_3^{\pm}Br^-$
[b] in 4-methyl-2-pentanone, tetrabutylammonium hydrogen sulfate

Scheme 2.48 $Mo(CO)_6$-mediated aminocarbonylation of aryl halides



In this chapter we have discussed the carbonylative transformations of C–X bonds using amines, alcohols and water as nucleophiles. From a reaction mechanism point of view, they all go through a nucleophilic attack on the acylmetal species by nucleophiles. No reductive elimination step was involved, and the active catalyst was regenerated under the assistant of base.

In Chap. 3, we will discuss using H^+ as a nucleophile for aldehydes production.

References

1. Yoneda, N., Kusano, S., Yasui, M., Pujado, P., Wilcher, S.: Appl. Catal. A: General **221**, 253 (2001)
2. Kutenpov, N., Himmele, W., Hohenshutz, H.: Hydrocarbon Proc. **45**, 141 (1996)
3. Paulik, F.E., Roth, J.R.: J. Am. Chem. Soc. Chem. Commun. 1578 (1968)
4. Grove, H.D.: Hydrocarbon Proc. **51**, 76 (1972)
5. US Patent 3769329 (1973)
6. Howard, K.J., Jones, M.D., Roberts, M.S., Taylor, S.A.: Catal. Today **18**, 325 (1993)
7. Murphy, M.A., Smith, B.L., Torrence, G.P., Agulio, A.J.: Organomet. Chem. **303**, 257 (1986)
8. Smith, B.L., Torrence, G.P., Murphy, M.A., Agulio, A.J.: Mol. Catal. **39**, 115 (1987)
9. Moser, W.R., Marshik-Guerts, B.J., Okrasinski, S.J.J.: Mol. Catal. A: Chem. **143**, 57 (1999)
10. Moser, W.R., Marshik-Guerts, B.J., Okrasinski, S.J.J.: Mol. Catal. A: Chem. **143**, 71 (1999)

11. Foster, D.: Adv. Organomet. Chem. **17**, 255 (1979)
12. Sunley, G.J., Watson, D.J.: Catal. Today **58**, 293 (2000)
13. Jones, J.H.: Platinum Metals Rev. **44**, 94 (2000)
14. Maitlis, P.M., Haynes, A., Sunley, G., Howard, M.J.: *J. Chem. Soc. Dalton Trans.* 2187 (1996)
15. Thomas, C.M., Süss-Fink, G.: Coord. Chem. Rev. **243**, 125 (2003)
16. Haynes, A.: Top. Organomet. Chem. **18**, 179 (2006)
17. Cheong, M., Schmid, R., Ziegler, T.: Organometallics **2000**, 19 (1973)
18. Griffin, T.R., Cook, D.B., Haynes, A., Pearson, J.M., Monti, D., Morris, G.E.J.: Am. Chem. Soc. **118**, 3029 (1996)
19. Ivanova, E.A., Gisdakis, P., Nasluzov, V.A., Rubailo, A.I., Rösch, N.: Organomtalics **20**, 1161 (2001)
20. Kinnunen, T., Laasonen, K.J.: Organomet. Chem. **628**, 222 (2001)
21. Rankin, J., Benyei, A.C., Poole, A.D., Cole-Hamilton, D.J.: J. Chem. Soc. Dalton Trans. 3771 (1999)
22. Wegman, R.W., Abatjoglou, A.G., Harrison, A.M.: J. Chem. Soc. Chem. Commun. 1891 (1987)
23. Baker, M.J., Giles, M.F., Orpen, A.G., Taylor, M. J., Watt, R.J.: J. Chem. Soc. Chem. Commun. 197 (1995)
24. Gonsalvi, L., Adams, H., Sunley, G.J., Ditzel, E., Haynes, A.J.: Am. Chem. Soc. **121**, 11233 (1999)
25. Gonsalvi, L., Adams, H., Sunley, G.J., Ditzel, E., Haynes, A.J.: Am. Chem. Soc. **124**, 13597 (2002)
26. Dilworth, J.R., Miller, J.R., Wheatley, N., Baker, M.J., Sunley, J.G.: J. Chem. Soc. Chem. Commun. 197 (1995)
27. Dutta, D.K., Woollins, J.D., Slawin, A.M.Z., Konwar, D., Das, P., Sharma, M., Bhattacharyya, P., Aucott, S.M.: Dalton Trans. 2674 (2003)
28. Carraz, C.A., Ditzel, E., Orpen, A.G., Ellis, D.D., Pringle, P.G.; Sunley, G.J.: Chem. Commun. 1277 (2000)
29. Thomas, C.M., Mafua, R., Therrien, B., Rusanov, E., Stockli-Evans, H., Süss-Fink, G.: Chem. Eur. J. **8**, 3343 (2002)
30. Burger, S., Therrien, B., Süss-Fink, G.: Helve. Chim. Acta **88**, 478 (2005)
31. Best, J., Wilson, J.M., Adams, H., Gonsalvi, L., Peruzzini, M., Haynes, A.: Organometallics **2007**, 26 (1960)
32. Jimenez-Rodriguez, C., Pogorzelec, P.J., Eastham, G.R., Slawin, A.M.Z., Cole-Hamilton, D.J.: Dalton Trans. 4160 (2007)
33. Lamb, G., Clarke, M., Slawin, A.M.Z., Williams, B., Key, L.: Dalton Trans. 5582 (2007)
34. Lamb, G.W., Clarke, M.L., Slawin, A.M.Z., Williams, B.: Dalton Trans. 4946 (2008)
35. Deb, B., Dutta, D.K.J.: Mol. Catal. A: Chem. **326**, 21 (2010)
36. Williams, G.L., Parks, C.M., Smith, C.R., Adams, H., Haynes, A., Meijer, A.J.H.M., Sunley, G.J., Gaemers, S.: Organometallics **30**, 6166 (2011)
37. Dingwall, L.D., Lee, A.F., Lynam, J.M., Wilson, K., Olivi, L., Deeley, J.M.S., Gaemers, S., Sunley, G.J.: ACS Catal. **2**, 1368 (2012)
38. Gonsalvi, L., Gaunt, J.A., Adams, H., Castro, A., Sunley, G.J., Haynes, A.: Organometallics **2003**, 22 (1047)
39. Martin, H.C., James, N.H., Aitken, J., Gaunt, J.A., Adams, H., Haynes, A.: Organometallics **22**, 4451 (2003)
40. Riisager, A., Jorgensen, B., Wasserscheid, P., Fehrmann, R.: Chem. Commun. 994 (2006)
41. Drago, R.S., Nyberg, E.D., El A'mma, A., Zombeck, A.: Inorg. Chem. **3**, 641 (1981)
42. Haynes, A., Maitlis, P.M., Quyoum, R., Pulling, C., Adams, H., Spey, S.E., Strangew, R.W.: J. Chem. Soc. Dalton Trans. 2565 (2002)
43. Garland, C.S., Giles, M.F., Sunley, J.G.: EP0643034 to BP Chemicals (1995)
44. Baker, M.J., Giles, M.F., Garland, C.S., Rafeletos, G.: EP0749948 to BP Chemicals (1996)
45. Garland, C.S., Giles, M.F., Poole, A.D., Sunley, J.G.: EP0728726 to BP Chemicals (1996)

46. Baker, M.J., Giles, M.F., Garland, C.S., Muskett, M.J., Rafeletos, G., Smith, S.J., Sunley, J.G., Watt, R.J., Williams, B.L.: EP0752406 to BP Chemicals (1997)
47. Dekleva, T.W., Forster, D.: Adv. Catal. **34**, 100 (1986)
48. Marr, A.C., Ditzel, E.J., Benyei, A.C., Lightfoot, P., Cole-Hamilton, D.J.: Chem. Commun. 1379 (1999)
49. Jayasree, S., Seayad, A., Chaudhari, R.V.: Org. Lett. **2**, 203 (2000)
50. Mukhopadhyay, K., Sarkar, B.R., Chaudhari, R.V.J.: Am. Chem. Soc. **124**, 9692 (2002)
51. Ormsby, G., Hargreaves, J.S.J., Ditzel, E.J.: Catal. Commun. **10**, 1292 (2009)
52. Cunico, R.F., Maity, B.C.: Org. Lett. **3**, 4947 (2003)
53. Xu, J., Burton, D.J.J.: Org. Chem. **70**, 4346 (2005)
54. Xu, J., Burton, D.J.: Org. Lett. **4**, 831 (2002)
55. Wesolowski, C.A., Burton, D.J.: Tetrahedron Lett. **40**, 2243 (1999)
56. Hara, S., Yamamoto, K., Yoshida, M., Fukuhara, T., Yoneda, N.: Tetrahedron Lett. **40**, 7815 (1999)
57. Balogh, J., Zsoldos-Mády, V., Frigyes, D., Bényei, A.C., Skoda-Földes, R., Sohár, P.J.: Organomet. Chem. **692**, 1614 (2007)
58. Ács, P., Müller, E., Czira, G., Mahó, S., Perreira, M., Kollár, L.: Steroids **71**, 875 (2006)
59. Szarka, Z., Skoda-Földes, R., Horváth, J., Tuba, Z., Kollár, L.: Steroids **67**, 581 (2002)
60. Skoda-Földes, R., Szarka, Z., Kollár, L., Dinya, Z., Horváth, J., Tuba, Z.J.: Org. Chem. **64**, 2134 (1999)
61. Yu, M.S., Baine, N.H.: Tetrahedron Lett. **40**, 3123 (1999)
62. Skoda-Földes, R., Csákai, Z., Kollár, L., Szalontai, G., Horváth, J., Tuba, Z.: Steroids **60**, 786 (1995)
63. Tsukada, N., Ohba, Y., Inoue, Y.J.: Organomet. Chem. **687**, 436 (2003)
64. Zhou, T., Chen, Z.-C.: J. Chem. Res. 116 (2001)
65. Lin, Y.-S., Alper, H.: Angew. Chem. Int. Ed. **40**, 779 (2001)
66. Couve-Bonnaire, S., Carpentier, J.-F., Castanet, Y., Mortreux, A.: Tetrahedron Lett. **40**, 3717 (1999)
67. Huang, L., Ozawa, F., Yamamoto, A.: Organometallics **9**, 2603 (1990)
68. Urata, H., Ishii, Y., Fuchikami, T.: Tetrahedron Lett. **30**, 4407 (1989)
69. Son, T., Yanagihara, H., Ozawa, F., Yamamoto, A.: Bull. Chem. Soc. Jpn. **61**, 1251 (1988)
70. Yamashita, H., Sakakura, T., Kobayashi, T., Tanaka, M.J.: Mol. Catal. **48**, 69 (1988)
71. Sakakura, T., Yamashita, H., Kobayashi, T., Hayashi, T., Tanaka, M.J.: Org. Chem. **52**, 5733 (1987)
72. Ozawa, F., Kawasaki, N., Okamoto, H., Yamamoto, T., Yamamoto, A.: Organometallics **6**, 1640 (1987)
73. Morin, B., Hirschauer, A., Hugues, F., Commereuc, D., Chauvin, Y.J.: Mol. Catal. **34**, 317 (1986)
74. Ozawa, F., Yanagihara, H., Yamamoto, A.J.: Org. Chem. **51**, 415 (1986)
75. Tanaka, M., Kobayashi, T., Sakakura, T.: J. Chem. Soc., Chem. Commun.837 (1985)
76. Ozawa, F., Kawasaki, N., Yamamoto, T., Yamamoto, A.: Chem. Lett. **14**, 567 (1985)
77. Ozawa, F., Soyama, H., Yanagihara, H., Aoyama, I., Takino, H., Izawa, K., Yamamoto, T., Yamamoto, A.J.: Am. Chem. Soc. **107**, 3235 (1985)
78. Tanaka, M., Kobayashi, T., Sakakura, T., Itatani, H., Danno, S., Zushi, K.J.: Mol. Catal. **32**, 115 (1985)
79. Ozawa, F., Sugimoto, T., Yuasa, Y., Santra, M., Yamamoto, T., Yamamoto, A.: Organometallics **3**, 683 (1984)
80. Ozawa, F., Yamamoto, A.: Chem. Lett. **11**, 865 (1982)
81. Kobayashi, T., Tanaka, M.J.: Organomet. Chem. **233**, C64 (1982)
82. Ozawa, F., Soyama, H., Yamamoto, T., Yamamoto, A.: Tetrahedron Lett. **23**, 3383 (1982)
83. Uozumi, Y., Arii, T., Watanabe, T.J.: Org. Chem. **66**, 5272 (2001)
84. Vinogradov, S.A., Wilson, D.F.: Tetrahedron Lett. **39**, 8935 (1998)
85. Chambers, R.J., Marfat, A.: Synth. Commun. **27**, 515 (1997)
86. Cai, M. -Z., Song, C.-S., Huang, X.: J. Chem. Soc., Perkin Trans. **1**, 2273 (1997)

87. Kubota, Y., Hanaoka, T., Takeuchi, K., Sugi, Y.J.: Mol. Catal. A: Chem. **111**, L187 (1996)
88. Satoh, T., Ikeda, M., Miura, M., Nomura, M.J.: Mol. Catal. A: Chem. **111**, 25 (1996)
89. Kubota, Y., Takeuchi, K., Hanaoka, T., Sugi, Y.: Catal. Today **31**, 27 (1996)
90. Kubota, Y., Hanaoka, T., Takeuchi, K., Sugi, Y.: Synlett 515 (1994)
91. Kubota, Y., Hanaoka, T., Takeuchi, K., Sugi, Y.: J. Chem. Soc., Chem. Commun. 1553 (1994)
92. Moser, W.R., Wang, A.W., Kildahl, N.K.J.: Am. Chem. Soc. **110**, 2816 (1988)
93. Stille, J.K., Wong, P.K.J.: Org. Chem. **40**, 532 (1975)
94. Hidai, M., Hikita, T., Wada, Y., Fujikura, Y., Uchida, Y.: Bull. Chem. Soc. Jpn. **48**, 2075 (1975)
95. Arcadi, A., Cacchi, S., Fabrizi, G., Marinelli, F., Moro, L.: Synlett 1432 (1999)
96. Takahashi, T., Inoue, H., Tomida, S., Doi, T.: Tetrahedron Lett. **40**, 7843 (1999)
97. Iro, T., Mori, K., Mizoroki, T., Ozaki, A.: Bull. Chem. Soc. Jpn. **48**, 2091 (1975)
98. Wu, G.G., Wong, Y., Poirier, M.: Org. Lett. **1**, 745 (1999)
99. Kihlberg, T., Långström, B.J.: Org. Chem. **64**, 9201 (1999)
100. Cai, M.-Z., Song, C.-S., Huang, X.: Synth. Commun. **27**, 361 (1997)
101. Horino, H., Sakaba, H., Arai, M.: Synthesis 715 (1989)
102. Kobayashi, T., Tanaka, M.J.: Organomet. Chem. **231**, C12 (1982)
103. Elmore, C.S., Dean, D.C., Melillo, D.G.J.: Labelled Compd. Radiopharm. **43**, 1135 (2000)
104. Uozumi, Y., Watanabe, T.J.: Org. Chem. **64**, 6921 (1999)
105. Cheprakov, A.V., Ponomareva, N.V., Beletskaya, I.P.J.: Organomet. Chem. **486**, 297 (1995)
106. Grushin, V.V., Alper, H.: Organometallics **12**, 3846 (1993)
107. Bumagin, N.A., Niitin, K.V., Beletskaya, I.P.J.: Organomet. Chem. **358**, 563 (1988)
108. Schoenberg, A., Bartoletti, I., Heck, R.F.J.: Org. Chem. **39**, 3318 (1974)
109. Mägerlein, W., Beller, M., Indolese, A.F.J.: Mol. Catal. A: Chem. **156**, 213 (2000)
110. Ramesh, C., Kubota, Y., Miwa, M., Sugi, Y.: Synthesis 2171 (2002)
111. Ko, S., Lee, C., Choi, M.-G., Na, Y., Chang, S.J.: Org. Chem. **68**, 1607 (2003)
112. Ramesh, C., Nakamura, R., Kubota, Y., Miwa, M., Sugi, Y.: Synthesis 501 (2003)
113. Ley, S.V., Ramarao, C., Gordon, R.S., Holmes, A.B., Morrison, A.J., McConvey, I.F., Shirley, I.M., Smith, S.C., Smith, M.D.: Chem. Commun. 1134 (2002)
114. Albaneze-Walker, J., Bazaral, C., Leavey, T., Dormer, P.G., Murry, J.A.: Org. Lett. **6**, 2097 (2004)
115. Wu, X.-F., Neumann, H., Beller, M.: ChemCatChem **2**, 509 (2010)
116. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **18**, 3831 (2012)
117. Kulkarni, S.M., Kelkar, A.A., Chaudhari, R.V.: Chem. Commun. 1276 (2001)
118. Schoenberg, A., Heck, R.F.J.: Org. Chem. **39**, 3327 (1974)
119. Morimoto, T., Kakiuchi, K.: Angew. Chem. Int. Ed. **43**, 5580 (2004)
120. Hosoi, K., Nozaki, K., Hiyama, T.: Org. Lett. **4**, 2849 (2002)
121. Cunico, R.F., Maity, B.C.: Org. Lett. **4**, 4357 (2002)
122. Bjerglund, K., Lindhardt, A.T., Skrydstrup, T.J.: Org. Chem. **77**, 3793 (2012)
123. Nielsen, D.U., Neumann, K., Taaning, R.H., Lindhardt, A.T., Modvig, A., Skrydstrup, T.J.: Org. Chem. **77**, 6155 (2012)
124. Burhardt, M.N., Taaning, R., Nielsen, N.C., Skrydstrup, T.J.: Org. Chem. **77**, 5357 (2012)
125. Yamazaki, K., Kondo, Y.J.: Comb. Chem. **6**, 121 (2004)
126. Szarka, Z., Kuik, A., Skoda-Földes, R., Kollár, L.J.: Organomet. Chem. **689**, 2770 (2004)
127. Szarka, Z., Skoda-Földes, R., Kuik, Á., Berente, Z., Kollár, L.: Synthesis 545 (2003)
128. Szarka, Z., Skoda-Földes, R., Kollár, L.: Tetrahedron Lett. **42**, 739 (2001)
129. Schnyder, A., Indolese, A.F.J.: Org. Chem. **67**, 594 (2002)
130. Kumar, K., Zapf, A., Michalik, D., Tillack, A., Heinrich, T., Böttcher, H., Arlt, M., Beller, M.: Org. Lett. **6**, 7 (2004)
131. Morera, E., Ortar, G.: Tetrahedron Lett. **39**, 2835 (1998)
132. Schnyder, A., Beller, M., Mehltretter, G., Nsenda, T., Studer, M., Indolese, A.F.J.: Org. Chem. **66**, 4311 (2001)
133. Ueda, K., Sato, Y., Mori, M.J.: Am. Chem. Soc. **122**, 10722 (2000)

134. Takács, E., Varga, C., Skoda-Földes, R., Kollár, L.: Tetrahedron Lett. **48**, 2453 (2007)
135. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **16**, 9750 (2010)
136. Wu, X.-F., Neumann, H., Beller, M.: Chem. Asian J. **5**, 2168 (2010)
137. Wu, X.-F., Schranck, J., Neumann, H., Beller, M.: Tetrahedron Lett. **52**, 3702 (2011)
138. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **18**, 419 (2012)
139. Wu, X.-F., Schranck, J., Neumann, H., Beller, M.: ChemCatChem **4**, 69 (2012)
140. Neumann, H., Brennführer, A., Groß, P., Riermeier, T., Almena, J., Beller, M.: Adv. Synth. Catal. **348**, 1255 (2006)
141. Brennführer, A., Neumann, H., Pews-Davtyan, A., Beller, M.: Eur. J. Org. Chem. 38 (2009)
142. Cacchi, S., Fabrizi, G., Goggiamani, A.: Org. Lett. **3**, 4269 (2003)
143. Berger, P., Bessmernykh, A., Caille, J. -C., Mignonac, S.: Synthesis 3106 (2006)
144. Cacchi, S., Cotet, C.L., Fabrizi, G., Forte, G., Goggiamani, A., Martín, L., Martínez, S., Molins, E., Moreno-Manãs, M., Petrucci, F., Roig, A., Vallribera, A.: Tetrahedron **63**, 2519 (2007)
145. Lou, R., VanAlstine, M., Sun, X., Wentland, M.P.: Tetrahedron Lett. **44**, 2477 (2003)
146. Rahman, O., Kihlberg, T., Långström, B.J.: Org. Chem. **68**, 3558 (2003)
147. Rahman, O., Kihlberg, T., Långström, B.: J. Chem. Soc., Perkin Trans. **1**, 2699 (2002)
148. Gerlach, U., Wollmann, T.: Tetrahedron Lett. **33**, 5499 (1992)
149. Cacchi, S., Lupi, A.: Tetrahedron Lett. **33**, 3939 (1992)
150. Dolle, R.E., Schmidt, S.J., Kruse, L.I.: J. Chem. Soc., Chem. Commun. 904 (1987)
151. Cacchi, S., Ciattini, P.G., Morera, E., Ortar, G.: Tetrahedron Lett. **27**, 3931 (1986)
152. Siegrist, U., Rapold, T., Blaser, H.-U.: Org. Proc. Res. Dev. **7**, 429 (2003)
153. Sengupta, S., Sadhukhan, S.K., Bhattacharyya, S., Guha, J.: J. Chem. Soc., Perkin Trans. **1**, 407 (1998)
154. Kikukawa, K., Kono, K., Nagira, K., Wada, F., Matsuda, T.J.: Org. Chem. **46**, 4413 (1981)
155. Kikukawa, K., Kono, K., Nagira, K., Wada, F., Matsuda, T.: Tetrahedron Lett. **21**, 2877 (1980)
156. Nagira, K., Kikukawa, K., Wada, F., Matsuda, T.J.: Org. Chem. **45**, 2365 (1980)
157. Zhou, T., Chen, Z.-C.: Synth. Commun. **32**, 887 (2002)
158. Wang, L., Chen, Z.-C.: Synth. Commun. **31**, 1633 (2001)
159. Zhou, T., Chen, Z.-C.: J. Chem. Res. 235 (2001)
160. Wang, L., Chen, Z.-C.: J. Chem. Res. 372 (2000)
161. Xia, M., Chen, Z.-C.: J. Chem. Res. (S) 328 (1999)
162. Kang, S.-K., Yamaguchi, T., Ho, P.-S., Kim, W.-Y., Ryu, H.-C.: J. Chem. Soc., Perkin Trans. **1**, 841 (1998)
163. Mizushima, E., Hayashi, T., Tanaka, M.: Green Chem. **3**, 76 (2001)
164. Fukuyama, T., Inouye, T., Ryu, I.J.: Organomet. Chem. **692**, 685 (2007)
165. Zhao, X., Alper, H., Yu, Z.J.: Org. Chem. **71**, 3988 (2006)
166. Zawartka, W., Trzeciak, A.M., Ziólkowski, J.J., Lis, T., Ciunik, Z., Pernak, J.: Adv. Synth. Catal. **348**, 1689 (2006)
167. Calò, V., Nacci, A., Monopoli, A.: Eur. J. Org. Chem., 3791 (2006)
168. Müller, E., Péczely, G., Skoda-Földes, R., Takács, E., Kokotos, G., Bellis, E., Kollár, L.: Tetrahedron **61**, 797 (2005)
169. Wojtków, W., Trzeciak, A.M., Choukroun, R., Pellegatta, J.L.J.: Mol. Catal. A: Chem. **224**, 81 (2004)
170. Mizushima, E., Hayashi, T., Tanaka, M.: Top. Catal. **29**, 163 (2004)
171. Skoda-Földes, R., Takács, E., Horváth, J., Tuba, Z., Kollár, L.: Green Chem. **5**, 643 (2003)
172. Trzeciak, A.M., Wojtków, W., Ziólkowski, J.J.: Inorg. Chem. Commun. **6**, 823 (2003)
173. Calò, V., Giannoccaro, P., Nacci, A., Monopoli, A.J.: Organomet. Chem. **645**, 152 (2002)
174. McNulty, J., Nair, J.J., Robertson, A.: Org. Lett. **9**, 4575 (2007)
175. Letavic, M.A., Ly, K.S.: Tetrahedron Lett. **48**, 2339 (2007)
176. Lesma, M., Sacchetti, A., Silvani, A.: Synthesis 594 (2006)
177. Wu, X., Wannberg, J., Larhed, M.: Tetrahedron **62**, 4665 (2006)
178. Wu, X., Ekegren, J.K., Larhed, M.: Organometallics **25**, 1434 (2006)

179. Wu, X., Larhed, M.: Org. Lett. **7**, 3327 (2005)
180. Wu, X., Rönn, R., Gossas, T., Larhed, M.J.: Org. Chem. **70**, 3094 (2005)
181. Herrero, M. A., Wannberg, J., Larhed, M.: Synlett 2335 (2004)
182. Georgsson, J., Hallberg, A., Larhed, M.J.: Comb. Chem. **5**, 350 (2003)
183. Wan, Y., Alterman, M., Larhed, M., Hallberg, A.J.: Comb. Chem. **5**, 82 (2003)
184. Wannberg, J., Larhed, M.J.: Org. Chem. **68**, 5750 (2003)
185. Wan, Y., Alterman, M., Larhed, M., Hallberg, A.J.: Org. Chem. **67**, 6232 (2002)
186. Kaiser, N.-F.K., Hallberg, A., Larhed, M.J.: Comb. Chem. **4**, 109 (2002)
187. Kormos, C.M., Leadbeater, N.E.: Org. Biomol. Chem. **5**, 65 (2007)
188. Kormos, C.M., Leadbeater, N.E.: Synlett 2006 (2007)
189. Kormos, C.M., Leadbeater, N.E.: Synlett 1663 (2006)
190. Appukkuttan, P., Axelsson, L., Van der Eycken, E., Larhed, M.: Tetrahedron Lett. **49**, 5625 (2008)
191. Odell, L.R., Russo, F., Larhed, M.: Synlett **23**, 685 (2012)
192. Huser, M., Youinou, M.-T., Osborn, J.A.: Angew. Chem. Int. Ed. **28**, 1386 (1989)
193. Ben-David, Y., Portnoy, M., Milstein, D.J.: Am. Chem. Soc. **111**, 8742 (1989)
194. Ben-David, Y., Portnoy, M., Milstein, D.: J. Chem. Soc., Chem. Commun. 1816 (1989)
195. Portnoy, M., Milstein, D.: Organometallics **12**, 1655 (1993)
196. Portnoy, M., Milstein, D.: Organometallics **12**, 1665 (1993)
197. Kim, J.S., Sen, A.J.: Mol. Catal. A: Chem. **143**, 197 (1999)
198. Mägerlein, W., Indolese, A.F., Beller, M.: Angew. Chem. Int. Ed. **40**, 2856 (2001)
199. Mägerlein, W., Indolese, A.F., Beller, M.J.: Organomet. Chem. **641**, 30 (2002)
200. Beller, M., Mägerlein, W., Indolese, A.F., Fischer, C.: Synthesis 1098 (2001)
201. Cai, C., Rivera, N.R., Balsells, J., Sidler, R.R., McWilliams, J.C., Shultz, C.S., Sun, Y.: Org. Lett. **8**, 5161 (2006)
202. Watson, D.A., Fan, X., Buchwald, S.L.J.: Org. Chem. **73**, 7096 (2008)
203. Munday, R.H., Martinelli, J.R., Buchwald, S.L.J.: Am. Chem. Soc. **130**, 2754 (2008)
204. Burhardt, M.N., Taaning, R., Nielsen, N.C., Skrystrup, T.: J. Org. Chem. **77**, 5357 (2012)
205. Jimenez-Rodriguez, C., Eastham, G.R., Cole-Hamilton, D.J.: Dalton Trans. 1826 (2008)
206. Dufaud, V., Thivolle-Cazat, J., Basset, J.-M.: J. Chem. Soc., Chem. Commun. 426 (1990)
207. Grushin, V.V., Alper, H.: J. Chem. Soc., Chem. Commun. 611 (1992)
208. Miyawaki, T., Nomura, K., Hazama, M., Suzukamo, G.J.: Mol. Catal. A: Chem. **120**, L9 (1997)
209. Noskov, Y.G., Petrov, E.S.: React. Kinet. Catal. Lett. **64**, 359 (1998)
210. Toniolo, L., Graziani, M.J.: Organomet. Chem. **194**, 221 (1980)
211. Calò, V., Giannoccaro, P., Nacci, A., Monopoli, A.J.: Organomet. Chem. **645**, 152 (2002)
212. Perry, R.J., Wilson, B.D.J.: Org. Chem. **61**, 7482 (1996)
213. Head, R.A., Ibbotson, A.: Tetrahedron Lett. **25**, 5939 (1984)
214. Ciufolini, M.A., Michell, J.W., Roschangar, F.: Tetrahedron Lett. **37**, 8281 (1996)
215. Najiba, D., Carpentier, J.-F., Castanet, Y., Biot, C., Brocard, J., Mortreux, A.: Tetrahedron Lett. **40**, 3719 (1999)
216. El-ghayoury, A., Ziessel, R.: Tetrahedron Lett. **39**, 4473 (1998)
217. El-ghayoury, A., Ziessel, R.J.: Org. Chem. **65**, 7757 (2000)
218. Takeuchi, R., Suzuki, K., Sato, N.: J. Mol. Catal. **66**, 277 (1991)
219. Bessard, Y., Roduit, J.P.: Tetrahedron **55**, 393 (1999)
220. Crettaz, R., Waser, J., Bessard, Y.: Org. Process Res. Dev. **5**, 572 (2001)
221. Blaser, H.-U., Diggelmann, M., Meier, H., Naud, F., Scheppach, E., Schnyder, A., Studer, M.J.: Org. Chem. **68**, 3725 (2003)
222. Albaneze-Walker, J., Bazaral, C., Leavey, T., Dormer, P.G., Murry, J.A.: Org. Lett. **6**, 2097 (2004)
223. Schnyder, A., Beller, M., Mehltretter, G., Nsenda, T., Studer, M., Indolese, A.F.J.: Org. Chem. **66**, 4311 (2001)
224. Jenner, G., Taleb, A.B.J.: Organomet. Chem. **470**, 257 (1994)

225. Schareina, T., Zapf, A., Cotté, A., Gotta, M., Beller, M.: Adv. Synth. Catal. **352**, 1205 (2010)
226. Lagerlund, O., Larhed, M.J.: Comb. Chem. **8**, 4 (2006)
227. Wu, X., Ekegren, J.K., Larhed, M.: Organometallics **25**, 1434 (2006)
228. Appukkuttan, P., Axelsson, L., der Eycken, E.V., Larhed, M.: Tetrahedron Lett. **49**, 5625 (2008)
229. Wu, X.-F., Neumann, H., Beller, M.: Chem. Rev. **113**, 1 (2013)
230. Cowell, A., Stille, J.K.J.: Am. Chem. Soc. **102**, 4193 (1980)
231. Qing, F.-L., Jiang, Z.-X.: J. Fluorine Chem. **114**, 177 (2002)
232. Suzuki, T., Uozumi, Y., Shibasaki, M.: J. Chem. Soc. Chem. Commun. 1593 (1991)
233. Sugihara, T., Copéret, C., Owczarczyk, Z., Harring, L.S., Negishi, E.J.: Am. Chem. Soc. **116**, 7923 (1994)
234. Negishi, E., Copéret, C., Ma, S., Mita, T., Sugihara, T., Tour, J.M.J.: Am. Chem. Soc. **118**, 5904 (1996)
235. Negishi, E., Ma, S., Amanfu, J., Copéret, C., Miller, J.A., Tour, J.M.J.: Am. Chem. Soc. **118**, 5919 (1996)
236. Zhang, C., Lu, X.: Tetrahedron Lett. **38**, 4831 (1997)
237. Coelho, F., Veronese, D., Pavam, C.H., de Paula, V.I., Buffon, R.: Tetrahedron **62**, 4563 (2006)
238. Qing, F.-L., Jiang, Z.-X.: Tetrahedron Lett. **42**, 5933 (2001)
239. Fukuyama, T., Nishitani, S., Inouye, T., Morimoto, K., Ryu, I.: Org. Lett. **8**, 1383 (2006)
240. Fusano, A., Sumino, S., Fukuyama, T., Ryu, I.: Org. Lett. **13**, 2114 (2011)
241. Larock, R.C., Fellows, C.A.: J. Am. Chem. Soc. **1982**, 104 (1900)
242. Mori, M., Chiba, K., Ban, Y.: J. Org. Chem. **43**, 1684 (1978)
243. Mori, M., Chiba, K., Inotsume, N., Ban, Y.: Heterocycles **12**, 921 (1979)
244. Mori, M., Washioka, Y., Urayama, T., Yoshiura, K., Chiba, K., Ban, Y.: J. Org. Chem. **48**, 4058 (1983)
245. Ishikura, M., Mori, M., Ikeda, T., Terashima, M., Ban, Y.: J. Org. Chem. **47**, 2456 (1982)
246. Grigg, R., Sridharan, V., Thayaparan, A.: Tetrahedron Lett. **44**, 9017 (2003)
247. Shim, S.C., Jiang, L.H., Lee, D.Y., Cho, C.S.: Bull. Korean Chem. Soc. **1995**, 16 (1064)
248. Grigg, R., Zhang, L., Collard, S., Keep, A.: Tetrahedron Lett. **44**, 6979 (2003)
249. Grigg, R., Sridharan, V., Suganthan, S., Bridge, A.W.: Tetrahedron **51**, 295 (1995)
250. Grigg, R., MacLachlan, W.S., MacPherson, D.T., Sridharan, V., Suganthan, S., Thornton-Pett, M., Zhang, J.: Tetrahedron **56**, 6585 (2000)
251. Ren, W., Yamane, M.: J. Org. Chem. **74**, 8332 (2009)
252. Marosvölgyi-Haskó, D., Takács, A., Riedl, Z., Kollár, L.: Tetrahedron **2011**, 67 (1036)
253. Gai, X., Grigg, R., Khamnaen, T., Rajviroongit, S., Sridharan, V., Zhang, L., Collard, S., Keep, A.: Tetrahedron Lett. **44**, 7441 (2003)
254. Cho, C.S., Lee, J.W., Lee, D.Y., Shim, S.C., Kim, T.J.: Chem. Commun. 2115 (1996)
255. Cho, C.S., Shim, H.S., Choi, H., Kim, T., Shim, S.C., Kim, M.C.: Tetrahedron Lett. **41**, 3891 (2000)
256. Cho, C.S., Chu, D.Y., Lee, D.Y., Shim, S.C., Kim, T.J., Lim, W.T., Heo, N.H.: Synth. Commun. **27**, 4141 (1997)
257. Cho, C.S., Jiang, L.H., Shim, S.C.: Synth. Commun. **28**, 849 (1998)
258. Cho, C.S., Ren, W.X.: Tetrahedron Lett. **50**, 2097 (2009)
259. Cho, C.S., Kim, H.B., Lee, S.Y.: J. Organomet. Chem. **695**, 1744 (2010)
260. Uozumi, Y., Kawasaki, N., Mori, E., Mori, M., Shibasaki, M.: J. Am. Chem. Soc. **111**, 3725 (1989)
261. Perry, R.J., Turner, S.R.: J. Org. Chem. **56**, 6573 (1991)
262. Perry, R.J., Wilson, B.D.: J. Org. Chem. **57**, 6351 (1992)
263. Perry, R.J., Wilson, B.D., Miller, R.J.: J. Org. Chem. **57**, 2883 (1992)
264. Perry, R.J., Wilson, B.D.: J. Org. Chem. **58**, 7016 (1993)
265. Cao, H., Alper, H.: Org. Lett. **12**, 4126 (2010)
266. Worlikar, S.A., Larock, R.C.: J. Org. Chem. **73**, 7175 (2008)

267. Begouin, A., Queiroz, M.R.P.: Eur. J. Org. Chem. 2820 (2009)
268. Meyers, A.I., Robichaud, A.J., McKennon, M.J.: Tetrahedron Lett. **33**, 1181 (1992)
269. Perry, R.J., Wilson, B.D.: Macromolecules **27**, 40 (1994)
270. Perry, R.J., Wilson, B.D.: Organometallics **13**, 3346 (1994)
271. Young, J.R., DeVita, R.J.: Tetrahedron Lett. **39**, 3931 (1998)
272. Zhou, T., Chen, Z.-C.: Synth. Commun. **32**, 887 (2002)
273. Zeng, F., Alper, H.: Org. Lett. **13**, 2868 (2011)
274. Tadd, A.C., Fielding, M.R., Willis, M.C.: Chem. Commun. 6744 (2009)
275. Wu, X.-F., Neumann, H., Neumann, S., Beller, M.: Chem. Eur. J. **18**, 13619 (2012)
276. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **18**, 12599 (2012)
277. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **18**, 12595 (2012)
278. Wu, X.-F., Neumann, H., Neumann, S., Beller, M.: Chem. Eur. J. **18**, 8596 (2012)
279. Wu, X.-F., Schranck, J., Neumann, H., Beller, M.: Chem. Eur. J. **17**, 12246 (2011)
280. Bocelli, G., Catellani, M., Cugini, F., Ferraccioli, R.: Tetrahedron Lett. **40**, 2623 (1999)
281. Lu, S.-M., Alper, H.: J. Am. Chem. Soc. **127**, 14776 (2005)
282. Lu, S.-M., Alper, H.: Chem. Eur. J. **13**, 5908 (2007)
283. Lu, S.-M., Alper, H.: J. Am. Chem. Soc. **130**, 6451 (2008)
284. Yang, Q., Cao, H., Robertson, A., Alper, H.: J. Org. Chem. **75**, 6297 (2010)
285. Elmore, C.S., Dorff, P.N., Heys, J.R.: J. Label Compd. Radiopharm. **53**, 787 (2010)
286. Cao, H., Vieira, T.O., Alper, H.: Org. Lett. **13**, 11 (2011)
287. Cho, C.-H., Larock, R.C.: Tetrahedron Lett. **51**, 3417 (2010)
288. Knight, J.C., Prabaharan, R., Ward, B.D., Amoroso, A.J., Edwards, P.G., Kariuki, B.M.: Dalton Trans. **39**, 10031 (2010)
289. Takahashi, T., Kusaka, S., Doi, T., Sunazuka, T., Omura, S.: Angew. Chem. Int. Ed. **42**, 5230 (2003)
290. Doi, T., Kamioka, S., Shimazu, S., Takahashi, T.: Org. Lett. **10**, 817 (2008)
291. Kamioka, S., Shimazu, S., Doi, T., Takahashi, T.: J. Comb. Chem. **10**, 681 (2008)
292. liu, J., Zhang, R., Wang, S., Sun, W., Xia, C.: Org. Lett. **11**, 1321 (2009)
293. Lee, J.-T., Alper, H.: Organometallics **9**, 3064 (1990)
294. Zucchi, C., Pályi, G., Galamb, V., Sámpár-Szerencsés, E., Markó, L., Li, P., Alper, H.: Organometallics **15**, 3222 (1996)
295. Hashimoto, I., Tsuruta, N., Ryang, M., Tsutsumi, S.: J. Org. Chem. **35**, 3748 (1970)
296. Bauld, N.L.: Tetrahedron Lett. **1963**, 27 (1841)
297. Chiusoli, G.P., Merzoni, S.: Chem. Commun. 522 (1971)
298. Amer, I., Alper, H.: J. Org. Chem. **53**, 5147 (1988)
299. Joo, F., Alper, H.: Organometallics **4**, 1775 (1985)
300. Heck, R.F.: J. Am. Chem. Soc. **1963**, 85 (2013)
301. Bottoni, A., Miscione, G.P., Novoa, J.J., Prat-Resina, X.: J. Am. Chem. Soc. **125**, 10412 (2003)
302. Ren, W., Yamane, M.: J. Org. Chem. **75**, 8410 (2010)
303. Roberts, B., Liptrot, D., Alcaraz, L., Luker, T., Stocks, M.: J. Org. Lett. **12**, 4280 (2010)

Chapter 3
Reductive Carbonylations

In reductive carbonylation reactions, aldehydes are produced as the terminal products. Aromatic aldehydes are an important class of compounds with wide applications in all areas of chemistry and are also used as key intermediates in the pharmaceutical, pesticide, perfume, and dye industries. More specifically, several name reactions and well-accepted reactions are begun with aldehydes as substrates (Scheme 3.1). Examples are the Wolff-Kishner reduction for reducing carbon to methyl group; the Pinacol coupling reaction for diol synthesis; the Witting reaction for ylide reagent preparation and the Johnson-Corey-Chaykovsky reaction for sulfonium ylide reagent making; the Takai reaction to make diorganochromiun reagents; the Corey-Fuchs reaction to synthesis phosphine-dibromomethylene reagent and the Ohira-Bestmann reaction for dimethyl (diazomethyl)phosphonate reagent synthesis; and the Oxo Diels–Alder reaction for pyran synthesis. Additionally, hydroacylation and decarbonylation are all well-known reactions related to aldehydes.

Regarding its importance, a number of procedures have been developed (Scheme 3.2), such as the oxidation of the corresponding benzylic substrates and ozonolysis of alkenes, or the reduction of esters and acid chlorides. Several name reactions, like the Gattermann-Koch, Gattermann, Reimer-Tiemann, Duff, Vilsmeier, Nef, Zincke, McFadyen-Stevens, Meyers and also the Stephen aldehyde synthesis were all developed for aldehyde synthesis [1, 2]. But for the demands of green chemistry and sustainable development, the reactions mentioned do not fit the standards of modern chemistry. Notably, the hydroformylation reaction that began from alkenes and CO/H_2 produces an ideal procedure for aliphatic aldehyde synthesis [3–14]. This reaction leads—unless ethylene is used as a substrate—to a mixture of isomeric products, *n*-aldehydes (linear), and isoaldehydes (branched). Because double-bond isomerization of the substrate may occur prior to the hydroformylation, various branched aldehydes can be formed even when a single terminal olefin has been subjected to the reaction. But the main problem for hydroformylation is that it is difficult for it to produce aromatic aldehydes as their product. Reductive carbonylation (also called formylation) catalyzed by transition metal offers a straightforward procedure for aryl aldehyde preparation. Starting from the corresponding aryl-X (X = I, Br, Cl, OTf, etc.), in the presence of

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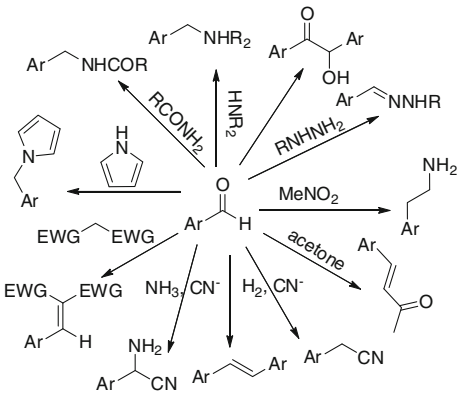
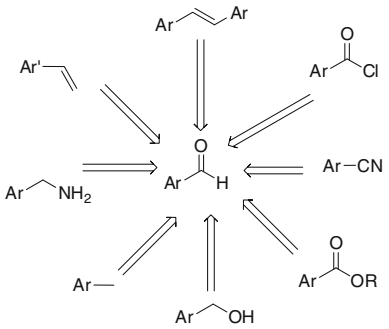
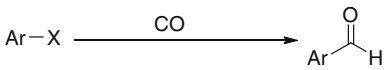
Scheme 3.1 Synthetic applications of aldehydes



Scheme 3.2 Methodologies for aldehyde synthesis



Scheme 3.3 Reductive carbonylation



catalyst and carbon monoxide, aromatic aldehydes can be easily prepared (Scheme 3.3).

Like alkoxycarbonylation, aminocarbonylation, and hydroxycarbonylation, the palladium-catalyzed reductive carbonylation reaction was originally discovered by Schoenberg and Heck in 1974 [15]. In the presence of a relatively large amount of $[PdX_2(PPh_3)_2]$ as a catalyst under 80–100 bar of synthesis gas and at 80–150 °C, aryl and vinyl bromides or iodides were converted into the corresponding aldehydes in good yields (Table 3.1).

Halobi(triphenylphosphine)phenylnickel(II) complexes as catalysts were also tested for the reductive carbonylation of bromobenzene and iodobenzene by the same authors. The yield of benzaldehyde based on iodobenzene was only 20 % at 100 °C using triethylamine (NEt_3) as its base. Bromobenzene did not react under the usual conditions, and a stoichiometric reaction with chlorobi(triphenylphosphine)phenylnickel gave only benzene and biphenyl at 100 °C. One decade later,

Table 3.1 The first palladium-catalyzed reductive carbonylation

$R-X \xrightarrow{[Pd],\ CO/H_2} R-CHO$

Substrate	Pressure [bar]	Temp. [°C]	Yield [%]
C_6H_5Br	91	125	94[a]
C_6H_5I	103	125	95[a]
4-$MeOC_6H_4Br$	100	150	84[a]
4-NCC_6H_4Br	104	150	76[a]
3,4-$(MeO)C_6H_3Br$	100	140	69[a]
3,4-$(MeO)(AcO)C_6H_3Br$	105	145	78[a]
1,4-$C_6H_4Br_2$	95	140	83[a]
1,2-$C_6H_4Br_2$	82	140	66[a]
1-$C_{10}H_7Br$	84	125	82[a]
3-Bromopyridine	93	145	80[a]
2-Bromopyridine	84	130	76[a]
(*E*)-$C_6H_5CHCHBr$	98	80	65[b]
(*E*)-$CH_3CH_2CHC(I)CH_2CH_3$	86	80	75[b]

[a] $PdBr_2(PPh_3)_2$, NBu_3. [b] $PdI_2(PPh_3)_2$, NEt_3

this pioneering work was improved by using metal hydrides as reducing agents. Baillargeon and Stille [16, 17] established the use of tributyltin hydride (Bu_3SnH) in reductive carbonylation reactions. Under mild conditions (50 °C, 1–3 bar CO), aryl iodides, benzylic halides, vinyl iodides and triflates and allylic halides were successfully carbonylated in 2.5–3.5 h reaction time. Since then, tin hydrides have been applied for reductive carbonylations in several natural product syntheses (Fig. 3.1).

Because of the toxicity and waste generation of tin hydrides, it should no longer be used despite the general application of tin hydrides in the past. Organosilanes [18–20] are certainly a better choice to be based in conjunction with carbon monoxide. Ashfield and Barnard recently took up this concept by testing the practicability of various R_3SiH systems for assorted known palladium catalysts [21]. The authors demonstrated that in many optimization experiments, finding the appropriate parameters (catalyst, base, solvent, temperature, pressure,

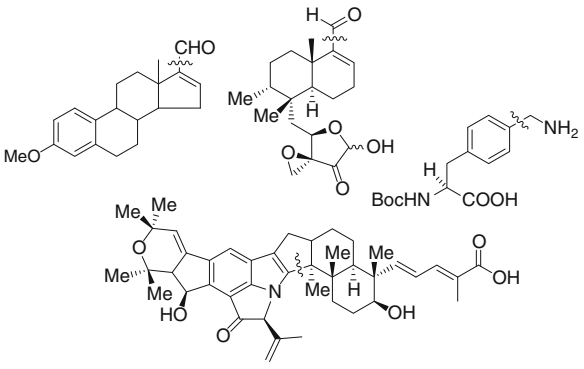


Fig. 3.1 Apply reductive carbonylations in natural product syntheses

concentration) for the transformation of (hetero)aryl bromides and iodides (Table 3.2) is inevitable. Thus, when Et_3SiH was used under mild conditions (3 bar CO, 60–120 °C), the [$PdCl_2$(dppp)]/DMF/Na_2CO_3 system produced good results for most of the substrates. In general, the desired aldehydes were obtained in 79–100 % yields. But in the cases of aryl chlorides and sterically hindered aryl bromides and iodides, the catalytic system still has difficulty.

The use of readily available and cheap formate salts is an economically attractive variant for performing palladium-catalyzed reductive carbonylations [22, 23]. For example, Cai and his associates developed a silica-supported phosphine palladium complex ("Si"-*P*-Pd) for the formylation of aryl bromides and iodides with sodium formate (1 bar CO, 90–110 °C) [24]. The polymeric catalyst could be recovered afterwards and shown in simple model reactions comparable catalytic activity than homogeneous $PdCl_2(PPh_3)_2$ (Table 3.3).

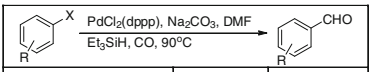
In 1989 Milstein and colleagues realized the reductive carbonylation of aryl chlorides [25]. Under the assistant of $Pd(dippp)_2$ complex, aryl chlorides were transformed into the corresponding aldehydes in good yields in the presence of CO and sodium formate (Scheme 3.4). In a step-by-step study, they also proved that the oxidative addition of chlorobenzene to palladium is the rate determining step, which undergoes easy carbonylation in the presence of CO and will produce aldehyde in the presence of sodium formate in THF at 100 °C.

Cacchi and his colleagues developed two general protocols for the transformation of aryl iodides to the corresponding substituted benzaldehydes (Scheme 3.5) [26]. Depending on the electronic properties of the substrates, the reaction conditions had to be modified. Thus, neutral, electron-rich, and slightly electron-deficient aryl iodides were carbonylated in CH_3CN in the presence of $Pd_2(dba)_3$/dppe/*i*-Pr_2EtN, applying Et_3SiH and acetic formic anhydride as an in situ CO source. By the addition of 3 equivalents of LiCl, electron-poor aryl iodides were successfully reacted in DMF under the same conditions. In general, good yields were achieved and several functional groups were tolerated.

Chiarotto's group developed a totally different electrochemical approach for aromatic and heteroaromatic aldehyde synthesis [27, 28]. Based on their preliminary investigations [29–31], the reductive carbonylation of aryl iodides was accomplished in the presence of formic acid and atmospheric pressure of carbon monoxide. Under electrolytic conditions (−1.2 V versus SCE), formate ions were generated from HCOOH in the presence of 10 mol % palladium-phosphine complexes. Good yields were achieved for most of the substrates under their conditions. This type of electrocarbonylation was also applied to the carbonylation of iodothiophenes, iodofurane, and iodopyridines in the presence of a phosphine-free palladium catalyst ($Pd(OAc)_2$/DABCO) and gave the desired products in moderate to good yields.

Holzapfel and colleagues published an alternative methodology for pyridine and quinoline carboxaldehydes by the reductive carbonylation of (hetero)aryl bromides and triflates [32]. Synthesis gas was used as the formylation source as various hydrogen donors, e.g., Bu_3SnH or polymethylhydrosiloxane (PMHS), which led to significant amounts of by-products resulting from reductive

Table 3.2 Palladium-catalyzed reductive carbonylation of aryl halides



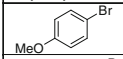
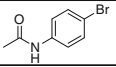
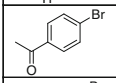
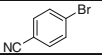
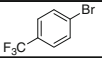
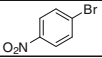
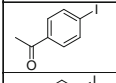
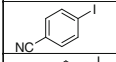
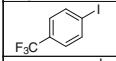
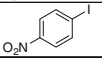
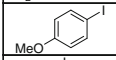
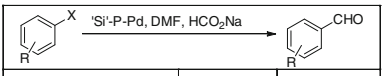
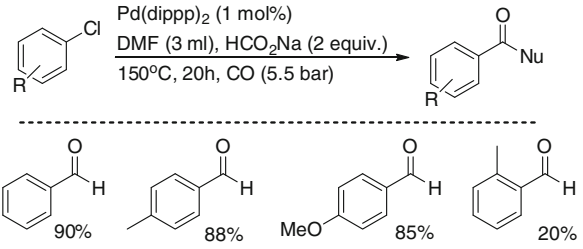
Substrate	Conv.[%]	Yield[%]
	100	79
	92	92
	0	0
	100	94
	81	81
	100	95
	100	82
	100	79
	100	78
	100	4
	100	100
	100	100
	100	97
	96	96
	97	97
	100	85
	100	83
	100	93
	98	98
	100	44
	100	97
	100	100
	31	5

Table 3.3 'Si'-Pd-catalyzed reductive carbonylation of aryl halides



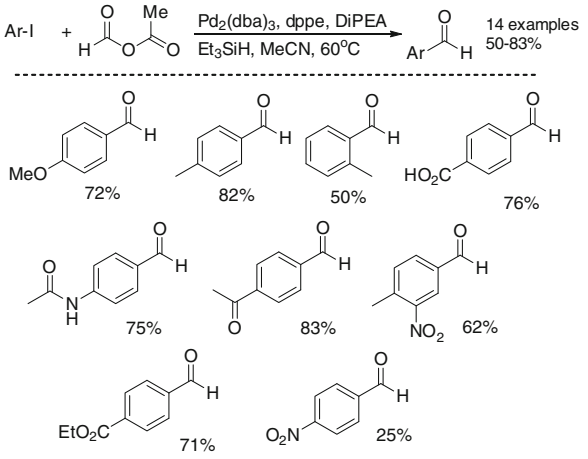
Substrate	Temp.[°C]	Yield[%]
	110	56
	110	51
	110	65
	110	53
	110	60
	90	78
	90	75
	90	80
	90	77
	90	81

Scheme 3.4 Palladium-catalyzed reductive carbonylation of aryl chlorides

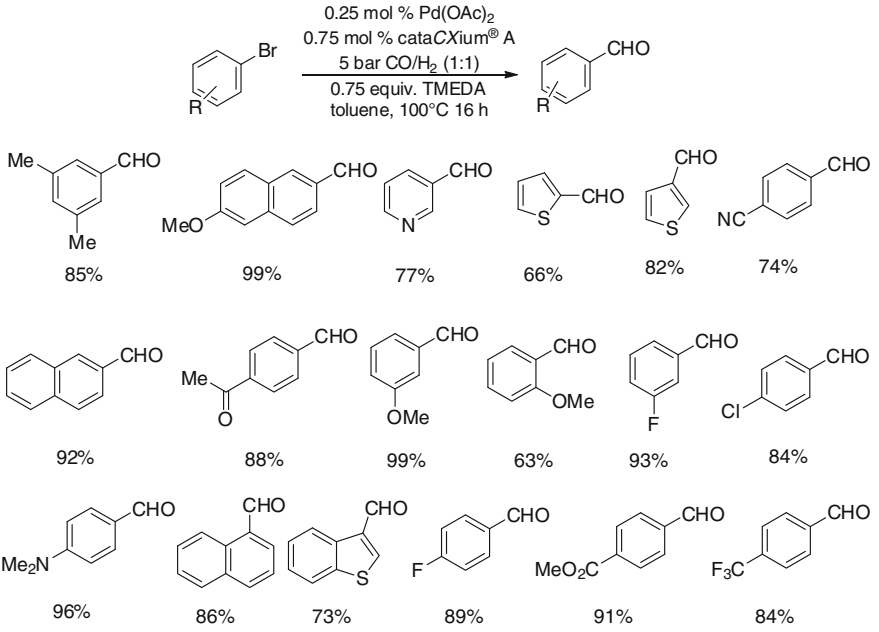


dehalogenation. Limited substrates were transformed into the corresponding aldehydes in 30–88 % yields in the presence of $Pd(OAc)_2/PPh_3$ and 30–40 bar of CO/H_2 (1:1).

Recently, Beller's group has developed the most general and efficient palladium-catalyzed formylation procedure for the synthesis of aromatic and heteroaromatic aldehydes (Scheme 3.6) [33–35]. Various (hetero)aryl bromides were successfully carbonylated with the cheap and environmentally benign formyl source, synthesis gas, in the presence of $Pd(OAc)_2$/cata*CX*ium® A[36] and *N*,*N*,*N*',*'*-tetramethylethylenediamine (TMEDA) at 100 °C. Advantageously, the catalyst system was active at low concentrations (0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A) and at much lower pressures (5 bar) than those



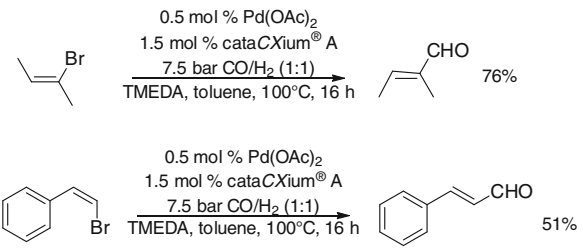
Scheme 3.5 Reductive carbonylation of ArI with acetic formic anhydride



Scheme 3.6 Pd/BuPAd$_2$-catalyzed reductive carbonylation of ArBr

previously reported in the literature. Besides, it was shown that vinyl halides could be formylated under similar conditions to form α,β-unsaturated aldehydes in 41–98 % yield [37]. Interestingly, the transformation of (*Z*)-2-bromo-2-butene and

Scheme 3.7 Pd/BuPAd$_2$-catalyzed reductive carbonylation of vinyl bromides



cis-β-bromo-styrene resulted in the selective formation of the corresponding *trans*-aldehydes (Scheme 3.7).

Notably, the catalyst system is currently used on multi-1,000 kg-scale. The efficiency and easy handling properties (stable to air and moisture) make this the first industrial palladium-catalyzed reductive carbonylation of aryl halides. At this point it is important to note that applied homogeneous catalysis benefits significantly from advancements in the area of organometallic chemistry. Hence, the mechanistic understanding of elementary steps and the synthesis of new organometallic compounds provide a valuable source for inspiration for new catalysts.

Due to the industrial importance of this protocol, we have investigated in detail the mechanism of the reductive carbonylation of aryl bromides with synthesis gas (Fig. 3.2) [38]. This reductive carbonylation proceeded efficiently in the presence of Pd/PR$^n_2$Bu (R = 1-Ad, ^{t}Bu), while Pd/P^{t}Bu$_3$ catalysts were not efficient. Comparing stoichiometric and catalytic reactions using P(1-Ad)$^n_2$Bu (cata*CX*ium® A) led to two significant results: (1) The corresponding carbonylpalladium(0) complex [Pd$_n$(CO)$_m$L$_n$] and the respective hydrobromide complex [Pd(Br)(H)L$_2$] are resting states of the active catalyst, and they are not directly involved in the catalytic cycle. These complexes maintain the concentration of most active PdL species at a low level throughout the reaction, making an oxidative addition the rate-determining step and providing high catalyst longevity. (2) The product-forming step proceeds via base-mediated hydrogenolysis of the corresponding acyl complex, e.g., [Pd(Br)(*p*-CF$_3$C$_6$H$_4$CO){P(1-Ad)$^n_2$Bu}]$_2$ under mild conditions (25–50 °C, 5 bar). Remarkably, in the presence of P(1-Ad)$^n_2$Bu/TMEDA, reductive dehalogenation, which is generally the most important side reaction pathway in the reductive carbonylations, was not observed. Stoichiometric studies using the less efficient Pd/P^{t}Bu$_3$ catalyst resulted in the isolation and characterization of the first stable three-coordinated neutral acyl palladium complex [Pd(Br)(*p*-CF$_3$C$_6$H$_4$CO)(P^{t}Bu$_3$)]. Hydrogenolysis of this complex needed significantly more drastic conditions compared to those of the corresponding dimeric complex. In the presence of the amine base, a catalytically inactive diamino acyl complex is formed, which explains the low activity of the Pd/P^{t}Bu$_3$ catalyst in the formylation of aryl bromides.

In 2007, Beller and his colleagues developed the first general palladium-catalyzed carbonylation of aryl triflates with synthesis gas [39]. In contrast to aryl bromides, only the bidentate ligands dppe and dppp led to significant conversion

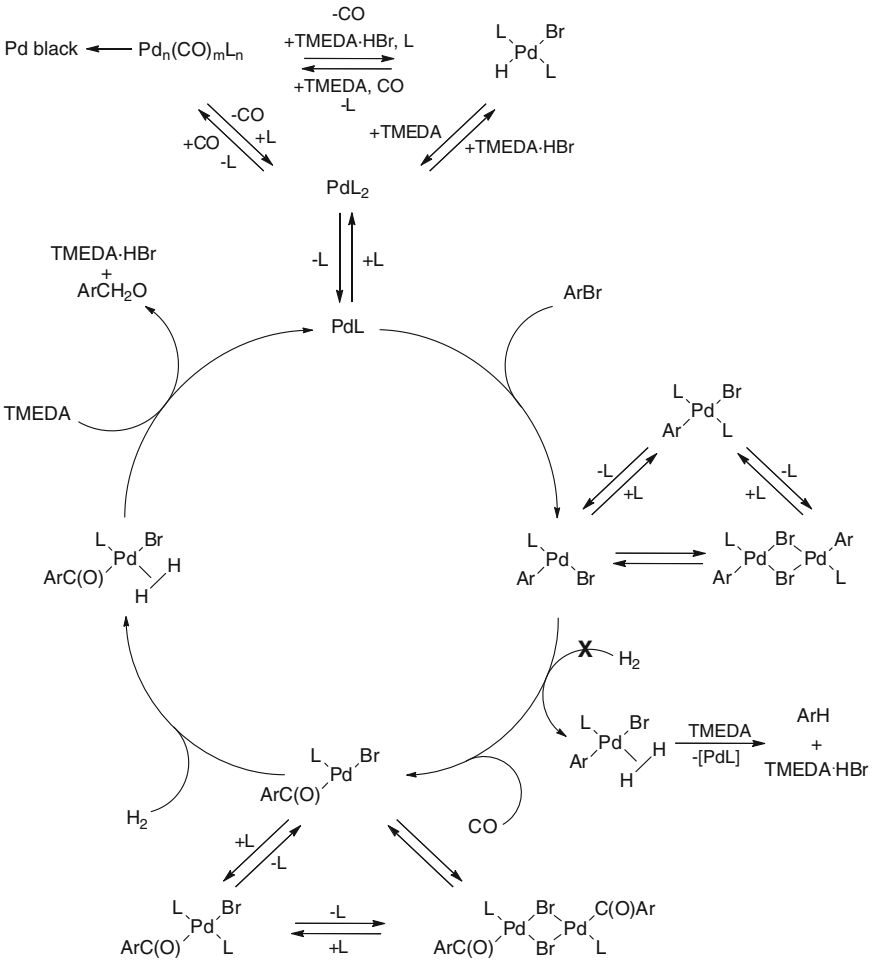


Fig. 3.2 Reaction mechanism study

and aldehyde formation. Under mild conditions, various aromatic aldehydes were obtained in a 50–92 % yield in the presence of 1.5 mol % $Pd(OAc)_2$, 2.25 mol % dppp and pyridine in DMF. In addition, it was demonstrated that 4-methoxybenzaldehyde could be prepared directly from 4-methoxyphenol via a one-pot sulfonylation-carbonylation sequence (Scheme 3.8).

Scheme 3.8 Palladium-catalyzed reductive carbonylation of ArOTf

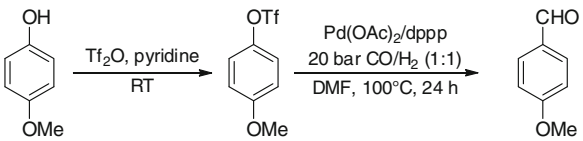
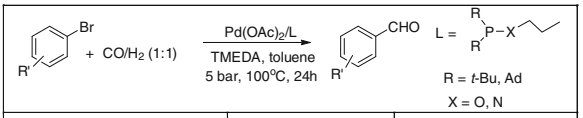
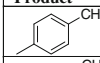
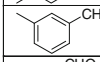
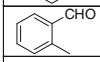
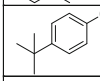
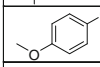
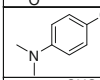
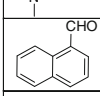
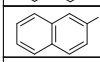
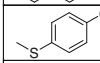
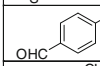
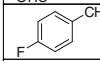
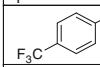
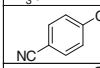
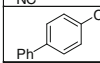
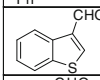
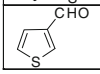


Table 3.4 Palladium phosphinite catalyzed reductive carbonylation of ArBr



Product	Conv.[%]	Yield[%]
	100	90
	99	89
	99	81
	99	97
	99	96
	99	95
	91	83
	100	89
	95	88
	84	68
	99	88
	100	65
	90	77
	99	89
	89	65
	100	82

Later on, the same group developed an efficient phosphinite ligand for the palladium-catalyzed reductive carbonylation of aryl bromides to aromatic aldehydes based on phosphinite ligands [40]. Several aryl bromides with electron-donating and electron-withdrawing substituents reacted to produce aldehydes in good to excellent yields (Table 3.4). Additionally, the reductive carbonylation can be carried out using in situ-prepared propyl di-*tert*-butylphosphinite, which is

synthesized by a commercially available treating $(^t\text{Bu})_2\text{PCl}$ with *n*-propanol in the presence of TMEDA. As $(^t\text{Bu})_2\text{PCl}$ is significantly cheaper than BuPAd_2, this new synthetic methodology is a valuable alternative to the established synthesis of BuPAd_2. Recently, a Pd(acac)_2/dppm system was also reported [41]. Aryl iodides were transformed under 10 bar of synthetic gas, and produced good yields in the corresponding aldehydes.

Reductive carbonylation offers an interesting pathway for aromatic aldehyde synthesis. Starting from the easily available corresponding parent molecules, aldehydes are selectively produced in good yields. For reductive carbonylation, the choice of hydrogen donor and ligand are important for the success of the transformation. From a mechanistic point of view, the reductive elimination of ArCHO from the ArCOPdH(L) complex should be involved—which is different from what was written in our previous chapter.

In the next chapter we will discuss reactions that involve the reductive elimination of the ArCOPdAr(L) complexes and ketones that will be their target products.

References

1. Ferguson, L.N. Chem. Rev. **38**, 227 (1946)
2. Aldabbagh, F. Comp. Org. Funct. Group Transforma. II. **3**, 99 (2005)
3. Franke, R., Selent, D., Börner, A. Chem. Rev. **112**, 5675 (2012)
4. van Leeuwen, P.W.N.M., Kamer, P.C.J., Reek, J.N.H., Dierkes, P. Chem. Rev. **100**, 2741 (2000)
5. Torrent, M., Solà, M., Frenking, G. Chem. Rev. **100**, 439 (2000)
6. Breit, B. Top. Curr. Chem. **297**, 139 (2007)
7. Dwyer, C., Assumption, H., Coetzee, J., Crause, C., Damoense, L., Kirk, M. Coord. Chem. Rev. **248**, 653 (2004)
8. Damoense, L., Datt, M., Green, M., Steenkamp, C. Coord. Chem. Rev. **248**, 2393 (2004)
9. Kamer, P.C.J., van Rooy, A., Schoemaker, G.C., van Leeuwen, P.W.N.M. Coord. Chem. Rev. **248**, 2409 (2004)
10. Lazzaroni, R., Settambolo, R., Alagona, G., Gio, C. Coord. Chem. Rev. **254**, 696 (2010)
11. Haumann, M., Riisager, A. Chem. Rev. **108**, 1474 (2008)
12. Hebrard, F., Kalck, P. Chem. Rev. **109**, 4272 (2009)
13. Gual, A., Godard, C., Castillón, S., Claver, C. Tetrahedron: Asymmetry. **21**, 1135 (2010)
14. Fernández-Pérez, H., Etayo, P., Panossian, A., Vidal-Ferran, A. Chem. Rev. **111**, 2119 (2011)
15. Schoenberg, A., Heck, R.F.J. Am. Chem. Soc. **96**, 7761 (1974)
16. Baillargeon, V.P., Stille, J.K.J. Am. Chem. Soc. **108**, 452 (1986)
17. Baillargeon, V.P., Stille, J.K.J. Am. Chem. Soc. **105**, 7175 (1983)
18. Kotsuki, H., Datta, P.K., Suenaga, H. Synthesis. **470** (1996)
19. Kikukawa, K., Totoki, T., Wada, F., Matsuda, T.J. Organomet. Chem. **207**, 283 (1984)
20. Pri-Bar, I., Buchman, O. J. Org. Chem. **49**, 4009 (1984)
21. Ashfield, L., Barnard, C.F.J. Org. Proc. Res. Dev. **11**, 39 (2007)
22. Okano, T., Harada, N., Kiji, J. Bull. Chem. Soc. Jpn. **67**, 2329 (1994)
23. Pri-Bar, I., Buchman, O. J. Org. Chem. **53**, 624 (1988)
24. Cai, M.-Z., Zhao, H., Zhou, J., Song, C.-S. Synth. Commun. **32**, 923 (2002)
25. Ben-David, Y., Portnoy, M., Milstein, D.J. Chem. Soc. Chem. Commun. 1816 (1989)

26. Cacchi, S., Fabrizi, G., Goggiamani, A.J. Comb. Chem. **6**, 692 (2004)
27. Chiarotto, I., Feroci, M.J. Organomet. Chem. **691**, 2589 (2006)
28. Chiarotto, I., Carelli, I., Cacchi, S., Pace, P., Amatore, C., Jutand, A., Meyer, G. Eur. J. Org. Chem. 1471 (1999)
29. Amatore, C., Jutand, A., Meyer, G., Carelli, I., Chiarotto, I. Eur. J. Inorg. Chem. **8**, 1855 (2000)
30. Amatore, C., Carré, E., Jutand, A., Tanaka, H., Torii, S., Chiarotto, I., Carelli, I. Electrochim. Acta. **42**, 2143 (1997)
31. Chiarotto, I., Carelli, I., Carnicelli, V., Marinelli, F., Arcadi, A. Electrochim. Acta. **41**, 2503 (1996)
32. Holzapfel, C.W., Ferreira, A.C., Marais, W.,J. Chem. Res. (S). **5**, 218 (2002)
33. Klaus, S., Neumann, H., Zapf, A., Strübing, D., Hübner, S., Almena, J., Riermeier, T., Groß, P., Sarich, M., Krahnert, W.-R., Rossen, K., Beller, M. Angew. Chem. 118, 161 (2006)
34. Klaus, S., Neumann, H., Zapf, A., Strübing, D., Hübner, S., Almena, J., Riermeier, T., Groß, P., Sarich, M., Krahnert, W.-R., Rossen, K., Beller, M. Angew. Chem. Int. Ed. **45**, 154 (2006)
35. Almena Perea, J.J., Monsees, A., Kadyrov, R., Riermeier, T., Rossen, K., Krahnert, W.-R., Beller, M., Klaus, S., Zapf, A (Degussa AG, Germany) PCT Int. Appl. WO 2006/103148. A1 (2006)
36. For the synthesis and characterization of palladium(0) and arylpalladium bromide complexes of cata*CX*ium® A, see Sergeev, A.G., Zapf, A., Spannenberg, A., Beller, M. Organometallics. **27**, 297 (2008)
37. Brennführer, A., Neumann, H., Klaus, S., Riermeier, T., Almena, J., Beller, M. Tetrahedron. **63**, 6252 (2007)
38. Sergeev, A.G., Spannenberg, A., Beller, M.J. Am. Chem. Soc. **130**, 15549 (2008)
39. Brennführer, A., Neumann, H., Beller, M. Synlett. 2537 (2007)
40. Neumann, H., Kadyrov, R., Wu, X.-F., Beller, M. Chem. Asian J. **7**, 2213 (2012)
41. Singh, S.A., Bhanage, B.M., Nagarkar, J.K. Tetrahedron Lett. **52**, 2383 (2011)

Chapter 4
Carbonylative Coupling Reactions with Organometallic Reagents

In carbonylative coupling with organometallic reagent reactions, transmetalation is normally involved in advance of reductive elimination. Diarylketones are their terminal products, which constitute an interesting and versatile structural motif [1] and are frequently present in natural products (e.g., Cotoin, Papaveraldine), in non-steroidal anti-inflammatory drugs (e.g., Suprofen, Ketoprofen), and they occur in UV screens (e.g., Sulisobenzone, Oxybenzone). Based on their importance, various methodologies have been developed for their preparation. An example is the Friedel–Crafts acylation of *ortho*/*para*-directing arenes with acyl halides, which requires over stoichiometric amount of Lewis acid and its regioselectivity is often limited to the *para*-position [2]. Cross-coupling reactions of benzoic halides with organotin compounds [3–5], palladium-catalyzed coupling of boronic acids with carboxylic anhydride [6], or nickel-catalyzed coupling reactions of aryl iodides with aromatic aldehydes offer alternative procedures for diarylketone synthesis [7]. An especially versatile approach for the synthesis of diarylketones [8] is the transition-metal-catalyzed three-component cross-coupling of Aryl-X (X = Br, I, OTf, N_2^+) derivatives, carbon monoxide, and organometallic reagents (Scheme 4.1). This procedure offers the direct and efficient synthesis of various ketones.

The palladium-catalyzed cross-coupling of organo halides with organoboranes is known as the Suzuki reaction and represents one of the most popular coupling reactions. The carbonylative Suzuki reaction can be understood as performing the Suzuki reaction under an atmosphere of CO, and ketones will be produced by inserting one carbonyl group into the two coupling partners.

As early as 1986, Kojima and colleagues reported on the carbonylative coupling of aryl iodides or benzyl halides with organoboranes in the presence of a catalytic amount of a palladium catalyst [9]. This was the first application of organoboranes in carbonylative coupling reactions mediated by 1.1 equivalent of $Zn(acac)_2$ to favor the transmetallation. Various ketones have been produced in good yields starting from aryl iodides and benzyl chloride (Scheme 4.2).

Later, in 1991, Suzuki and colleagues developed another methodology for the carbonylative coupling of vinyl halides with organoboranes using $Pd(PPh_3)_4$ and K_3PO_4 as a base [10] to synthesize vinyl ketones in moderate to excellent yields (Scheme 4.3). However, the chemoselectivity dropped and a mixture of

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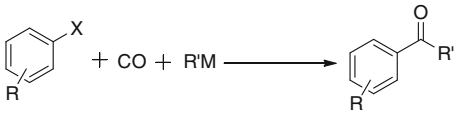
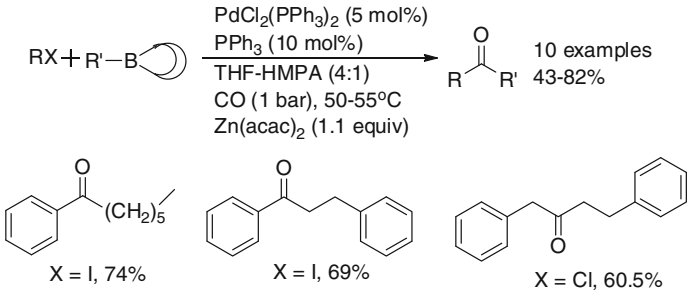
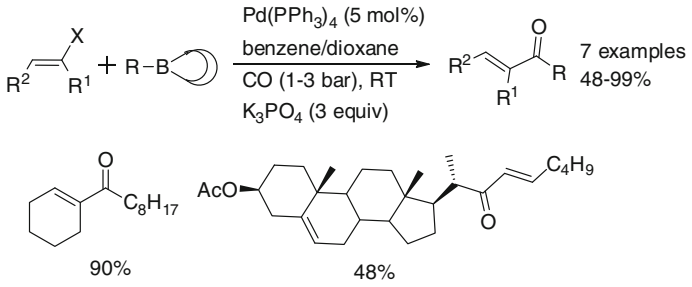
Scheme 4.1 Carbonylative synthesis of ketones





Scheme 4.2 First Pd-catalyzed carbonylative coupling of organoboranes

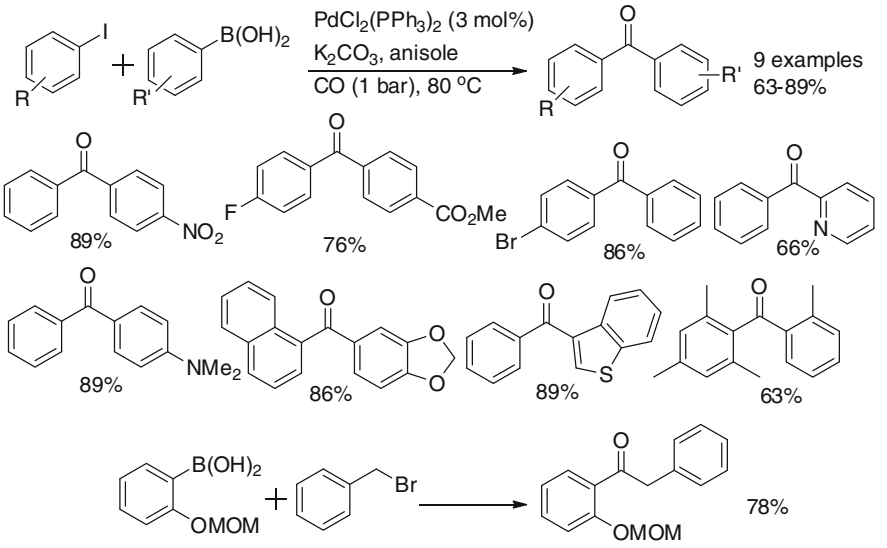


Scheme 4.3 Pd-catalyzed carbonylative Suzuki coupling of organoboranes with vinyl halides

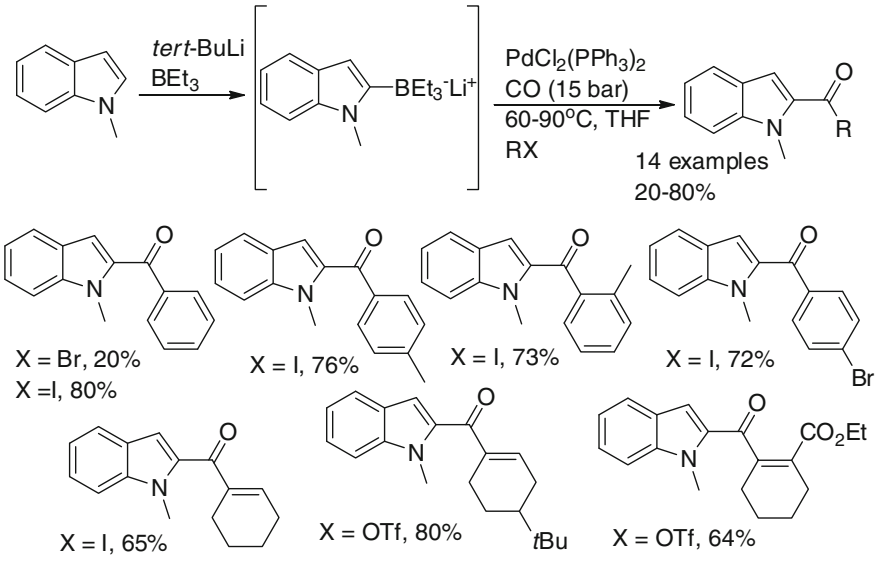
carbonylated and non-carbonylated products was observed when iodoalkenes bearing electron-withdrawing substituents were used as substrates. In the same year this methodology was extended to iodoalkanes under the assistance of light [11, 12].

In 1993 Suzuki and colleagues described the palladium-catalyzed carbonylative coupling of aryl iodides with aryl boronic acids [13]. Various diarylketones were produced in high yields (Scheme 4.4). The choice of base and solvent was essential to obtain the desired ketones without biaryl by-products. The coupling of benzyl bromide was also described. In 1998 the group extended this methodology to aryl bromides and triflates [14]. In the case of aryl bromides, NaI or KI was required as an additive. The in situ transformation of aryl bromides to aryl iodides may be involved.

Ishikura and Terashima described an application of the carbonylative coupling of organohalides or vinyl triflates in a one-pot procedure using indolylborates as a

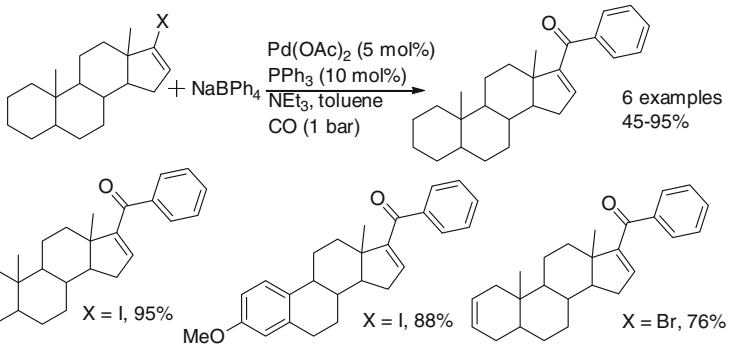


Scheme 4.4 Pd-catalyzed carbonylative Suzuki coupling of aryl iodides with aryl boronic acids

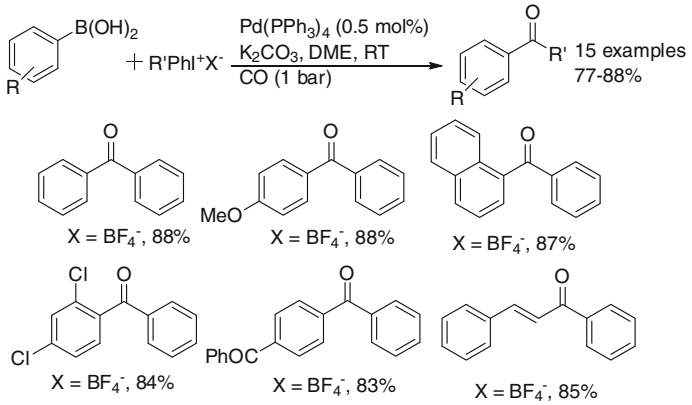


Scheme 4.5 Pd-catalyzed synthesis of indol-2-yl ketones

coupling partner to achieve indol-2-yl ketones in good yields (Scheme 4.5) [15]. In 1998 Kang and colleagues used—instead of aryl halides—hypervalent iodonium salts to couple organoboronic acids in the presence of CO to obtain asymmetric aromatic ketones [16]. Here, moderate yields were achieved on the carbonylation of



Scheme 4.7 Pd-catalyzed carbonylative synthesis of steroidal ketones

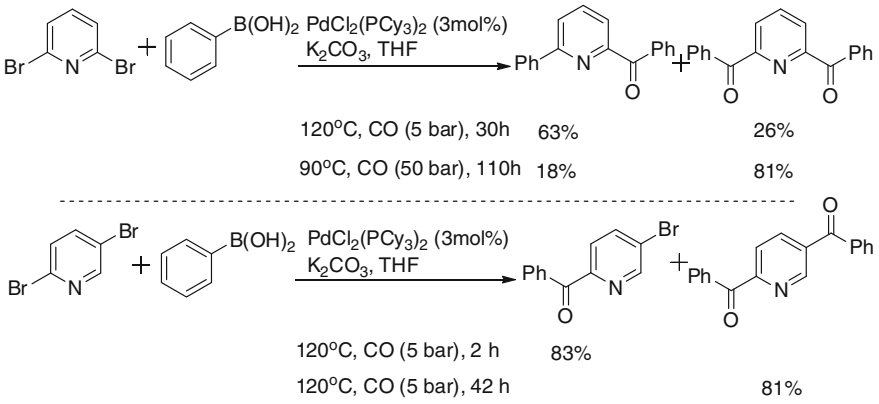


Scheme 4.6 Pd-catalyzed carbonylative Suzuki coupling of aryl boronic acids with hypervalent iodonium salts

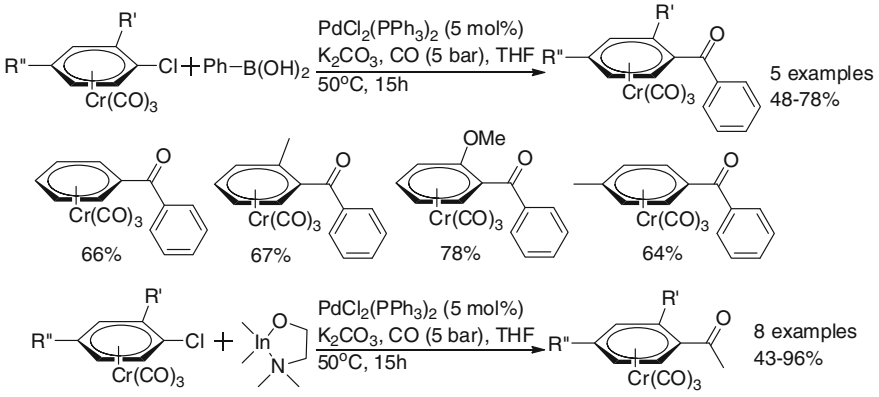
aryl boronic acids with aryl-, alkenyl-, and alkynyliodonium salts at room temperature under 1 bar of CO (Scheme 4.6). Starting from aryl trifluoroborates, Chen and Xia were able to extend this methodology using $Pd(OAc)_2$ as a precursor [17].

Steroidal phenyl ketones were synthesized by Skoda-Foeldes and colleagues via a related carbonylation pathway [18]. The ketones were produced in high yields by the carbonylation of 17-iodo-androst-16-ene derivatives in the presence of $NaBPh_4$ (Scheme 4.7). Alkenyl bromides or enol triflates produced lower yields under the same reaction conditions.

Castanet and his team demonstrated a palladium-catalyzed carbonylative Suzuki reaction of pyridine halides in 2001. Under their conditions, pyridine halides reacted with aryl boronic acids to 2-pyridyl ketones in good yields (81–95 %; Scheme 4.8). The proper choice of solvent, catalyst precursor, and CO pressure enabled the selective transformation of mono- and dihalopyridines. Later on, they



Scheme 4.8 Pd-catalyzed Suzuki carbonylation of halopyridines

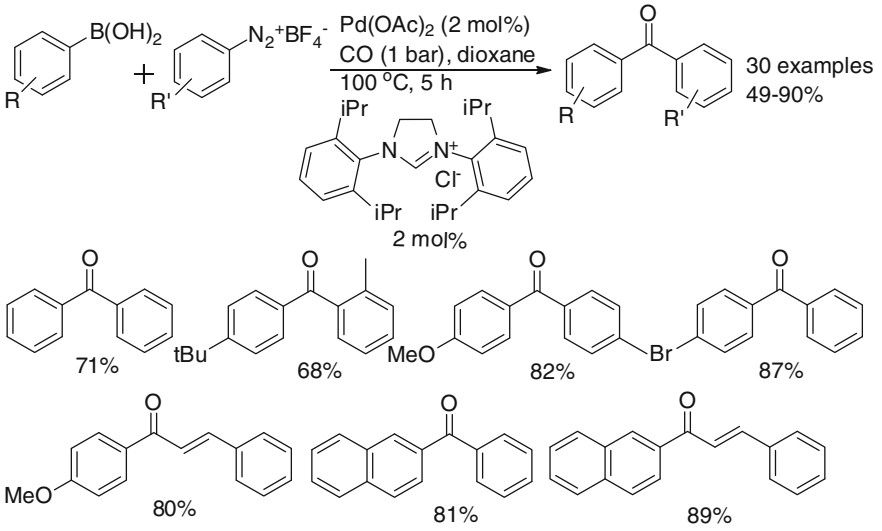


Scheme 4.9 Pd-catalyzed carbonylative coupling of chloroarene-$Cr(CO)_3$ complexes

extended this methodology to pyridine chlorides by applying an NHC ligand and Cs_2CO_3 as a base [19–22].

Schmalz and his colleagues investigated the carbonylative Suzuki reaction of their chloroarene-$Cr(CO)_3$ complexes with phenyl boronic acid [23]. Using $PdCl_2(PPh_3)_2$ as a catalyst precursor, benzophenone derivatives were achieved in good yields (Scheme 4.9). Palladium-catalyzed carbonylative cross-methylation reactions of various chloroarene-$Cr(CO)_3$ complexes mediated by a stabilized dimethylindium(III) reagent were also described. As discussed in Chap. 2, the carbonylative activation of the C–Cl bond is difficult, but applying chloroarene-$Cr(CO)_3$ complexes offers a procedure to solve this problem.

The palladium-catalyzed carbonylative coupling of aryl diazonium ions with aryl boronic acids was published in 2002 [24]. Various aryl ketones were produced in moderate to high yields under mild conditions (Scheme 4.10). The benefit of



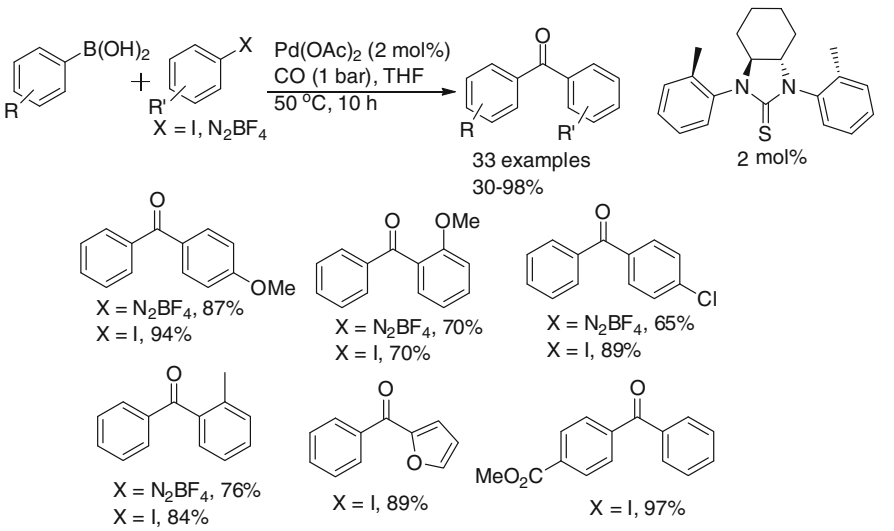
Scheme 4.10 Pd-catalyzed carbonylative coupling of aryl diazonium salts

applying aryl diazonium ions as electrophiles is the possibility of performing coupling reactions under base-free conditions. Neither electron-donating nor electron-withdrawing substituents on the aryl diazonium reduced product yields, and also *ortho*-substituted aryl boronic acids resulted in good yields. In 2004 Yang, Chen and their colleagues described a thiourea-based ligand for the palladium-catalyzed carbonylative coupling of aryl iodides or aryl diazonium salts with aryl boronic acids [25]. This sterically bulky thiourea ligand was successfully applied under aerobic conditions, and ketones were synthesized in good to excellent yields (Scheme 4.11).

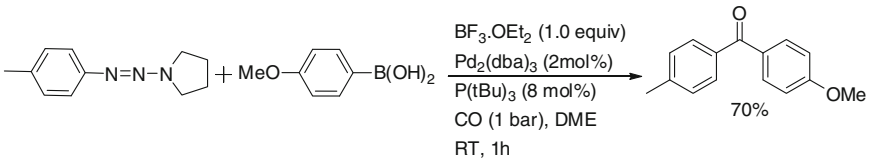
Tamao and his group reported on one example of the carbonylative coupling of 1-aryltriazene with a boronic acid in 2004 [26]. The corresponding diaryl ketone was produced in a 70 % yield under 1 bar of CO, in the presence of a catalytic amount of $Pd_2(dba)_3$ and $P(^tBu)_3$ (Scheme 4.12).

Långström and colleagues described the synthesis of ^{11}C- and ^{13}C-labeled ketones by palladium-catalyzed carbonylative Suzuki coupling [27]. Aryl triflates with methyl- or arylboronic acids, and a low concentration of ^{11}CO were used in the synthesis of ^{11}C-labeled ketones using $Pd(PPh)_4$ as the catalyst. The ^{11}C-labeled products were obtained with decay-corrected radiochemical yields in the 10–70 % range after a 5-min. reaction time at 150 °C.

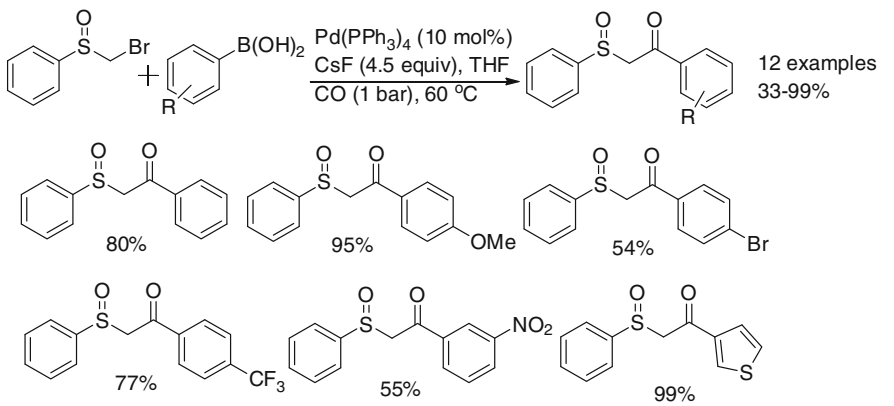
The first report of the synthesis of β-keto sulfoxides using a palladium-catalyzed carbonylative Suzuki reaction of α-bromosulfoxide with arylboronic acids appeared in 2005 [28]. Asensio and his associates described the synthesis of 12 different β-keto sulfoxides in moderate to excellent yields using $Pd(PPh_3)_4$ and CsF as the base in the presence of 1 bar CO (Scheme 4.13). The carbonylative coupling reaction is strongly favored over the competing non-carbonylation and homocoupling processes. However, the chemoselectivity drops and by-products



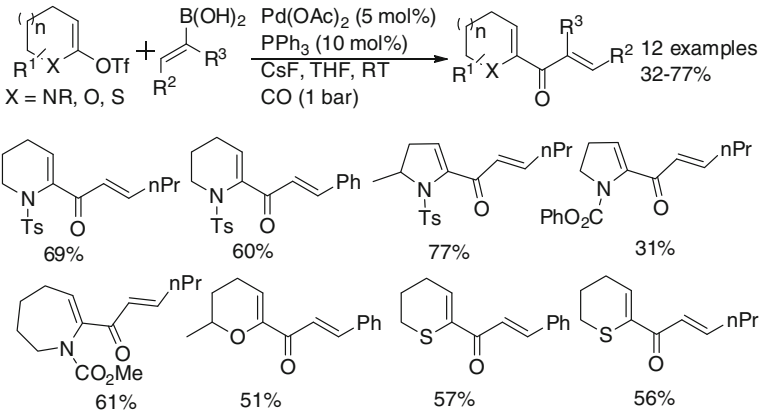
Scheme 4.11 A thiourea-based ligand in carbonylative Suzuki reactions



Scheme 4.12 Pd-catalyzed carbonylative coupling of 1-aryltriazene



Scheme 4.13 Pd-catalyzed synthesis of β-keto sulfoxides

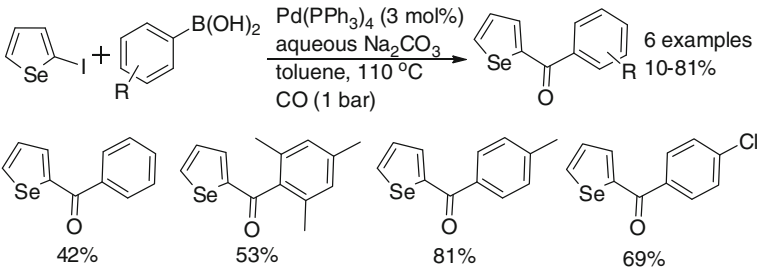


Scheme 4.14 Pd-catalyzed carbonylative coupling of enol triflates

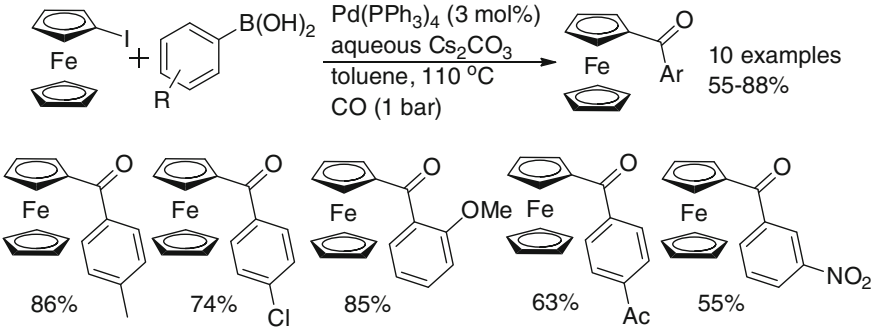
were observed in the case of boronic acids carrying strong electron-withdrawing substituents.

Occhiato and colleagues published the carbonylative coupling of lactam-, lactone-, and thiolactone-derived enoltriflates with boronic acids [29]. Several asymmetrical dienones were formed in moderate to good yields at room temperature under 1 bar of CO with 1–5 mol% of palladium catalyst (Scheme 4.14). This methodology allows for a convergent and rapid preparation of substrates, which are useful in conjugate additions and Nazarov reactions.

Kollar and colleagues discussed the carbonylative coupling of 1-iodo-cyclohexene with aryl boronic acids [30]. From among all the possible products, alkenyl ketones were selectively synthesized under appropriate conditions. The yields were strongly dependent both on the reaction conditions and the type of the arylboronic acid. Zeni and colleagues described the coupling of 2-iodoselenophenes with arylboronic acids and CO in 2006 (Scheme 4.15) [31]. Interestingly, the reaction proceeded with aqueous Na_2CO_3 as base under 1 bar of CO. Concerning the variation of arylboronic acids, strong electron-withdrawing substituted or *ortho*-substituted arylboronic acids gave low or no yields.



Scheme 4.15 Pd-catalyzed carbonylative coupling of 2-iodoselenophenes

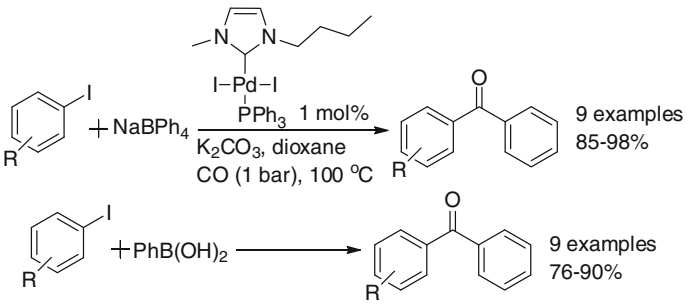


Scheme 4.16 Pd-catalyzed carbonylative coupling of iodoferrocene

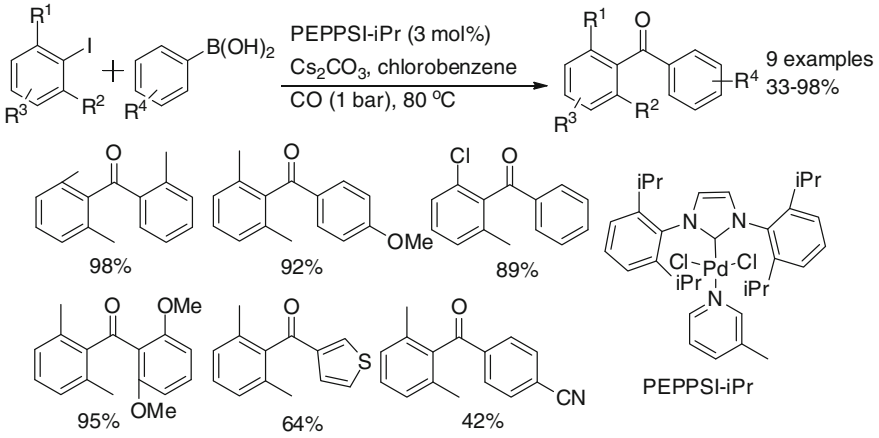
Palladium-catalyzed carbonylative couplings of iodoferrocene with arylboronic acids were reported by Yang and colleagues [32]. A series of aryl ferrocenyl ketones was prepared in good yields under mild conditions (Scheme 4.16). Both strongly activated and *ortho*-substituted arylboronic acids gave the corresponding ketones in moderate yields.

NHC-palladium complexes as efficient catalysts for carbonylative Suzuki coupling of aryl iodides with organoboranes were reported by Xia and colleagues in 2007 [33]. Aryl ketones were produced in high yields under mild conditions (Scheme 4.17). Interestingly, both $NaBPh_4$ and $ArB(OH)_2$ could be used as phenylating reagents. Here the pre-formation of the NHC-palladium complex is important for the success, since the free carbene may react with CO to form ketene and consume the ligand.

Ortho-disubstituted aryl iodides as representative examples of sterically hindered substrates are more challenging in palladium-catalyzed coupling reactions. In this respect it is interesting to note that Martin et al. reported a synthesis of sterically hindered aryl ketones by using the NHC palladium complex PEPPSI-iPr [34]. Several diaryl ketones were produced in moderate to good yields by this method (Scheme 4.18).



Scheme 4.17 NHC-Pd-catalyzed carbonylative coupling of aryl iodides

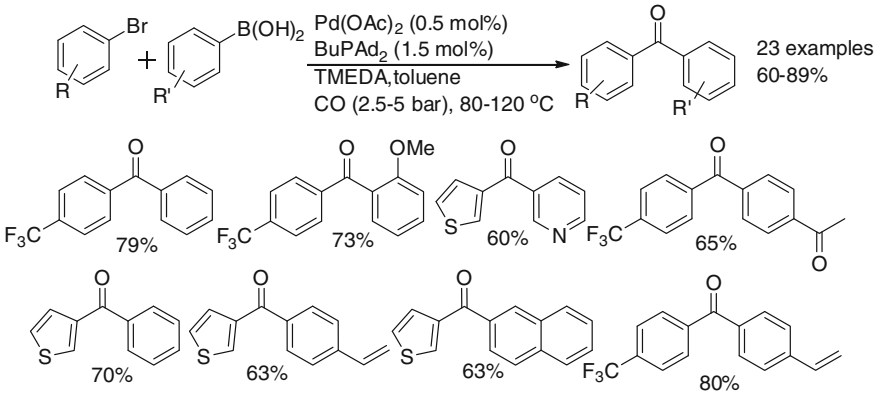


Scheme 4.18 Pd-catalyzed carbonylative coupling of *ortho*-disubstituted ArI

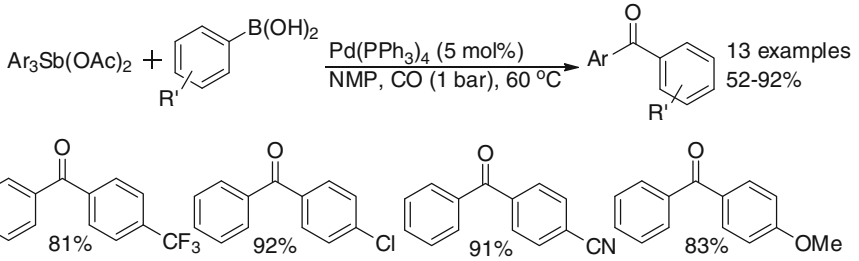
In 2008 Beller's group developed a general method for diaryl ketone synthesis by palladium-catalyzed carbonylative coupling of aryl bromides with arylboronic acids [35]. The combination of $Pd(OAc)_2$ and $BuPAd_2$ allowed the coupling of aryl/heteroaryl bromides with arylboronic acids to produce a wide range of ketones in good yields (Scheme 4.19). With this catalyst, they were also able to synthesize Suprofen, a non-steroidal anti-inflammatory drug.

Kurita and colleagues described a carbonylative coupling of triarylantimony dicarboxylates with arylboronic acids (Scheme 4.20) [36]. Remarkably, no base was needed in this system.

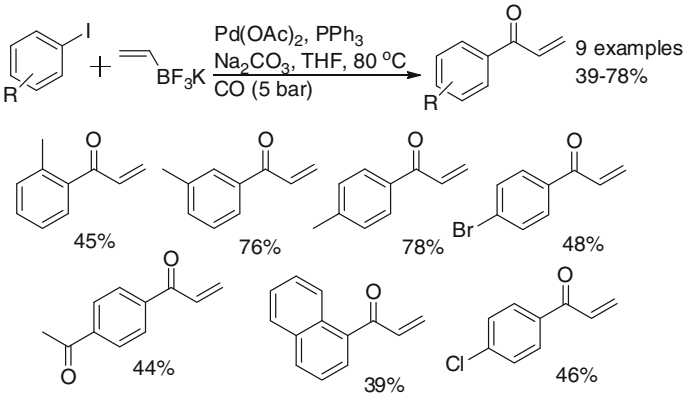
In 2009 Castanet, Sauthier and their colleagues reported on a useful protocol for aryl vinyl ketone synthesis [37]. The carbonylative cross-coupling of potassium vinyl trifluoroborate or 2,3,6-trivinylcycloboroxane with aryl iodides afford



Scheme 4.19 Pd-catalyzed carbonylative Suzuki reaction of aryl bromides



Scheme 4.20 Pd-catalyzed carbonylative coupling of triarylantimony dicarboxylates



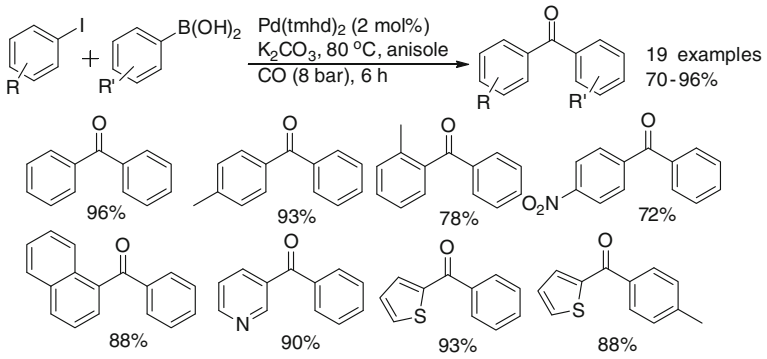
Scheme 4.21 Pd-catalyzed carbonylative synthesis of aryl vinyl ketones

vinylketones in moderate yields (Scheme 4.21). This reaction is strongly influenced by substituents. While activated and *ortho*-substituted aryl iodides produced low yields, good yields were achieved in the case of electron-donating decorated aryl iodides. These can be explained by the stability of the oragnopalladium complexes before CO insertion, and also whether CO insertion is favored.

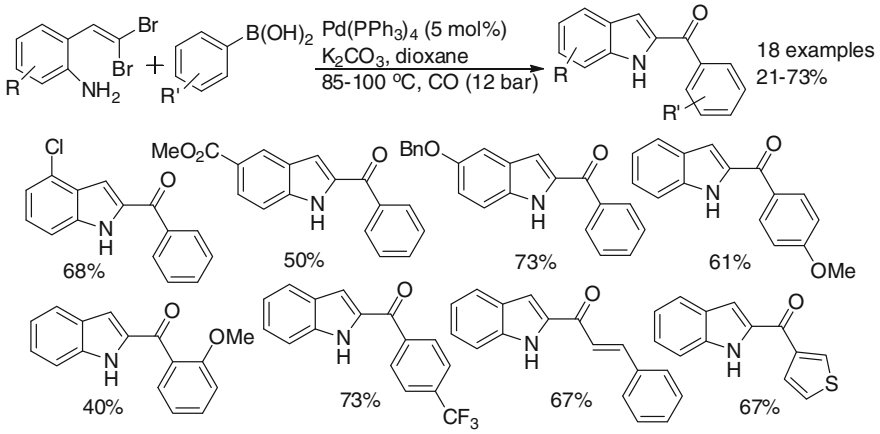
Also in 2009, Cai et al. published a paper on the use of an MCM-41-supported bidentate phosphine palladium(0) complex as a catalyst to the carbonylative Suzuki coupling of aryl iodides with arylboronic acids [38, 39]. This procedure makes the recycling of palladium catalysts possible.

$Pd(tmhd)_2$ (thmd = 2,2,6,6-tetramethyl-3,5-heptanedionate) as another catalyst for carbonylative coupling of aryl iodides with arylboronic acids was described by Bhanage and colleagues (Scheme 4.22) [40]. The diketone (tmhd) can act as a ligand in this methodology and no additional ligand was required. The advantage of the ketone ligand is that they are resistant to oxidation and are also cheaper and easier to modify.

Pontikis and colleagues described a convenient one-pot procedure for the synthesis of 2-aroylindoles [41]. Using a domino palladium-catalyzed CN-



Scheme 4.22 $Pd(tmhd)_2$-catalyzed carbonylative coupling of aryl iodides

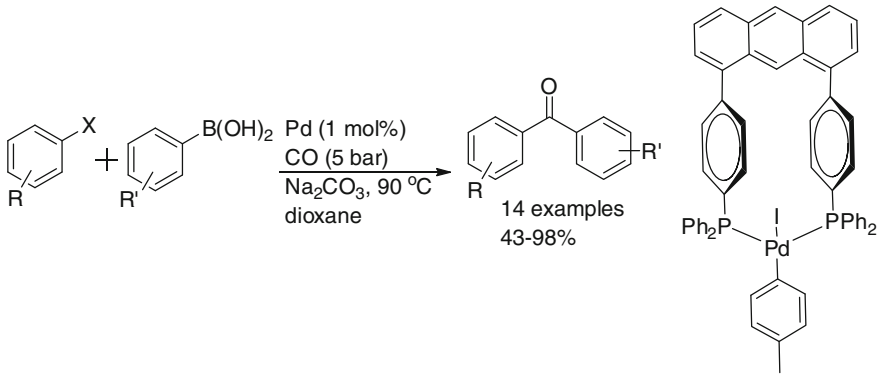


Scheme 4.23 Pd-catalyzed synthesis of 2-aroylindoles

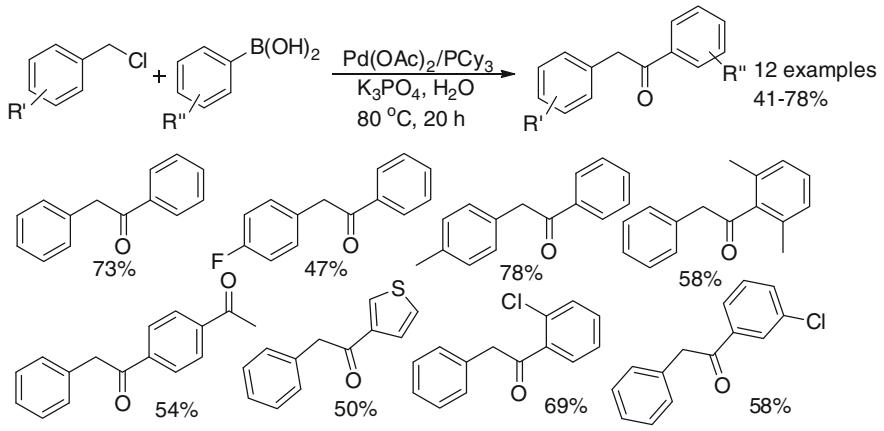
coupling/carbonylation/CC-coupling sequence, 2-aroylindoles were produced in good yields (Scheme 4.23). Since this reaction tolerates various functional groups, a practical access to a wide range of 2-aroylindoles is possible, starting from 2-geminal-dibromovinylanilines.

Recently, Gelman and colleagues reported on a new bidentate phosphine ligand for palladium-catalyzed carbonylative Suzuki coupling reactions [42]. Aryl iodides and bromides were coupled with arylboronic acids in the presence of 0.01–1 mol % of the catalyst. Ketones have been produced with high selectivity in good yields (Scheme 4.24).

Very recently, Beller and colleagues described a novel carbonylative coupling of benzyl chlorides with aryl boronic acids [43]. This was the first report on carbonylative Suzuki couplings of benzyl chlorides with arylboronic acids (Scheme 4.25). The reaction was carried out using a commercially available



Scheme 4.24 Pd-catalyzed carbonylative Suzuki coupling of aryl halides with arylboronic acids

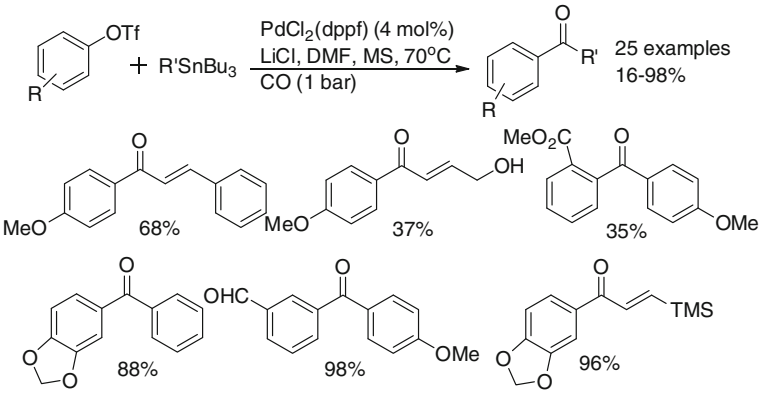


Scheme 4.25 Pd-catalyzed carbonylative coupling of benzyl chlorides

$Pd(OAc)_2/PCy_3$ catalyst in the presence of K_2CO_3 and water as the solvent. 12 ketones have been synthesized in good yields. Later on, they succeeded in extending their reaction to $ArBF_3K$, a more stable class of borane compounds [44].

Despite the drawback of using tin reagents, the palladium-catalyzed Stille coupling provides a powerful pathway for C–C bond formation. Nowadays, numerous applications exist for organic synthesis. Nevertheless, the toxicity of the tin compounds limits their application on a larger scale [45].

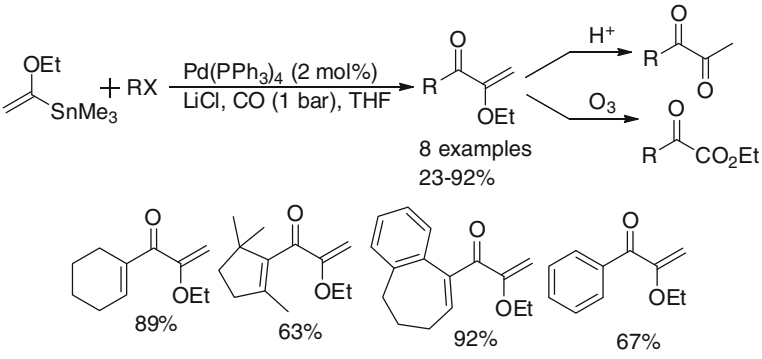
In 1982 Kikukawa and his colleagues reported on the first palladium-catalyzed carbonylative coupling reactions of aryl diazonium salts with organotin regents [46, 47]. Various ketones were produced in moderate to good yields (40–95 %) at room temperature. Shortly after, Stille and Echavarren described a palladium-catalyzed carbonylative coupling of aryl triflates with organostannanes in 1988 [48]. This reaction took place under relatively mild conditions to give good yields



Scheme 4.26 Pd-catalyzed carbonylative Stille coupling of aryl triflates

of diaryl ketones (Scheme 4.26). A wide range of functional groups, such as alcohol, aldehyde, and ester was tolerated. But when the tin partner contained strong electron-withdrawing groups, the coupling reaction was slow and led preferentially to the decomposition of both the tin reagent and triflates.

In 1990 Stille and his associates described the palladium-catalyzed carbonylative coupling of vinyl triflates and aryl iodides with (α-ethoxyvinyl)trimethylstannane [49] and trimethyl(vinyl)stannane [50]. Synthetically useful divinyl ketones were hydrolyzed to α-diketones in a one-pot, two-step manner, or ozonolyzed to obtain glyoxylates (Scheme 4.27). This methodology was applied to the synthesis of large-ring keto lactones containing 12–16 members by the coupling of long-chain esters having vinyl triflates and vinylstannane groups at the termini. A polystyrene-supported ligand system was also synthesized and tested in this reaction [51].



Scheme 4.27 Pd-catalyzed carbonylative Stille coupling of vinyl triflates

The palladium-catalyzed coupling of steroids with vinyltributylstannane and CO was reported by Skoda-Foeldes and colleagues in 1995 [52]. In the steroid part, an acryloyl group in the 17-position was introduced in good yields by direct carbonylative coupling of substrates having an iodo or bromo leaving group. With ethynyltributylstannane, no carbonylation product was obtained under the same conditions, but only the non-carbonylative coupling product was observed.

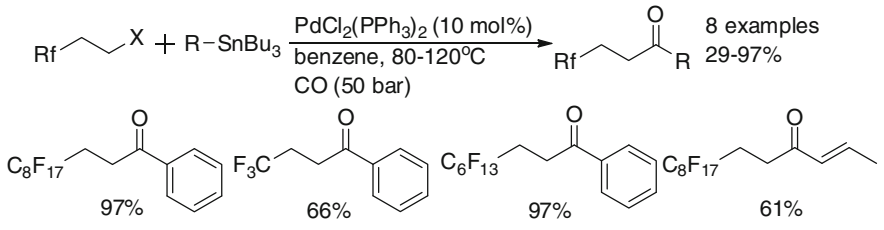
In 1995 Johansson and his group described the carbonylative coupling of arene-$Cr(CO)_3$ complexes, which are substrates and a CO source at the same time [53].

Aryl ketones were formed from the $Cr(CO)_3$ complex of (trialkylstannyl)benzene or chlorobenzene by a palladium-catalyzed cross-coupling reaction in the absence of external CO. The $Cr(CO)_3$ moiety provides the required CO predominantly by an intramolecular mechanism. However, non-carbonylation products were also observed.

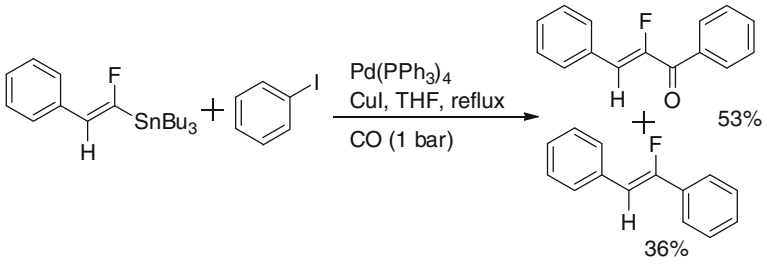
Another application of carbonylative couplings was published by Fuchikami and Shimizu, who reported on the reaction of β-perfluoroalkyl-substituted alkyl halides with organostannanes [54]. The fluorinated ketones were produced in good yields (Scheme 4.28).

In 1997 Vogel's group reported on the palladium-catalyzed carbonylative synthesis of C-glycosides and C-disaccharide precursors [55]. Under 50 bar of CO and in the presence of $Pd_2(dba)_3$ and $AsPh_3$, a suitably protected 1-stannylglucal derivative was carbonylated and coupled to 5-bromo-7-oxabicyclo[2,2,1]hept-5-en-2-yl derivatives. The carbonylative Stille coupling was also successful between 1-iodoglucals and tributyl(vinyl)stannane or tributyl(fur-2-yl)stannane. However, non-carbonylation products were also formed. McCarthy and colleagues described one example of a carbonylative coupling of 1-fluorovinylstannane with iodobenzene. Here, 53 % of the carbonylated product was isolated together with 36 % of the non-carbonylation product (Scheme 4.29) [56].

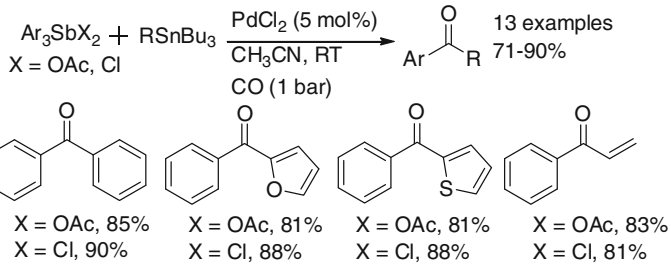
^{11}C-labelled benzophenones were synthesized by Pike and Ai-Qahtani in 2000 [57]. By using the carbonylative coupling of aryl iodides with phenyltributylstannane at room temperature in a DME-water mixture, ^{11}C-benzophenones were obtained in good yields. Similar to the carbonylative Suzuki coupling forming labelled diarylketones, in 2005 Långström and colleagues reported on the synthesis of alkyl/aryl ^{11}C-ketones by appling the carbonylative Stille reaction. Using



Scheme 4.28 Pd-catalyzed carbonylative Stille reaction with fluorinated alkyl halides



Scheme 4.29 Pd-catalyzed carbonylative Stille reaction



Scheme 4.30 Pd-catalyzed carbonylative coupling of triarylantimony diacetates with organostannanes

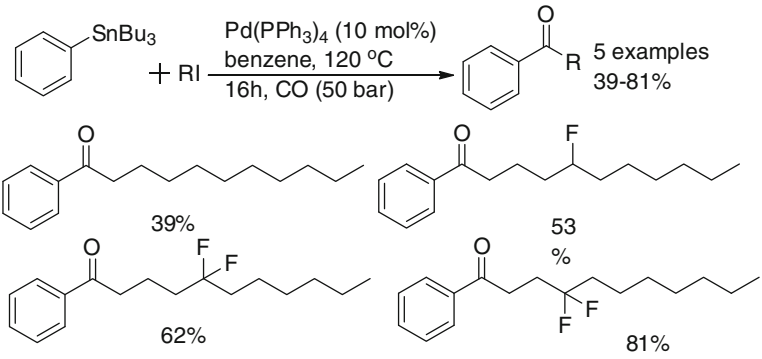
$Pd_2(dba)_3/P(o\text{-toyl})_3$ in the presence of labelled ^{11}CO, ketones were formed in 37–98 % yields [58].

In 2000 Kang and colleagues described the carbonylative coupling of triarylantimony(V) diacetates and dichlorides in the palladium-catalyzed reaction with organostannanes [59]. Diaryl ketones were produced in good yields using 5 mol % of $PdCl_2$ in CH_3CN at room temperature (Scheme 4.30).

Ortar and Morera have published a concise methodology for the synthesis of photoactive ketones [60]. More specifically, 4-aroyl-L-phenylalanines were used to study peptide protein interactions. They were synthesized by palladium-catalyzed coupling of 4-iodo-L-phenylalanines with organostannanes and carbon monoxide. The reaction proceeds under mild conditions with a $PdCl_2/PPh_3$ system in the presence of 1 bar CO at 90 °C in DMF.

Gennari and his group reported a more sophisticated palladium-catalyzed carbonylative coupling of vinyl stannanes with electron-poor enol triflates [61]. The effect of ligands and additives was tested, and a combination of Pd_2dba_3, $AsPh_3$, LiCl, CuI and NMP proved to be the optimal system. Later, this methodology was applied to the total synthesis of sarcodictyins [62].

In 2001 Yun and colleagues used a solid-supported organostannane, which was reacted with aryl halides in a palladium-catalyzed carbonylative coupling reaction [63] to produce a wide range of diaryl ketones.

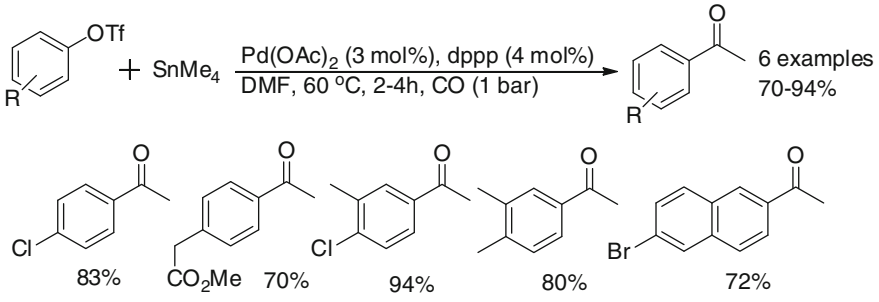


Scheme 4.31 Pd-catalyzed carbonylative coupling of alkyl halides

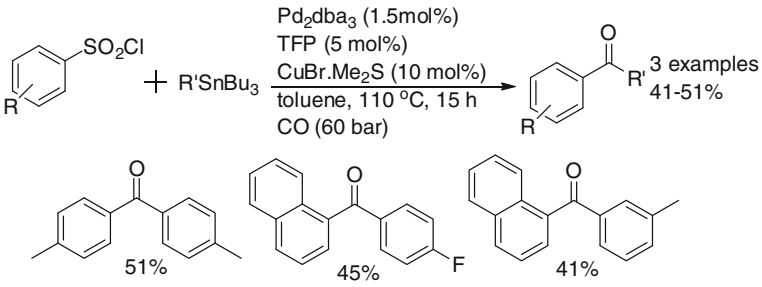
Fuchikami and Shimizu reported the carbonylative coupling of alkyl halides with $PhSnBu_3$ in 2001 [64]. As shown in Scheme 4.31, ketones were synthesized in moderate to good yields. Furthermore, the effect of fluorine substitutents on the selectivity was checked.

Mann et al. showed that various acetophenones can be synthesized by carbonylative coupling of aryl triflates with $SnMe_4$ [65]. Under mild conditions using the catalyst system $Pd(OAc)_2$/dppp, good yields (70–94 %) were obtained (Scheme 4.32). In 2002 Mido and colleagues reported the palladium-catalyzed carbonylative coupling of tributyl(1-fluorovinyl)stannane with aryl halides and aryl triflates [66]. In the presence of a catalytic amount of palladium catalyst and CsF in DMF, aryl 1-fluorovinyl ketones were formed in good yields.

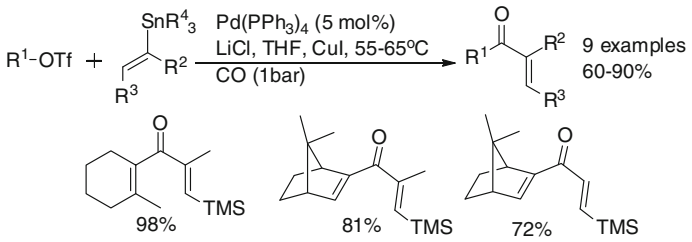
The first report of a palladium-catalyzed carbonylative coupling of sulfonyl chlorides with organostannanes appeared in 2003 [67]. Vogel and Dubbaka used sulfonyl chlorides as a coupling partner to form diarylketones by releasing SO_2 (Scheme 4.33). Later on, a palladium-catalyzed carbonylative coupling of tinglycals and sulfonyl chlorides was developed and *C*-glycoside derivatives were obtained in moderate yields [68]. In 2004 the same group reported on the synthesis



Scheme 4.32 Pd-catalyzed carbonylative Stille coupling to acetophenones



Scheme 4.33 Pd-catalyzed carbonylative coupling of sulfonyl chlorides



Scheme 4.34 Pd-catalyzed carbonylative synthesis of 1,4-dien-3-ones

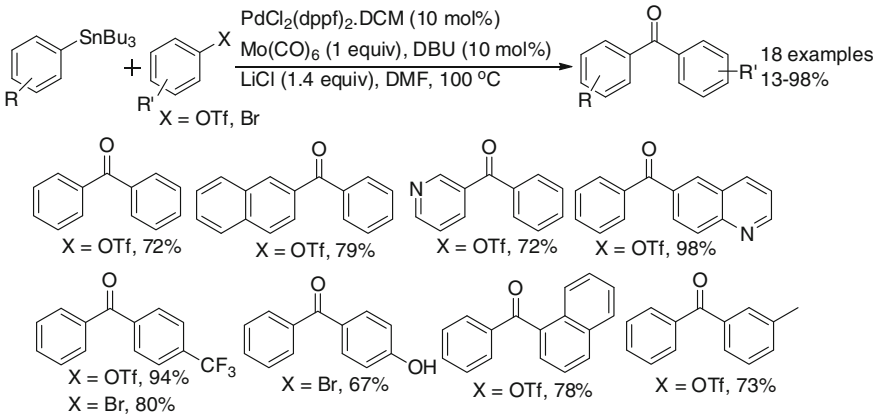
of C(1-4)-linked disaccharides via palladium-catalyzed carbonylative Stille coupling [69]. Besides Pd_2dba_3 $AsPh_3$ and LiCl, charcoal as a co-catalyst was required.

In 2004 West and colleagues reported on the carbonylative coupling of vinylstannanes with vinyl triflates [70]. Using standard carbonylative conditions, the addition of 35 mol % of CuI or CuBr was necessary to improve the yields significantly. Under these conditions, 1,4-dien-3-ones are produced in good to excellent yields (Scheme 4.34).

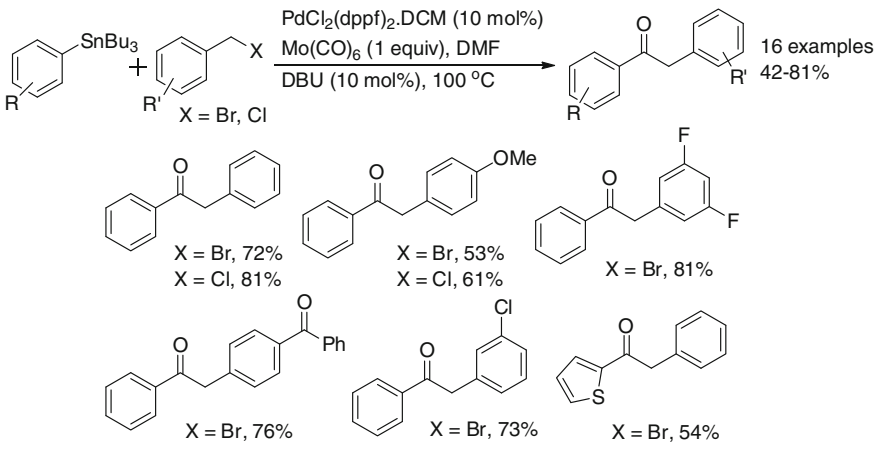
The Stille carbonylation continued to be explored in 2009 by Cai and colleagues, using their heterogeneous MCM-41-supported bidentate phosphine palladium(0) complex. The authors reported the coupling of aryl iodides with organostannanes [71]. This method allows reusing the catalyst, and asymmetrical ketones were produced in high yields.

In 2010 Nilsson and his group described the carbonylative Stille coupling of aryl triflates and aryl bromides with organostannanes by using $Mo(CO)_6$ as a CO source [72]. Various ketones were synthesized in good yields in closed vessels at 100 °C (Scheme 4.35). In this case, DBU was needed to accelerate the release of CO from $Mo(CO)_6$.

Soon afterwards, the group extended their methodology to benzyl halides [73]. Under similar reaction conditions, deoxybenzoins were produced in moderate to good yields (Scheme 4.36).



Scheme 4.35 Pd-catalyzed carbonylative Stille coupling using $Mo(CO)_6$ as CO source

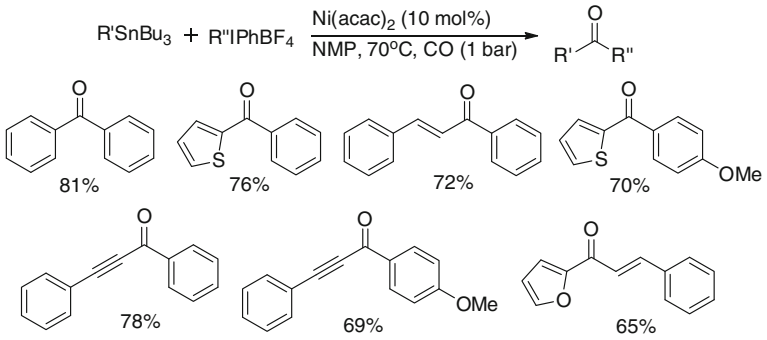


Scheme 4.36 Pd-catalyzed carbonylative Stille coupling of benzyl halides using $Mo(CO)_6$

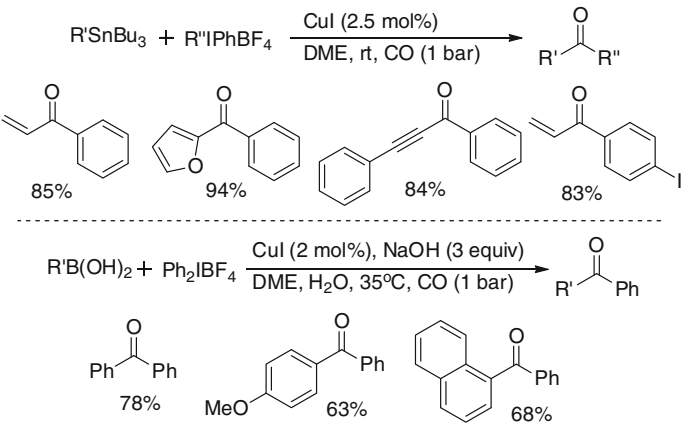
In addition to palladium catalysts, nickel—as a less expensive catalyst—was also explored in the carbonylative coupling of organostannanes with hypervalent iodonium salts [74]. In the presence of $Ni(acac)_2$ (10 mol%) in NMP at 70 °C, organostannanes and hypervalent iodonium salts were carbonylative coupled and gave the corresponding ketones in good yields (Scheme 4.37).

Additionally, copper was used as a powerful catalyst in the carbonylative coupling of hypervalent iodonium salts with organostannanes and organoboranes as well [75]. In the presence catalytic amount of CuI, ketones were produced in good yields from their parent molecules under mild conditions (Scheme 4.38).

Moreover, manganese chloride as a catalyst for carbonylative coupling of organostannanes and hypervalent iodonium salts was developed by Kang and

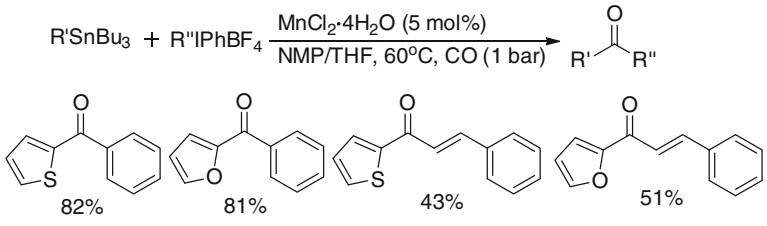


Scheme 4.37 $Ni(acac)_2$-catalyzed carbonylative coupling of organostannanes

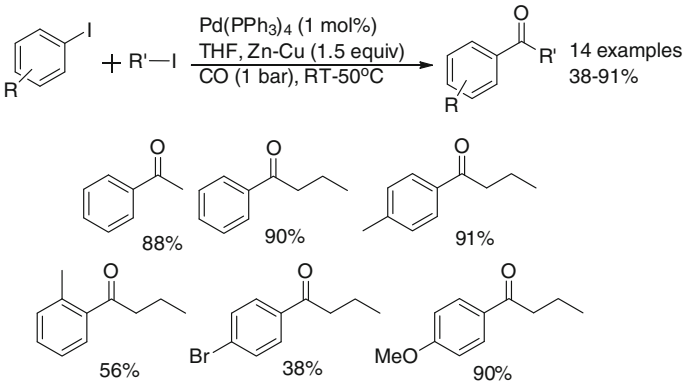


Scheme 4.38 CuI-catalyzed carbonylative coupling of organostannanes and organoboranes

colleagues as well [76]. Under 1 bar of CO at 60 °C, ketones were produced in moderate to good yields (Scheme 4.39). Notably, this is the rare report on $MnCl_2$ catalyzed carbonylative coupling reaction.



Scheme 4.39 $MnCl_2$-catalyzed carbonylative coupling of organostannanes



Scheme 4.40 Pd-catalyzed carbonylative Negishi reaction

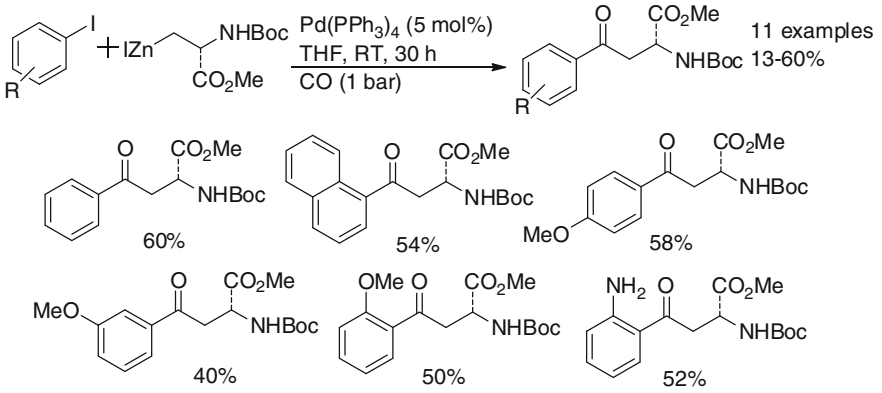
The Negishi coupling is generally considered to be a coupling of organozinc compounds with various organic halides in the presence of palladium or nickel catalysts. The first report of this methodology appeared in 1977, which allowed the preparation of asymmetrical biaryls in good yields. Until today, the Negishi reaction is an important methodology that is used for all kinds of C–C bond formations. However, carbonylative Negishi coupling reactions are rarely reported. The first report of such a reaction appeared in 1983 by Yoshida and colleagues [77]. Aryl alkyl ketones were selectively prepared by the reaction of aryl iodides with alkyl iodides in the presence of a stoichiometric amount of a zinc-copper couple and a catalytic amount of a palladium(0) complex under atmospheric pressure of CO (Scheme 4.40). However, in the case of benzyl chlorides, more drastic conditions were required to reach moderate yields.

In 1995 Tamaru and colleagues described the carbonylative coupling of organozinc reagents with allylating agents to asymmetrical ketones [78]. A variety of organozinc compounds (diethylzinc, alkylzinc halides, and organozincs) underwent smooth coupling with allylic benzoates or phosphates to furnish ketones in good yields under 1 bar of CO in the presence of $Pd(PPh_3)_4$ in a THF/HMPA mixture.

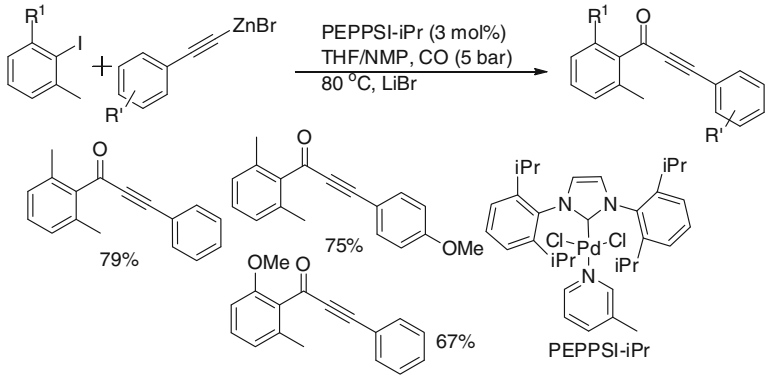
Jackson and colleagues reported an application of the carbonylative Negishi reaction for the synthesis of Kynurenine derivatives [79, 80]. More specifically, an amino acid-derived organozinc reagent was coupled with aryl iodides under one atmosphere of CO (Scheme 4.41).

The palladium-catalyzed carbonylative Negishi coupling of *ortho*-disubstituted aryl iodides with an alkynyl zinc reagent was investigated by Martin and colleagues in 2008 [34]. Alkynones were produced in good yields under mild conditions (Scheme 4.42).

More recently, Morken and colleagues described a rare example of using unsaturated carbonyls for palladium-catalyzed carbonylative coupling reactions with dialkylzinc reagents [81]. 1,4-Diketones were synthesized in good yields



Scheme 4.41 Pd-catalyzed carbonylative coupling of an amino acid-derived organozinc reagent

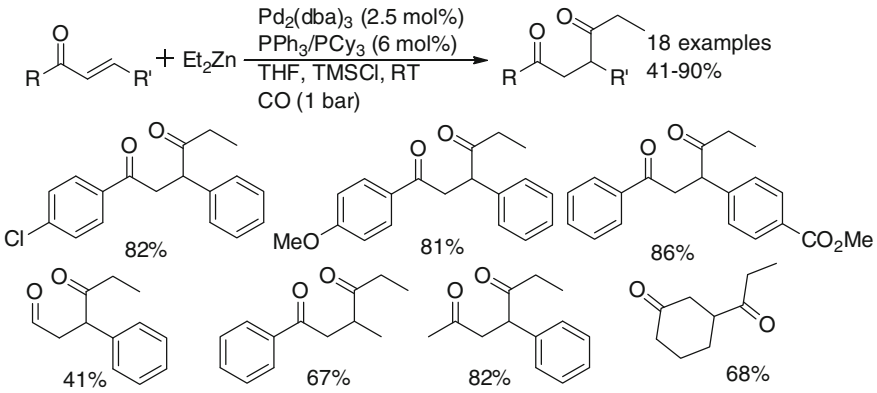


Scheme 4.42 Pd-catalyzed carbonylative Negishi reaction of 2,6-disubstituted aryl iodides

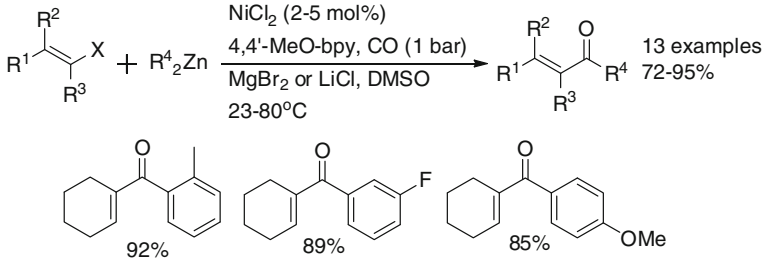
from a number of substituted cyclic and acyclic ketones as well as unsaturated aldehydes (Scheme 4.43).

Chen and Wang described a nickel-catalyzed carbonylative Negishi coupling reactions [82]. In the presence of a catalytic amount of nickel chloride and 4,4′-dimethoxyl-2,2′-bypyridyl under carbon monoxide atmosphere, various enones were produced from enol triflates and diorganozinc reagents (Scheme 4.44). They demonstrate that the rate of CO insertion is increased by the addition of lithium or magnesium halides and the use of polar solvents. Alkenyl iodides can also be used instead of enol triflates.

Additionally, the Hiyama coupling is called the palladium-catalyzed C–C bond formation between aryl, alkenyl, or alkyl halides with organosilanes. Among all the publications concerning Hiyama reactions, only a few described carbonylative Hiyama-type reactions. The first example was published in 1989 by Hiyama himself [83, 84]. Here, diaryl ketones were produced in good yields via the



Scheme 4.43 Pd-catalyzed carbonylative Negishi coupling of unsaturated carbonyls



Scheme 4.44 Nickel-catalyzed carbonylative Negishi coupling reactions

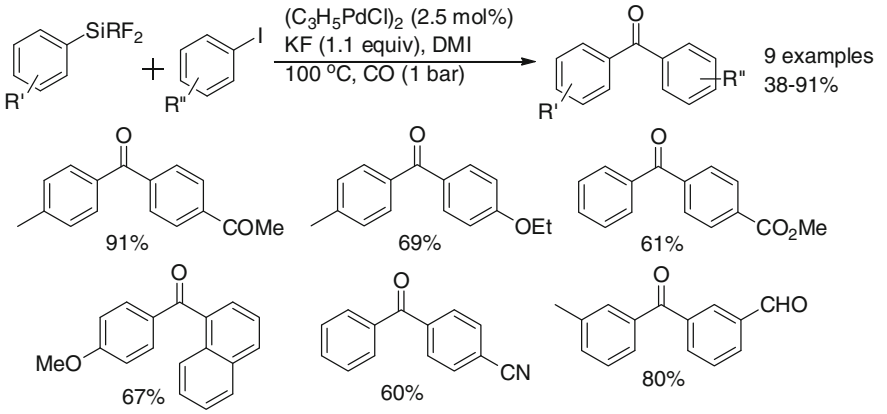
palladium-catalyzed carbonylative coupling of arylfluorosilanes with aryl iodides in the presence of KF (Scheme 4.45).

Later, they extended their methodology to alkenylsilanes and alkenyl iodides. In 2001 Kang and his team reported on the carbonylative coupling of alkynylsilanes with triarylantimony diacetates [85]. Alkynones were synthesized in good yields in the presence of a Pd catalyst and CuI at 50 °C (Scheme 4.46).

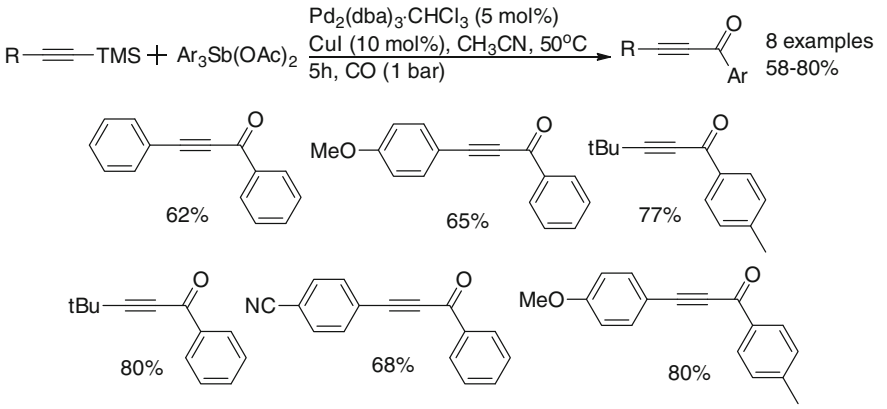
Beller's group reported on a novel procedure for the synthesis of acyl silanes [86]. Starting from aryl iodides and hexamethyldisilane, in the presence of palladium and CO, various benzoyl silanes were produced in moderate to good yields (Scheme 4.47).

More recently, Lee and Park described a palladium-catalyzed carbonylative coupling of aryl iodides with trimethylsilylacetonitrile to benzoylacetonitriles (Scheme 4.48) [87]. A high functional group tolerance was observed, and no additional ligands were needed.

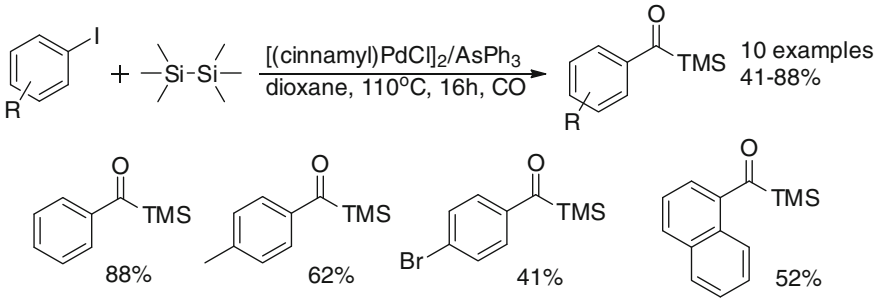
The first carbonylative coupling of organoaluminum compounds appeared in 1985. Beletskaya and colleagues [88] demonstrated that ketones are produced in good yields by a palladium-catalyzed reaction of arylaluminium compounds with aryl iodides in the presence of CO (Scheme 4.49). That same year, the



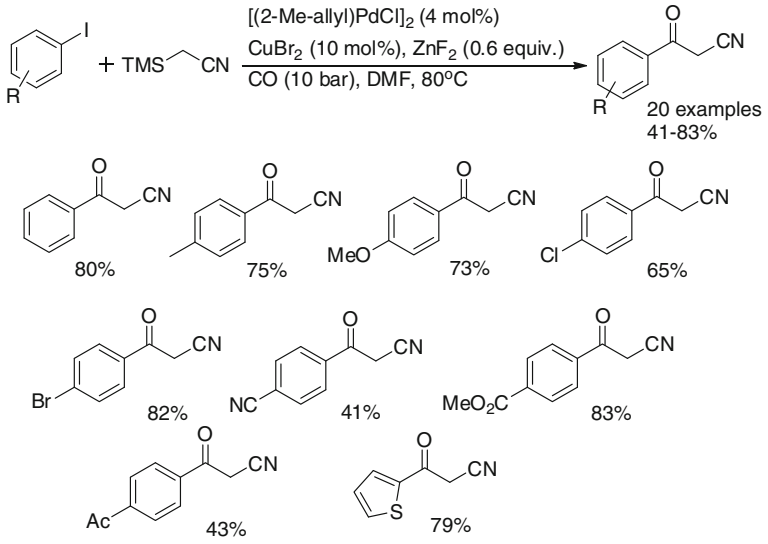
Scheme 4.45 Pd-catalyzed carbonylative Hiyama coupling of aryl iodides



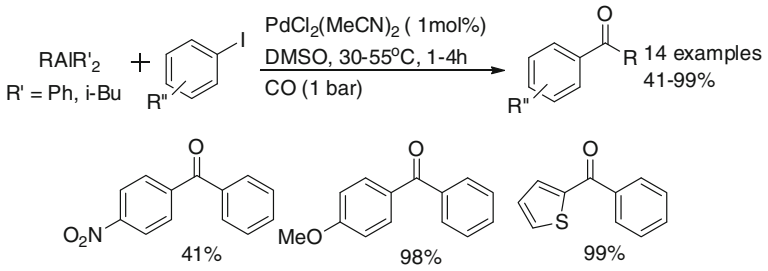
Scheme 4.46 Pd-catalyzed carbonylative Hiyama reaction



Scheme 4.47 Palladium-catalyzed carbonylative synthesis of acyl silanes



Scheme 4.48 Palladium-catalyzed carbonylative coupling of aryl iodides and trimethylsilylacetonitrile

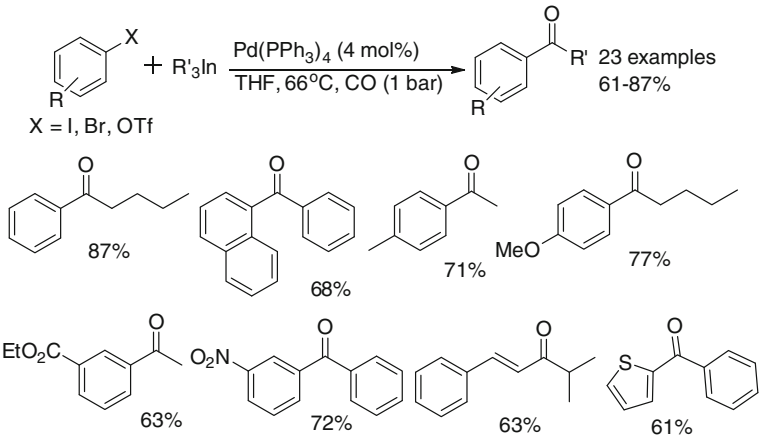


Scheme 4.49 Pd-catalyzed carbonylative coupling of organoaluminum compounds

carbonylative coupling of alkylaluminums with aryl iodides was reported by Kojima's group [89]. Secondary and tertiary alcohols as well as asymmetrical ketones were produced in moderate to good yields in the presence of 5 mol % of a palladium catalyst.

In 2003 the first carbonylative coupling of indium reagents was reported both by Lee [90] and Sarandeses [91]. Asymmetrical ketones were produced by the carbonylative coupling of trialkyl- and triarylindiums with aryl halides in the presence of a palladium catalyst under one bar of CO in THF at 66 °C (Scheme 4.50).

Later, Lee and colleagues reported on the carbonylative coupling of tetraorganoindates with aryl iodides and bromides [92]. Tetraorganoindates were easily prepared from the reaction of 1 equiv. of $InCl_3$ with 4 equiv. of organometallics

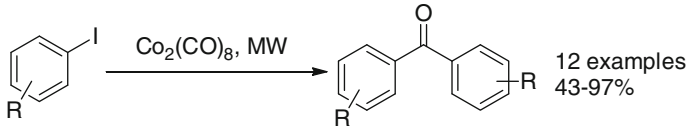


Scheme 4.50 Pd-catalyzed carbonylative coupling of organoindiums

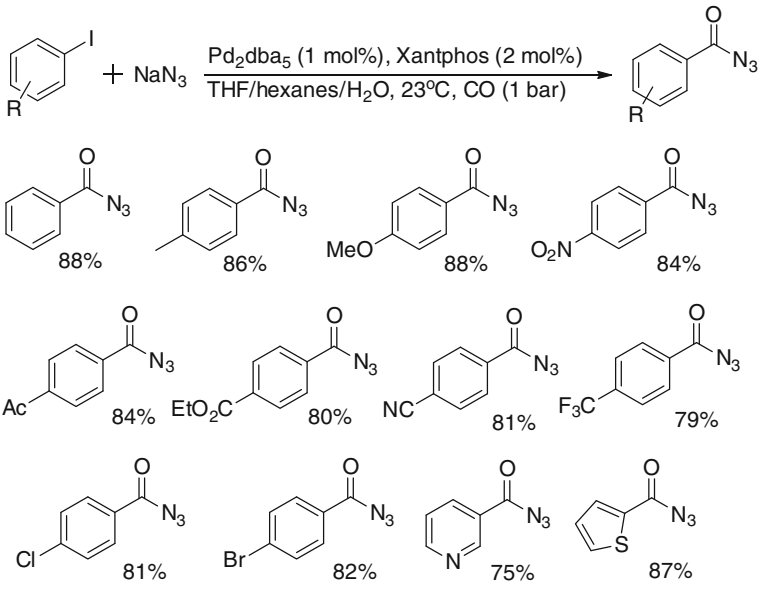
and have been applied in carbonylative coupling reactions with various organic electrophiles as an effective nucleophilic reagent. For example, ketones were produced in good yields under 1 bar of CO in THF at 60 °C. Finally, a palladium-catalyzed carbonylative coupling of organolead compounds to symmetrical ketones was also reported [93].

Additionally, symmetric ketones have also been produced by the carbonylative homo-coupling of organometallic reagents [94–99]. Under the assistant of palladium catalysts and under the pressure of carbon monoxide, ketones were produced from alkenyl- and arylborates and boronic acids, diaryliodonium salts, organolead compounds and arylmercuric salts. $[Rh(CO)_2Cl]_2$ was also applied as a catalyst for the carbonylative homo-coupling of vinyl- and arylmercurials.

Cobalt catalysts were also applied in the carbonlytive coupling reactions. In the presence of $CoBr_2$ in THF/NMP, functionalized organozinc halides were carbonylative coupled under atmospheric pressure of carbon monoxide and gave symmetrical ketones in 56–80 % yields [100]. By combining the advantages of metal activation, $Co_2(CO)_8$ mediated carbonylative coupling of aryl iodides under microwave irradiation was developed by Larhed and colleagues [101]. A number of ketones were produced in moderate to excellent yields (Scheme 4.51). Addi-



Scheme 4.51 Cobalt-mediated carbonylative coupling of aryl iodides



Scheme 4.52 Palladium-catalyzed carbonylative coupling of ArI and NaN_3

tionally, $[Bu_4][HFe(CO)_4]$ was also found to be efficient for the carbonylation of iodobenzene under phase transfer conditions. Benzophenone was produced in an 85 % yield at 70 °C under atmospheric pressure of carbon monoxide [102].

In 2012, Grushin's team developed a palladium-catalyzed carbonylative coupling of aryl iodides with sodium azide [103]. This catalytic reaction occurs smoothly at temperatures as low as 25–50 °C and 1 bar to cleanly produce aroyl azides from the corresponding aryl iodides, CO and NaN_3 (Scheme 4.52). The reaction exhibits high-functional group tolerance and can also be conveniently used for one-pot, two-step procedures furnishing primary benzamides, iminophosphoranes, isocyanates, and ureas in high yield without isolation of the primary benzoyl azide product.

In this chapter we have discussed the carbonylative transformation of C–X with organometallic reagents as coupling partners. Ketones were produced selectively. In the reaction mechanism, transmetalation is normally involved before reductive elimination.

In the next chapter we will discuss the use of alkynes as nucleophiles. From the reaction mechanism for Sonogashira reactions, the in situ-formed alkynylcopper intermediate should do transmetalation with palladium center and followed by reductive elimination, which is similar to the carbonylative reactions described in this chapter.

References

1. Budavari, S.: The Merck Index, 11th edn. Merck, Rahway (1989)
2. Olah, G.A.: Friedel-Crafts Chemistry. Wiley, New York (1973)
3. Silbestri, G.F., Bogel-Masson, R., Lockhart, M.T., Chopa, A.B.: J. Organomet. Chem. **691**, 1520 (2006)
4. Neumann, W.P., Hillgärtner, H., Baines, K.M., Dicke, R., Vorspohl, K., Kowe, U., Nussbeutel, U.: Tetrahedron **45**, 951 (1989)
5. Labadie, J.W., Stille, J.K.: J. Am. Chem. Soc. **105**, 6129 (1983)
6. Gooßen, L.J., Ghosh, K.: Angew. Chem. Int. Ed. **40**, 3458 (2001)
7. Huang, Y.C., Majumdar, K.K., Cheng, C.-H.: J. Org. Chem. **67**, 1682 (2002)
8. Brunet, J.-J., Chauvin, R.: Chem. Soc. Rev. **24**, 89 (1995)
9. Wakita, Y., Yasunaga, T., Akita, M., Kojima, M.: J. Organomet. Chem. **301**, C17 (1986)
10. Ishiyama, T., Miyaura, N., Suzuki, A.: Bull. Chem. Soc. Jpn. **1991**, 64 (1999)
11. Ishiyama, T., Miyaura, N., Suzuki, A.: Tetrahdron Lett. **32**, 6923 (1991)
12. Ishiyama, T., Murata, M., Suzuki, A., Miyaura, N.: J. Chem. Soc. Chem. Commun. 295 (1995)
13. Ishiyama, T., Kizaki, H., Miyaura, N., Suzuki, A.: Tetrahedron Lett. **34**, 7595 (1993)
14. Ishiyama, T., Kizaki, H., Hayashi, T., Suzuki, A., Miyaura, N.: J. Org. Chem. **63**, 4726 (1998)
15. Ishikura, M., Terashima, M.: J. Org. Chem. **59**, 2634 (1994)
16. Kang, S.-K., Lim, K.-H., Ho, P.-S., Yoon, S.-K., Son, H.-J.: Synth. Commun. **28**, 1481 (1998)
17. Xia, M., Chen, Z.: J. Chem. Res. 400 (1999)
18. Skoda-Foeldes, R., Szekvoelgyi, Z., Kollar, L., Berente, Z., Horvath, J., Tuba, Z.: Tetrahedron **56**, 3415 (2000)
19. Couve-Bonnaire, S., Carpentier, J.-F., Mortreux, A., Castanet, Y.: Tetrahedron Lett. **42**, 3689 (2001)
20. Maerten, E., Hassouna, F., Couve-Bonnaire, S., Mortreux, A., Carpentier, J. -F.: Synlett 1874 (2003)
21. Couve-Bonnaire, S., Carpentier, J.-F., Mortreux, A., Castanet, Y.: Tetrahedron **59**, 2793 (2003)
22. Maerten, E., Sauthier, M., Mortreux, A., Castanet, Y.: Tetrahedron **63**, 682 (2007)
23. Gotov, B., Kaufmann, J., Schumann, H., Schmalz, H.-G.: Synlett 1161 (2002)
24. Andrus, M.B., Ma, Y., Zang, Y., Song, C.: Tetrahedron Lett. **43**, 9137 (2002)
25. Mingli, D., Liang, B., Wang, C., You, Z., Xiang, J., Dong, G., Chen, J., Yang, Z.: Adv. Synth. Catal. **346**, 1669 (2004)
26. Saeki, T., Son, E.-C., Tamao, K.: Org. Lett. **6**, 617 (2004)
27. Rahman, O., Kihlberg, T., Långström, B.: Eur. J. Org. Chem. 474 (2004)
28. Medio-Simon, M., Mollar, C., Rodriguez, N., Asensio, G.: Org. Lett. **7**, 4669 (2005)
29. Bartali, L., Guarna, A., Larini, P., Occhiato, E.G.: Eur. J. Org. Chem. 2152 (2007)
30. Petz, A., Peczely, G., Pinter, Z., Kollar, L.: J. Molec. Catal. A: Chem. **255**, 97 (2006)
31. Prediger, P., Moro, A.V., Nogueira, C.W., Saegnago, L., Menezes, P.H., Rocha, J.B.T., Zeni, G.: J. Org. Chem. **71**, 3786 (2006)
32. Yang, D., Liu, Z., Li, Y., Chen, B.: Synth. Commun. **37**, 3759 (2007)
33. Zheng, S., Xu, L., Xia, C.: Appl. Organometal. Chem. **21**, 772 (2007)
34. O'Keefe, B.M., Simmons, N., Martin, S.F.: Org. Lett. **10**, 5301 (2008)
35. Neumann, H., Brennführer, A., Beller, M.: Chem. Eur. J. **14**, 3645 (2008)
36. Qin, W., Yasuike, S., Kakusawa, N., Kurita, J.: J. Organometal. Chem. **693**, 2949 (2008)
37. Pirez, C., Dheur, J., Sauthier, M., Castanet, Y., Mortreux, A.: Synlett 1745 (2009)
38. Cai, M., Zheng, G., Zha, L., Peng, J.: Eur. J. Org. Chem. 1585 (2009)
39. Zheng, G., Wang, P., Cai, M.: Chin. J. Chem. **27**, 1420 (2009)
40. Tambade, P.J., Patil, Y.P., Panda, A.G., Bhanage, B.M.: Eur. J. Org. Chem. 3022 (2009)

41. Arthuis, M., Pontikis, R., Florent, J.-C.: Org. Lett. **11**, 4608 (2009)
42. Kaganovsky, L., Gelman, D., Rueck-Braun, K.: J. Organometal. Chem. **695**, 260 (2010)
43. Wu, X.-F., Neumann, H., Beller, M.: Tetrahedron Lett. **51**, 6146 (2010)
44. Wu, X.-F., Neumann, H., Beller, M.: Adv. Synth. Catal. **353**, 788 (2011)
45. Stille, J.K.: Angew. Chem. Int. Ed. Engl. **25**, 508 (1986)
46. Kikukawa, K., Idemoto, T., Katayama, A., Kono, K., Wada, F., Matsuda, T.: J. Chem. Soc. Perkin Trans. I 1511 (1987)
47. Kikukawa, K., Kono, K., Wada, F., Matsuda, T.: Chem. Lett. 35 (1982)
48. Echavarren, A.M., Stille, J.K.: J. Am. Chem. Soc. **110**, 1557 (1988)
49. Kwon, H.B., McKee, B.H., Stille, J.K.: J. Org. Chem. **55**, 3114 (1990)
50. Scott, W.J., Crisp, G.T., Stille, J.K.: Org. Synth. **68**, 116 (1990)
51. Stille, J.K., Su, H., Hill, D.H., Schnelder, P., Tanaka, M., Morrison, D.L., Hegedus, L.S.: Organometallics **1991**, 10 (1993)
52. Skoda-Foeldes, R., Csakai, Z., Kollar, L., Horvath, J., Tuba, Z.: Steroids **60**, 812 (1995)
53. Caldirola, P., Chowdhury, R., Johansson, A.M., Hacksell, U.: Organometallics **14**, 3897 (1995)
54. Shimizu, R., Fuchikami, T.: Tetrahedron Lett. **37**, 8405 (1996)
55. Jeanneret, V., Meerpoel, L., Vogel, P.: Tetrahedron Lett. **38**, 543 (1997)
56. Chen, C., Wilcoxen, K., Zhu, Y.-F., Kim, K.-i., McCarthy, J.R.: J. Org. Chem. **64**, 3476 (1999)
57. Al-Qahtani, M.H., Pike, V.W.: J. Labelled Cpd. Radiopharm. **43**, 825 (2000)
58. Karimi, F., Barletta, J., Långström, B.: Eur. J. Org. Chem. 2374 (2005)
59. Kang, S.-K., Ryu, H.-C., Lee, S.-W.: J. Organometal. Chem. **610**, 38 (2000)
60. Morera, E., Ortar, G.: Bioorg. Med. Chem. Lett. **2000**, 10 (1815)
61. Ceccarelli, S., Piarulli, U., Gennari, C.: J. Org. Chem. **65**, 6254 (2000)
62. Ceccarelli, S.M., Piarulli, U., Telser, J., Gennari, C.: Tetrahedron Lett. **42**, 7421 (2001)
63. Yun, W., Li, S., Wang, B., Chen, L.: Tetrahedron Lett. **42**, 175 (2001)
64. Shimizu, R., Fuchikami, T.: Tetrahedron Lett. **42**, 6891 (2001)
65. Garrido, F., Raeppel, S., Mann, A., Lautens, M.: Tetrahedron Lett. **42**, 265 (2001)
66. Hanamoto, T., Handa, K., Mido, T.: Bull. Chem. Soc. Jpn. **75**, 2497 (2002)
67. Dubbaka, S.R., Vogel, P.: J. Am. Chem. Soc. **125**, 15292 (2003)
68. Dubbaka, S.R., Steunenberg, P., Vogel, P.: Synlett 1235 (2004)
69. Steunenberg, P., Jeanneret, V., Zhu, Y.-H., Vogel, P.: Tetrahedron: Asymmetry **16**, 337 (2005)
70. Mazzola, R.D., Giese Jr, S., Benson, C.L., West, F.G.: J. Org. Chem. **69**, 220 (2004)
71. Cai, M., Zheng, G., Ding, G.: Green Chem. **11**, 1687 (2009)
72. Lindh, J., Fardost, A., Almeida, M., Nilsson, P.: Tetrahedron Lett. **51**, 2470 (2010)
73. Savmarker, J., Lindh, J., Nilsson, P.: Tetrahedron Lett. **51**, 6886 (2010)
74. Kang, S.-K., Ryu, H.-C., Lee, S.-W.: J. Chem. Soc. Perkin Trans. **1**, 2661 (1999)
75. Kang, S.-K., Yamaguchi, T., Kim, T.-H., Ho, P.-S.: J. Org. Chem. **61**, 9082 (1996)
76. Kang, S.-K., Kim, W.-Y., Lee, Y.-T., Ahn, S.-K., Kim, J.-C.: Tetrahedron Lett. **39**, 2131 (1998)
77. Tamaru, Y., Ochiai, H., Yamada, Y., Yoshida, Z.-i.: Tetrahedron Lett. **24**, 3869 (1983)
78. Yasui, K., Fugami, K., Tanaka, S., Tamaru, Y.: J. Org. Chem. **60**, 1365 (1995)
79. Jackson, R.F.W., Turner, D., Block, M.H.: J. Chem. Soc. Chem. Commun. 2207 (1995)
80. Jackson, R.F.W., Turner, D., Block, M.H.: J. Chem. Soc. Perkin Trans. **I**, 865 (1997)
81. Custar, D.W., Le, H., Morken, J.P.: Org. Lett. **12**, 3760 (2010)
82. Wang, Q., Chen, C.: Tetrahedron Lett. **49**, 2916 (2008)
83. Natanaka, Y., Hiyama, T.: Chem. Lett. 2049 (1989)
84. Hatanaka, Y., Fukushima, S., Hiyama, T.: Tetrahedron **48**, 2113 (1992)
85. Kang, S.-K., Ryu, H.-C., Hong, Y.-T.: J. Chem. Soc. Perkin Trans. **I**, 736 (2001)
86. Wu, X.-F., Neumann, H., Beller, M.: Tetrahedron Lett. **53**, 582 (2012)
87. Park, A., Lee, S.: Org. Lett. **14**, 1118 (2012)
88. Bumagin, N.A., Ponomaryov, A.B., Beletskaya, I.P.: Tetrahedron Lett. **26**, 4819 (1985)

89. Wakita, Y., Yasunaga, T., Kojima, M.: J. Organometal. Chem. **288**, 261 (1985)
90. Lee, P.H., Lee, S.W., Lee, K.: Org. Lett. **5**, 1103 (2003)
91. Pena, M.A., Sestelo, J.P., Sarandeses, L.A.: Synthesis 780 (2003)
92. Lee, S.W., Lee, K., Seomoon, D., Kim, S., Kim, H., Kim, H., Shim, E., Lee, M., Lee, S., Kim, M., Lee, P.H.: J. Org. Chem. **69**, 4852 (2004)
93. Kang, S.-K., Ryu, H.-C., Choi, S.-C.: Synth. Commun. **2001**, 31 (1035)
94. Ohe, T., Ohe, K., Uemura, S., Sugita, N.: J. Organometa. Chem. **344**, C5 (1988)
95. Cho, C.S., Ohe, T., Uemura, S.: J. Organomet. Chem. **496**, 221 (1995)
96. Zhou, T., Chen, Z.-C.: Synth. Commun. **32**, 3431 (2002)
97. Kang, S.-K., Ryu, H.-C., Choi, S.-C.: Synth. Commun. **31**, 1035 (2001)
98. Heck, R.F.: J. Am. Chem. Soc. **90**, 5546 (1968)
99. Larock, R.C., Hershberger, S.S.: J. Org. Chem. **45**, 3840 (1980)
100. Devasagayaraj, A., Knochel, P.: Tetrahedron Lett. **36**, 8411 (1995)
101. Enquist, P.-A., Nilsson, P., Larhed, M.: Org. Lett. **5**, 4875 (2003)
102. Brunet, J.-J., Zaizi, A.E.: J. Organomet. Chem. **486**, 275 (1995)
103. Miloserdov, F.M., Grushin, V.V.: Angew. Chem. Int. Ed. **51**, 3668 (2012)

Chapter 5
Carbonylative Sonogashira Reactions

The Sonogashira reaction is generally known as a coupling reaction of terminal alkynes with aryl or vinyl halides. This reaction was first reported by Sonogashira and Hagihara in 1975 (Scheme 5.1) [1]. Today the Sonogashira coupling reaction is one of most powerful processes for C–C bond formation, especially for the synthesis of substituted alkynes [2–4]. From the reaction mechanism aspect, a transmetalation step was included between the palladium center and the in situ-formed organocopper intermediate.

If the Sonogashira reaction is carried out in a CO atmosphere, the reactions are called Carbonylative Sonogashira Reactions, which will give alkynone as an interesting structural motif found in numerous biologically active molecules [5–7]. Notably, this class of compounds plays a crucial role in the synthesis of natural products [8–12] and as key intermediates for the efficient formation of several heterocycles [13–15]. Traditionally, alkynones have been synthesized by transition metal catalyzed cross-coupling reactions of acid chlorides and terminal alkynes (Scheme 5.2) [16–24]. However, the stability of the respective acid chlorides is limited and a lack of functional tolerance is another problem of this methodology. Without a doubt, carbonylative Sonogashira coupling of corresponding terminal alkynes and aryl halides represents the most straightforward way to set up alkynones.

The first palladium-catalyzed carbonylative Sonogashira coupling was reported in 1981 by Kobayashi and Tanaka [25]. Aryl, heterocyclic, and vinylic halides reacted with CO and terminal acetylenes at 120 °C and 80 bar in the presence of NEt_3 and a catalytic amount of a palladium(II) complex to form alkynones in a 46–93 % yield (Scheme 5.3). Remarkably, aryl bromides and aliphatic alkynes were also included in the range of substrates. But NEt_3 was used as a solvent for this transformation and a relatively high pressure of CO was needed.

Interestingly, in 1991 Alper and Huang described another type of palladium-catalyzed carbonylative Sonogashira coupling of aryl iodides with benzyl acetylenes. Here, furanones were isolated as the terminal products and not the predicted alkynones [26]. In the presence of $Pd(OAc)_2/PPh_3$, aryl iodides and benzyl acetylenes were transformed into furanones in 33–88 % yields (Scheme 5.4). Palladium-catalyzed carbonylative Sonogashira coupling reactions of iodobenzene and

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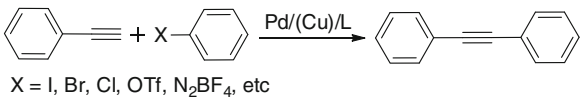
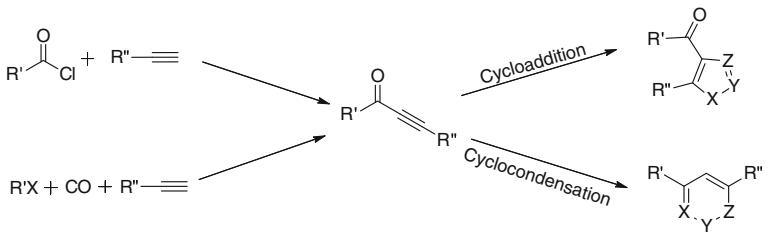
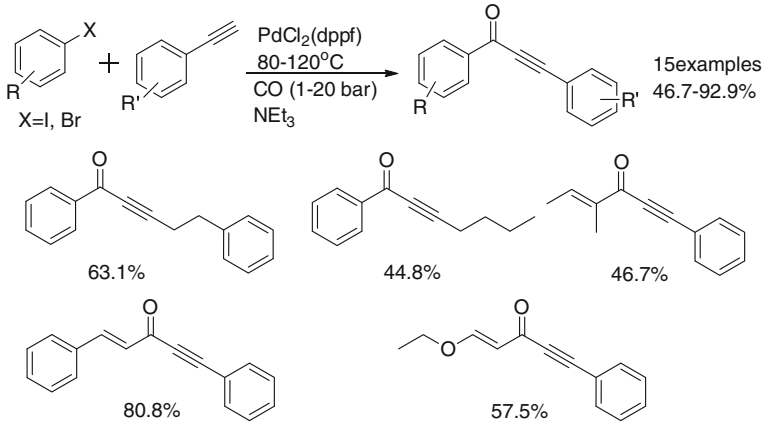


Scheme 5.1 Palladium-catalyzed Sonogashira coupling reaction



Scheme 5.2 Selected synthesis and applications of alkynones

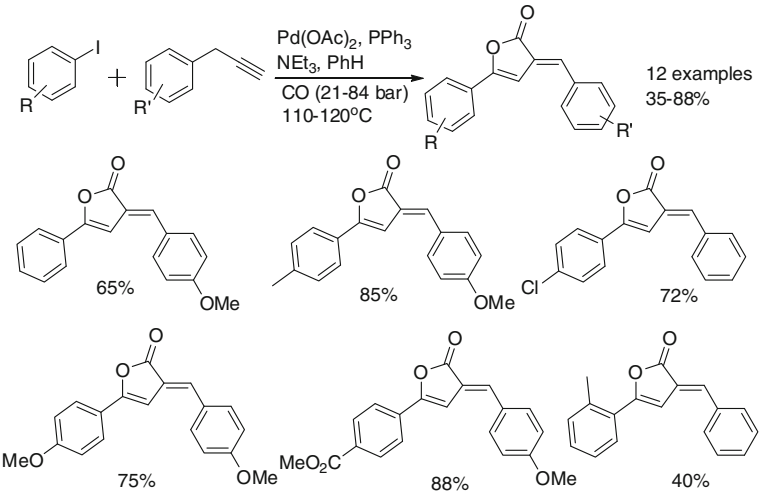


Scheme 5.3 First Pd-catalyzed carbonylative Sonogashira coupling of organic halides

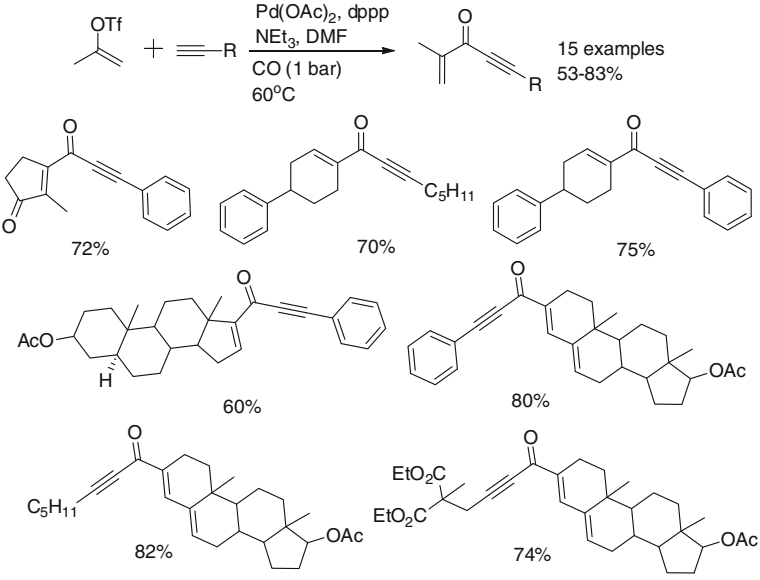
2-methyl-3-butyn-2-ol under biphasic conditions to furanones were also described by Kiji and colleagues [27].

In 1991 Ortar and colleagues published a general procedure for the carbonylative Sonogashira couplings of vinyl triflates with terminal acetylenes [28]. Various alkynyl ketones were produced in moderate to good yields (Scheme 5.5). However, this methodology failed in the case of activated alkynes or aryl triflates.

The catalytic ability of dimeric palladium hydroxide in carbonylative Sonogashira coupling was demonstrated by Alper and his team in 1994 [29]. In this report, terminal alkynes and alkynols were coupled with aryl iodides in the presence of carbon monoxide in moderate to good yields (Scheme 5.6). In 1995 Cacchi and colleagues presented a general methodology for 5-(2-acylethynyl)-

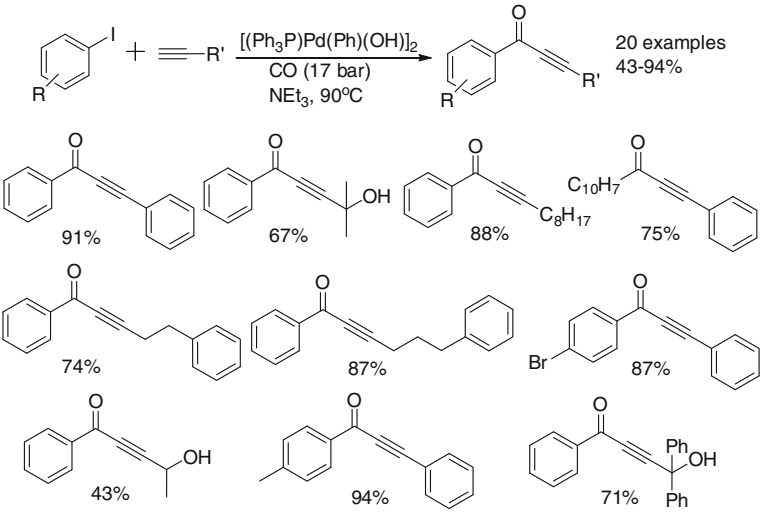


Scheme 5.4 Pd-catalyzed carbonylation of benzyl acetylenes to fuanones



Scheme 5.5 Pd-catalyzed carbonylative Sonogashira coupling of vinyl triflates with 1-alkynes

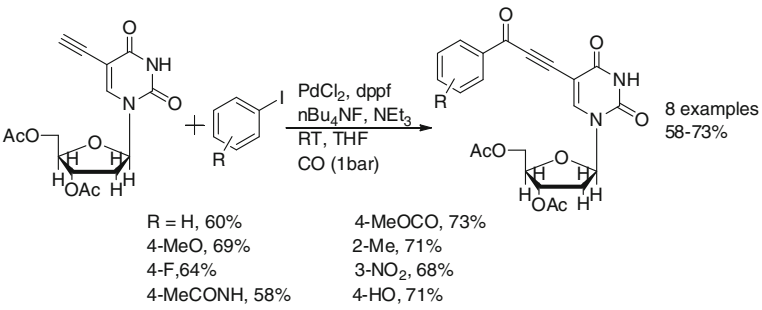
3′,5′-di-*O*-acetyl-2′-deoxyuridines synthesis [30]. In the presence of a palladium-catalyst, the corresponding alkynones were synthesized from aryl iodides and alkynes (Scheme 5.7).



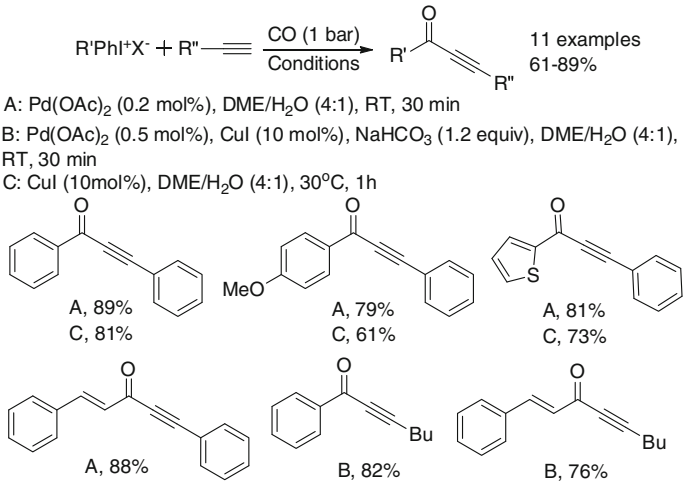
Scheme 5.6 Dimeric palladium hydroxide-catalyzed carbonylative Sonogashira coupling

The carbonylative Sonogashira reaction of iodonium salts with terminal alkynes was described by Kang and colleagues [31]. Both palladium/copper and palladium-catalyst systems alone could be used and various alkynones were synthesized in moderate to good yield in aqueous media (Scheme 5.8). Interestingly, a catalytic amount of CuI could also catalyze the reaction, and gave the corresponding alkynones in good yields.

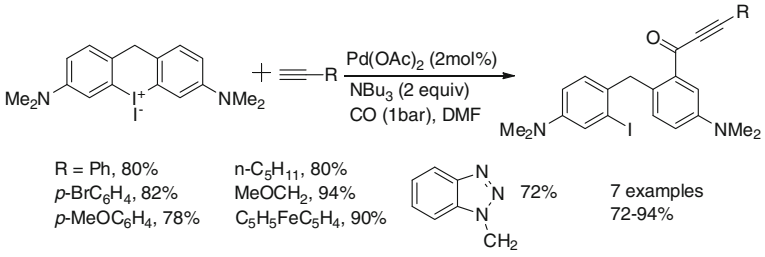
Another example of carbonylative Sonogashira coupling reactions with iodinium iodide and 1-alkynes was published by Ma and colleagues in 2001 [32]. Under mild conditions, iodine-substituted alkynones were produced in good yields (Scheme 5.9). Both aromatic, aliphatic and heterocyclic terminal acetylenes can be applied as their substrates.



Scheme 5.7 Pd-catalyzed carbonylative Sonogashira coupling of aryl iodides



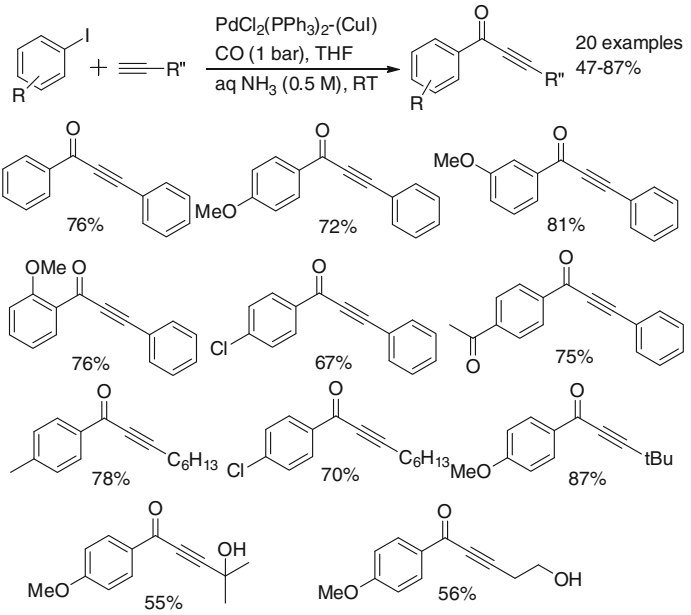
Scheme 5.8 Pd-catalyzed carbonylative Sonogashira coupling of iodonium salts with and without Cu co-catalysts



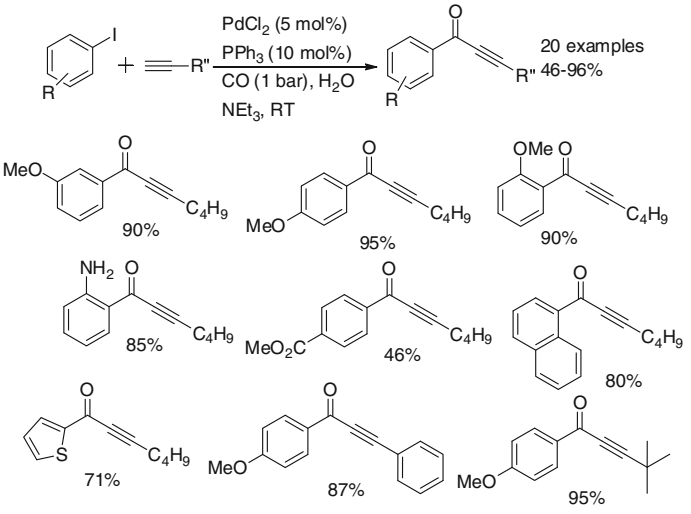
Scheme 5.9 Pd-catalyzed carbonylative Sonogashira coupling of iodinium iodide

An interesting room temperature carbonylation using a palladium/copper-catalyst system was published by Mori and Ahmed in 2003 [33–35]. As shown in Scheme 5.10, various aromatic alkynones were produced in moderate to good yields using aqueous ammonia as a base. Surprisingly, no competitive amination reaction occurred. This methodology was further exploited by Bishop's group to generate pyrazoles [35].

Water as a green solvent has been successfully applied as a reaction medium for palladium-catalyzed carbonylative Sonogashira reactions (Scheme 5.11) [36]. Instead of using alkynes, activated acetylenes stibanes can also be applied as coupling partners in carbonylations. An example is the palladium-catalyzed carbonylative Sonogashira coupling of alkynyl stibanes with aryl iodides that was published by Kakusawa and Kurita in 2006 [37]. The reaction was carried out under 1 bar of CO in DMAc using 5 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3.

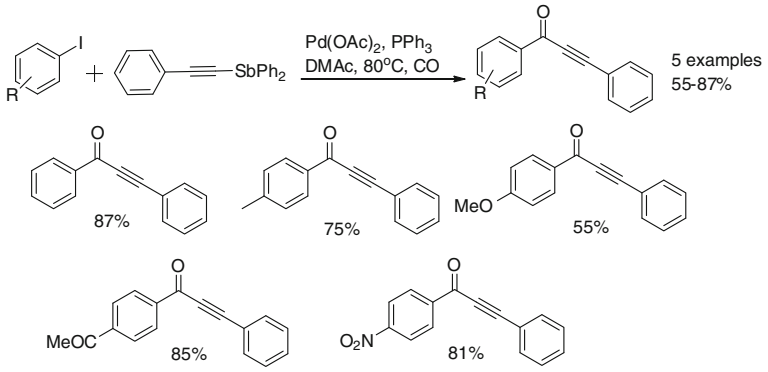


Scheme 5.10 Carbonylative room temperature Sonogashira reaction in aqueous ammonia



Scheme 5.11 Pd-catalyzed carbonylative Sonogashira coupling in water

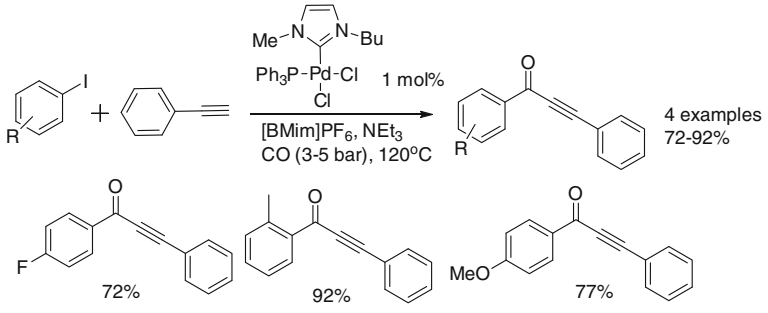
Alkynones were obtained in good yields along with a small amount of non-carbonylative coupling products (Scheme 5.12). However, this side reaction can be completely suppressed by increasing the CO pressure to 20 bar.



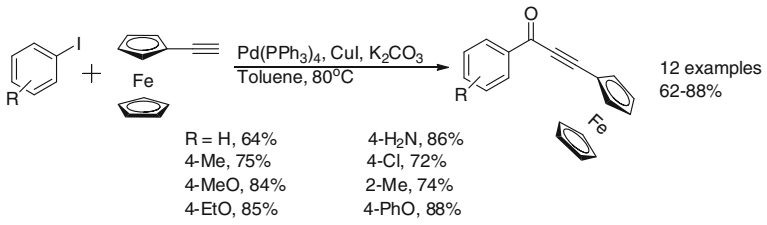
Scheme 5.12 Pd-catalyzed carbonylative Sonogashira coupling of ethynyl stibane with aryl iodides

The use of ionic liquids and flow chemistry technologies attract increasing attention. Consequently, these novel tools have also been successfully used in carbonylative Sonogashira reactions by Ryu and colleagues [38, 39]. Various alkynones were synthesized in moderate to good yields at a low pressure of CO in *n*-butyl methyl imidazolium hexafluorophosphate. The microreactor-based flow system was compared with typical batch conditions, and higher yields could be achieved with flow system (Scheme 5.13).

In 2006 Chen and his colleagues described a convenient, effective method for the carbonylative Sonogashira coupling of aryl iodides with ethynyl ferrocene under one atmosphere of CO [40]. Various aryl ferrocenylethynyl ketones have been synthesized in a 62–88 % yield (Scheme 5.14). Unexpectedly, strongly activated aryl iodides (4-Ac, 4-NO_2) and iodopyridine gave no desired carbonylation product. However, this methodology was also applied to a two-step synthesis of ferrocenyl pyrazole and pyrimidine derivatives by Skoda–Foldes and co-worker [41]. In 2009, this group reported on another protocol for the synthesis of ferrocenylethynyl ketones in water [42].



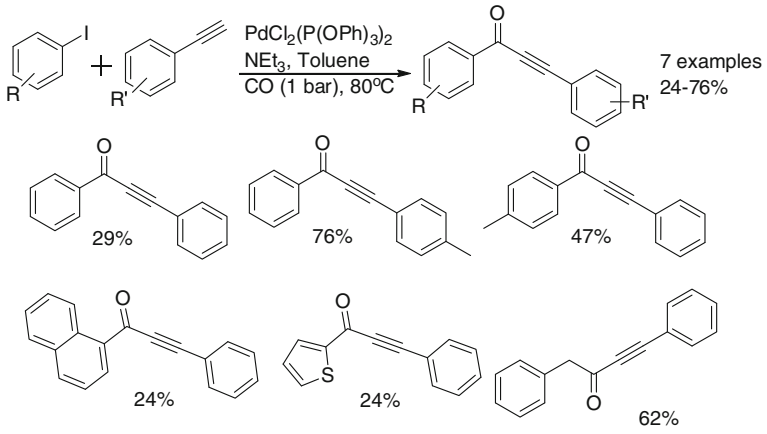
Scheme 5.13 Pd-catalyzed carbonylative Sonogashira reaction in ionic liquids



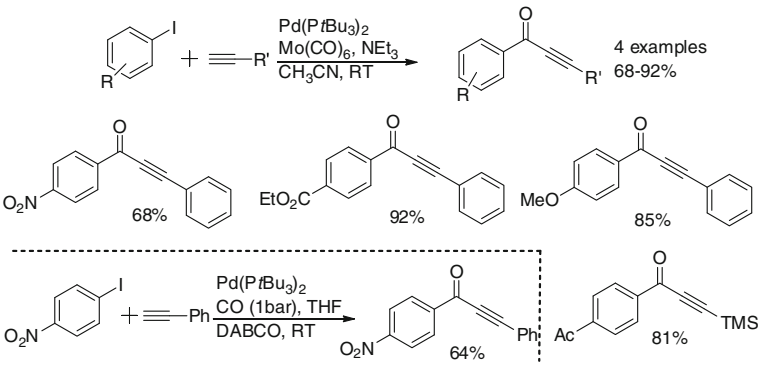
Scheme 5.14 Pd-catalyzed carbonylative Sonogashira coupling of ethynyl ferrocene with aryl iodides

The use of phosphites, e.g., $P(OPh)_3$ as a ligand in palladium-catalyzed carbonylative Sonogashira coupling, was first reported by Trzeciak and colleagues [43]. Using the defined complex $PdCl_2[P(OPh)_3]_2$ as a catalyst, alkynones were produced in low to moderate yields at 1 bar of CO (Scheme 5.15). When the reaction was conducted in an ionic liquid, the catalyst could be reused in four consecutive catalytic runs with high activity. Notably, benzyl bromide was reported as a substrate for the first time, but 2 equivalents of acetylenes were required for this system.

Kondo and Iizuka presented a palladium-catalyzed "CO-free" method for alkynone synthesis, which applies stoichiometric amounts of $Mo(CO)_6$ as a CO source [44]. The reaction was carried out at room temperature, and P*t*Bu$_3$ was found to be an essential ligand under these conditions. When strong electron-withdrawing substituted aryl iodides were used as substrates in this protocol, the corresponding alkynones were produced in good to excellent yields (Scheme 5.16). Again, a one-pot synthesis of pyrazoles via condensation of corresponding alkynones with hydrazine



Scheme 5.15 $PdCl_2[P(OPh)_3]_2$-catalyzed carbonylative Sonogashira coupling of aryl iodides with alkynes

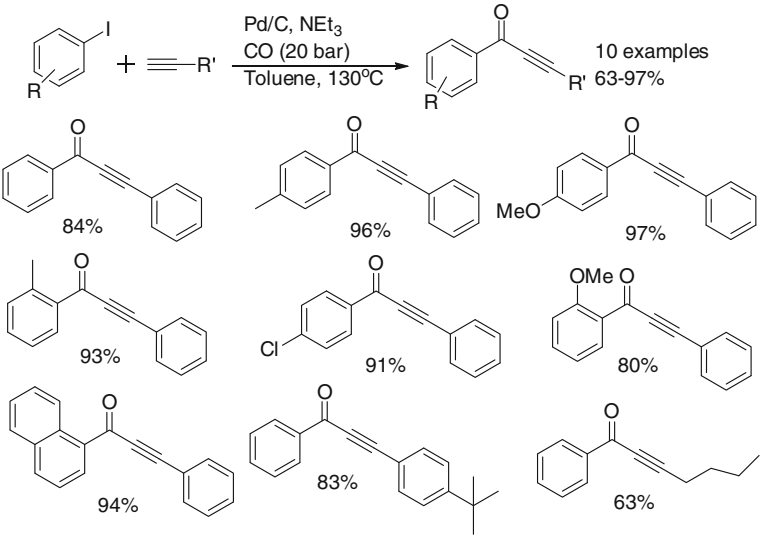


Scheme 5.16 Pd-catalyzed carbonylative Sonogashira coupling reaction with $Mo(CO)_6$ as a CO source

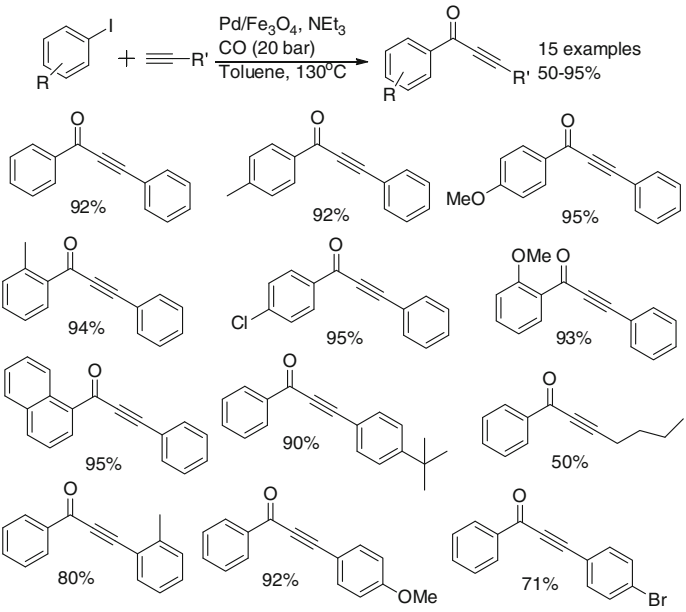
was also conducted and the corresponding products were obtained in good yields at room temperature.

In 2008, Xia and Chen described a recyclable phosphine-free catalyst system for alkynone synthesis [45]. Using palladium on charcoal (Pd/C) and NEt_3, the carbonylative Sonogashira coupling of aryl iodides with alkynes was smoothly carried out and the desired products were isolated in moderate to excellent yields (Scheme 5.17).

Later on, the same group presented an unusual variation of the palladium-catalyzed carbonylative Sonogashira coupling reaction [46]. Here, a magnetically



Scheme 5.17 Pd/C-catalyzed carbonylative Sonogashira reaction of aryl iodides

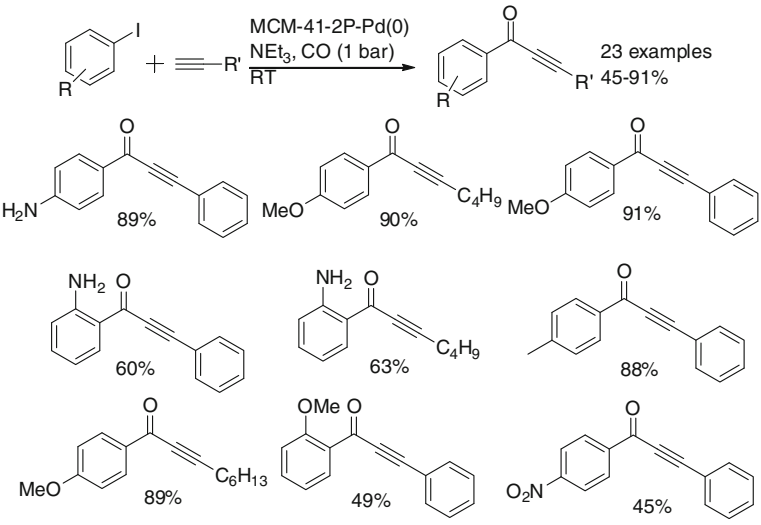


Scheme 5.18 Pd/Fe_3O_4-catalyzed carbonylative Sonogashira coupling of aryl iodides

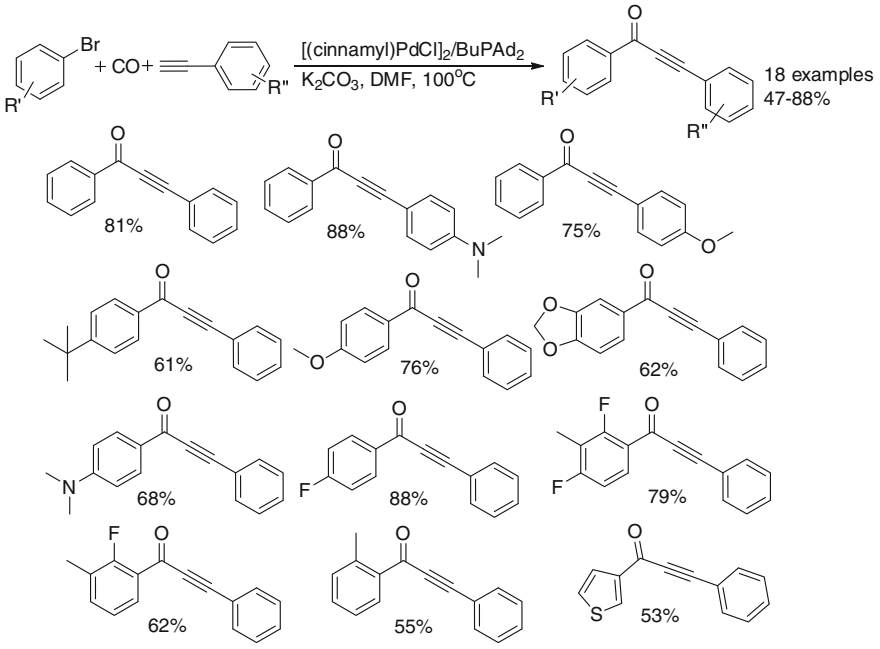
separable palladium-catalyst was synthesized by combining palladium nanoparticles and superparamagnetic Fe_3O_4 nanoparticles in a KBH_4 solution. This catalyst proved to be effective for the carbonylation reaction of aryl iodides with alkynes under phosphine-free conditions. Because of the magnetic behavior of Fe_3O_4, the catalyst could be reused with sustained selectivity and activity. Various alkynones have been synthesized in good to excellent yields (Scheme 5.18).

Another approach applying a heterogeneous palladium-catalyst was recently published by Cai and colleagues. They disclosed the MCM-41-supported bidentate phosphine palladium complex [MCM-41-2p-Pd(0)] as a polymer-supported palladium-catalyst [47]. Terminal alkynes were converted with aryl iodides under 1 bar CO to give alkynones in good to high yields (Scheme 5.19). Noteworthy is the fact that the use of a polymer as support in a Sonogashira coupling reaction was already reported by Takahashi and colleagues in 2008. The products can be released from the polymer by adding acid [48].

So far, basically all methodology developments in this area have focused on the use of expensive and easy-to-activate aryl iodides. Thus it was interesting that in 2010 Beller's group discovered a general and convenient palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides [49]. The key to the success was the application of $BuPAd_2$ as a ligand in the presence of K_2CO_3. Alkynones have been generated in moderate to good yields from the corresponding aryl bromides and terminal alkynes (Scheme 5.20). The one-pot synthesis of isoxazolines and pyrazoles was also successful.



Scheme 5.19 [MCM-41-Pd]-catalyzed carbonylative Sonogashira coupling reaction of aryl iodides

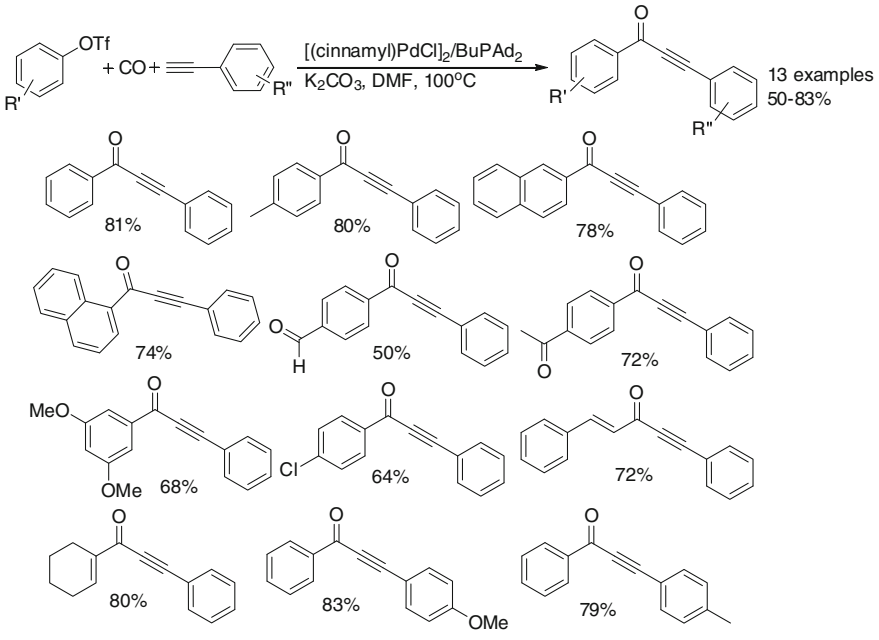


Scheme 5.20 Pd-catalyzed carbonylative Sonogashira coupling of aryl bromides

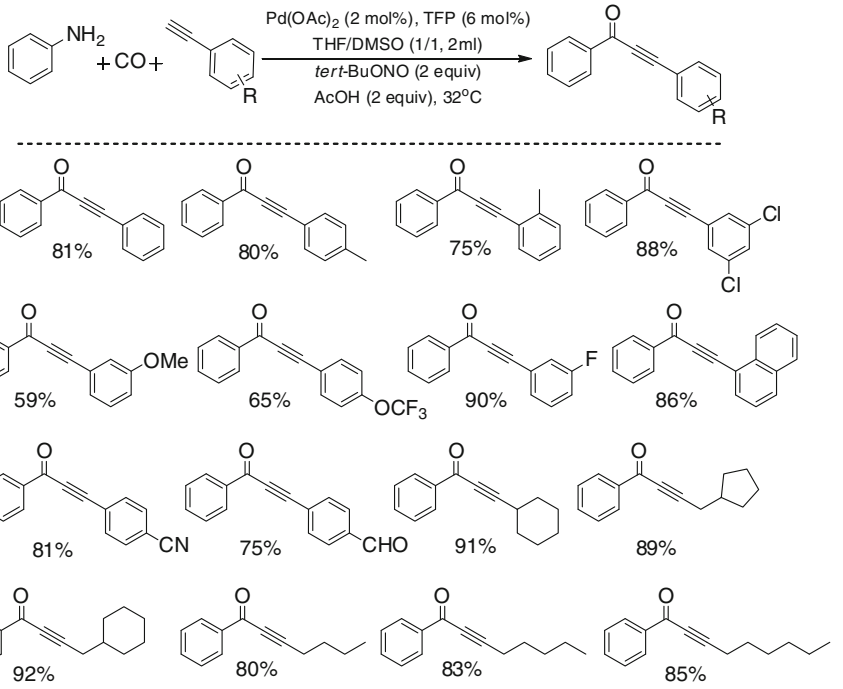
Since aryl triflates can easily be generated from corresponding phenols, Beller also developed a palladium-catalyzed carbonylative Sonogashira coupling of aryl triflates in 2010 [50]. This is the first carbonylative Sonogashira protocol that can apply aryl triflates as substrates. Various alkynones were produced in moderate to good yields under low pressure of CO (Scheme 5.21). A one-pot synthesis of enaminones was also achieved by running the reaction in the presence of primary amines.

Taking the advantages of anilines, Beller and his colleagues developed the first general and efficient methodology for carbonylative Sonogashira reaction of anilines [51]. This transformation proceeded under mild reaction conditions, and no base was needed. Both aromatic and aliphatic alkynes are suitable starting materials, and 30 different kinds of alkynones were produced in moderate to excellent yields (Scheme 5.22).

They also extended their methodologies to benzyl chlorides [52]. Applying an unusual $Pd(PPh_3)_2Cl_2/P(OPh)_3$ catalyst system, eight different alkynones are produced in moderate to good yields (45–80 %) by the carbonylation of benzyl chlorides and alkynes. Benzyl acetylene gave the corresponding furanones in moderate a yield (45–68 %) via palladium-catalyzed domino double carbonylation reactions. Based on this work, the carbonylative synthesis of furanones from aryl bromides and aryl triflates were developed as well [53]. The generality of this methodology was proved by more than 30 examples that proceeded good yields



Scheme 5.21 Pd-catalyzed carbonylative Sonogashira coupling of aryl triflates



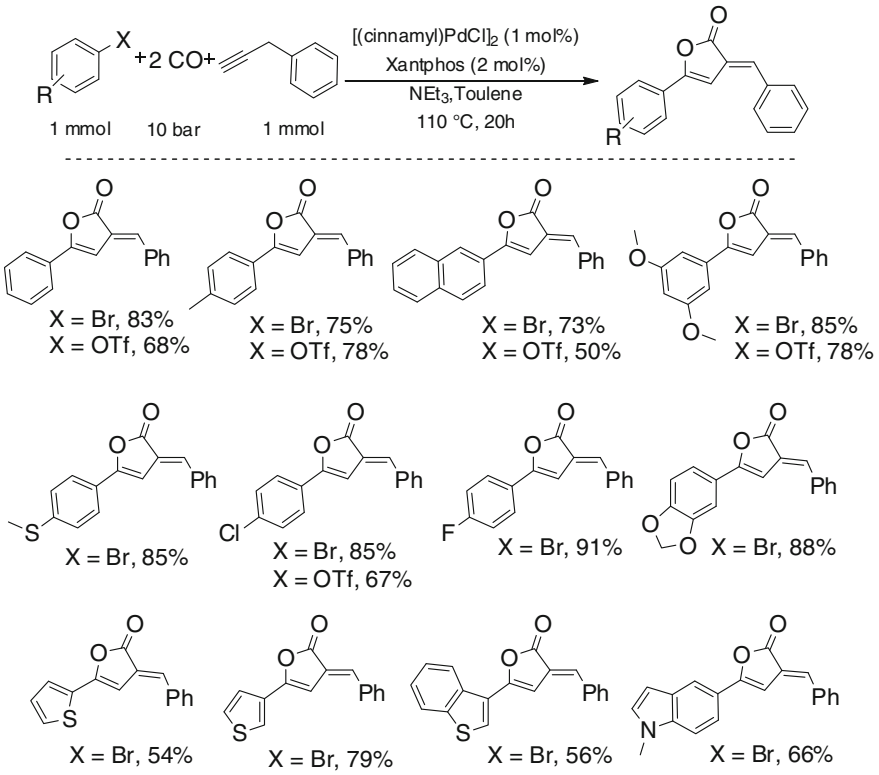
Scheme 5.22 Palladium-catalyzed Sonogashira carbonylation of anilines

(Scheme 5.23). Notably, the straightforward synthesis of permethylated BE-23372M, a kinase inhibitor, was achieved. Later on, they found that the carbonylation of aryl iodides with benzylacetylenes could even be carried out at room temperature under 1 bar of CO [54].

Ryu and colleagues described the synthesis of alkyl alkynyl ketones via the Pd/light-induced carbonylative Sonogashira coupling of iodoalkanes with terminal alkynes [55]. Using xenon light, in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and NEt_3, alkynones were produced in good yields (Scheme 5.24). This represents the first examples for Sonogashira carbonylations of alkyl iodides [56].

Despite all the synthetic developments, relatively little detailed mechanistic work has been performed on Sonogashira carbonylations until the present. The generally accepted mechanism is shown in Scheme 5.25. The typical reaction begins with the oxidative addition of ArX to a palladium(0) complex to form an aryl palladium(II) intermediate. The subsequent insertion of CO leads to the respective palladium acyl complex. Transmetallation, and finally reductive elimination, releases the product and a new catalytic cycle can be started. Notably, all species passing through the cycle are believed to be in a reversible equilibrium.

Besides the intermolecular Sonogashira carbonylation reactions, intramolecular Sonogashira carbonylations offer various possibilities for the preparation of interesting heterocycles. Typically, in these reactions 2-halophenols and

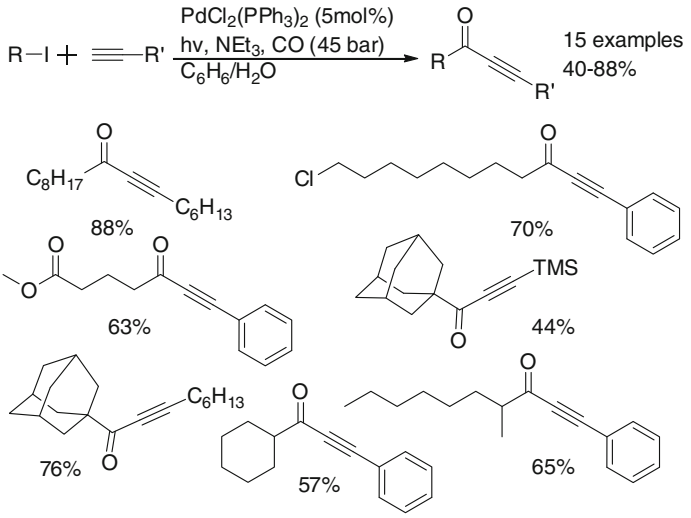


Scheme 5.23 Palladium-catalyzed furanones synthesis

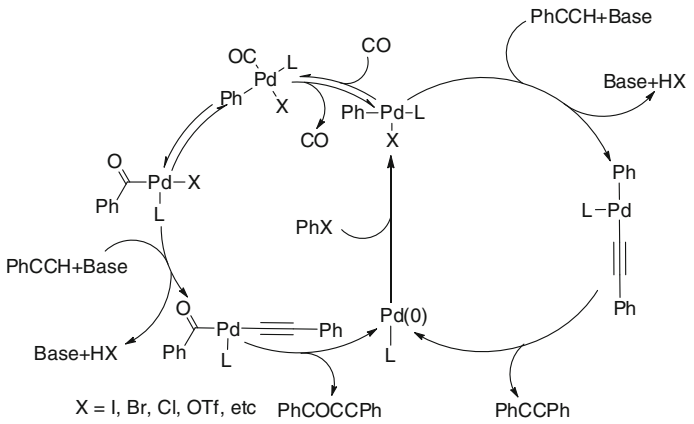
2-haloanilines or their derivatives are used with terminal alkynes. As early as 1990, Chiusoli and colleagues reported on the palladium-catalyzed synthesis of indoxyl derivatives (Scheme 5.26) [57].

Shortly afterwards, Torii and co-worker reported a novel methodology for the synthesis of quinolines [58, 59]. Here, quinolines were produced in good yields via palladium-catalyzed carbonylation of 2-haloaniline with terminal alkynes in the presence of CO (Scheme 5.27).

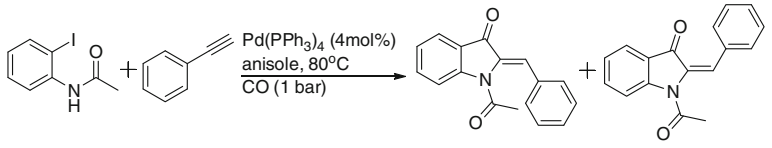
When the amino group of the 2-haloaniline substrate is primary, the cyclization proceeded without problem. But using alkylated anilines under the same conditions, the yield of the corresponding cyclization product decreased dramatically. A similar methodology was reported by Kalinin and colleagues in 1992, using $PdCl_2$(dppf) as a palladium precursor [60]. This cyclization was applied to synthesize the quinolone substructure of BILN 2061, a serin protease inhibitor [61, 62]. That same year, Chiusoli and colleagues published an interesting methodology for indenone synthesis [63]. The sequential oxidative addition of *ortho*-alkoxycarbonylmethylene or alkylamido-methylene-substituted aryl iodides, CO insertion, reductive coupling with terminal alkynes, nucleophilic attack by the activated methylene group, and



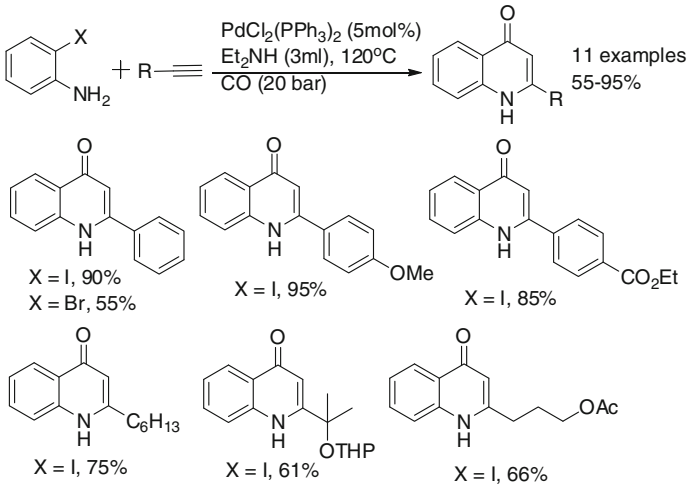
Scheme 5.24 Pd-catalyzed carbonylative Sonogashira coupling of iodoalkanes using xenon light



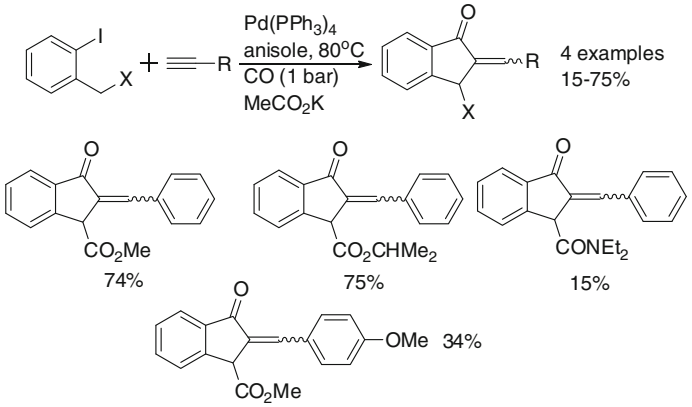
Scheme 5.25 Proposed reaction mechanism for carbonylation Sonogashira reaction



Scheme 5.26 Pd-catalyzed carbonylative synthesis of indoxyls



Scheme 5.27 Pd-catalyzed carbonylative synthesis of quinolines

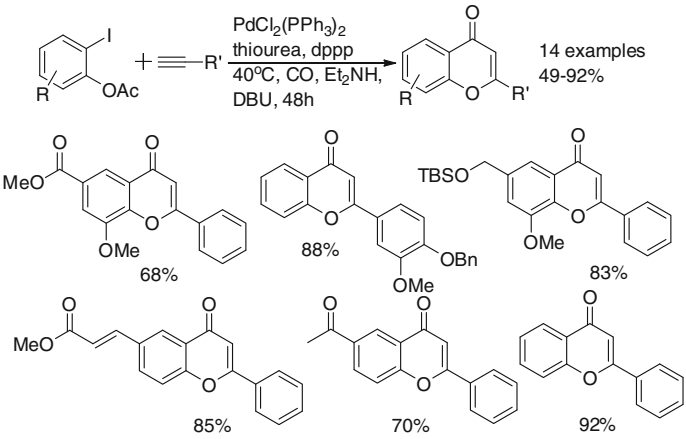


Scheme 5.28 Pd-catalyzed carbonylative synthesis of indenones

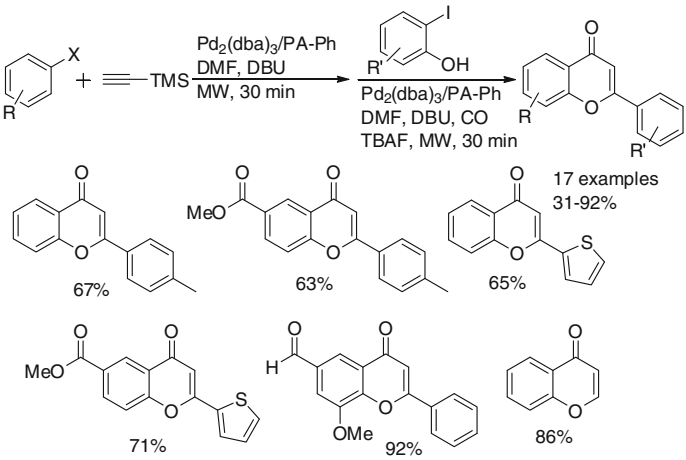
protonation with metal elimination, afford the indenones high yields in a one-pot process (Scheme 5.28).

In 2000 Yang and Miao reported a novel method for the preparation of flavones [64]. Various flavones are easily synthesized via palladium-catalyzed carbonylative annulation of iodophenol acetates with terminal acetylenes in high yields (Scheme 5.29). This novel reaction provides the possibility of a combinatorial synthesis of flavones on solid supports.

More recently, Capretta and Awuah described a microwave-assisted, one-pot palladium-catalyzed carbonylative Sonogashira annulation reaction [65]. Various flavones have been produced in moderate to good yields (Scheme 5.30). Alper and



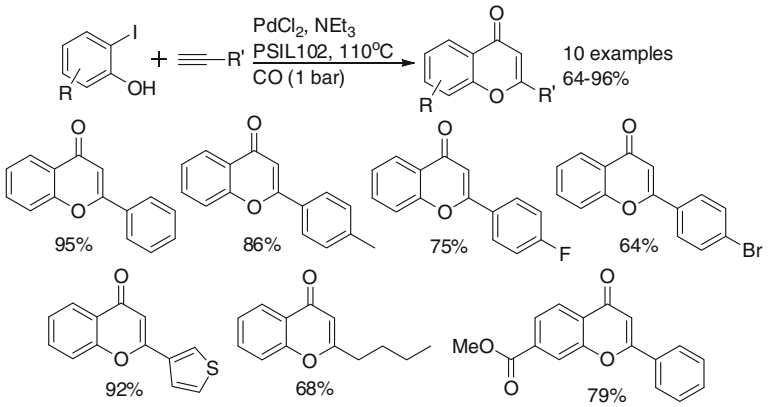
Scheme 5.29 Pd-catalyzed carbonylative synthesis of flavones



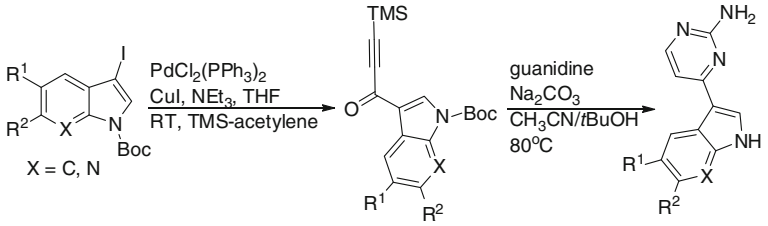
Scheme 5.30 Pd-catalyzed carbonylative synthesis of flavones

Yang reported another example of carbonylations of *o*-iodophenols with terminal acetylenes to obtain flavones. Their reaction proceeded under 1 bar of CO in ionic liquids based on phosphonium salt (PSIL102, $C_{14}H_{29}(C_6H_{13})_3)P^+Br^-$) [66]. It should be noted that by using PSIL102 as an ionic liquid, no phosphine ligand was required (Scheme 5.31).

Elegant synthetic applications of carbonylative Sonogashira reactions were described by Müller and his group. For example, in 2005 they succeeded in producing palladium-catalyzed one-pot, four-component carbonylations for the



Scheme 5.31 Pd-catalyzed carbonylative synthesis of flavones in PSIL102



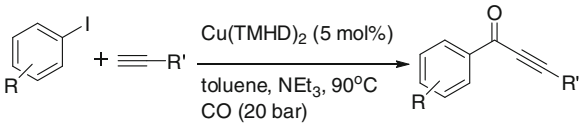
Scheme 5.32 Pd-catalyzed carbonylative synthesis of meridianins

synthesis of meridianins [67], which are natural and biologically activated compounds (Scheme 5.32).

In 2008 Bhanage's team reported on a copper-catalyzed carbonylative Sonogashira reaction of aryl iodides [68]. In this procedure, copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) [$Cu(TMHD)_2$] was used as the catalyst for this transformation and using NEt_3 as a base. Alkynones were produced in good yields (Scheme 5.33). A nickel-catalyzed carbonylation of allyl halides and acetylenes was reported on by Moretó and colleagues [69]. Cyclopentane skeletons were produced in high yields and with controlled stereochemistry.

In this chapter, we have discussed the carbonylative Sonogashira reaction of organohalides and their synthetic applications. Palladium-catalysts are still the main catalysts in this area. From the mechanism point of view, the same as the

Scheme 5.33 Copper-catalyzed carbonylative Sonogashira reaction



contents of Chap. 4, transmetalation is involved in the case of in situ formation of alkynylcopper intermediate. But the mechanism is different if a palladium-catalyst is the sole catalyst, which should be similar to the contents that will be discussed in the next chapter.

References

1. Sonogashira, K., Tohda, Y., Hagihara, N.: Tetrahedron Lett. **16**, 4467 (1975)
2. Doucet, H., Hierso, J.-C.: Angew. Chem. Int. Ed. **46**, 834 (2007)
3. Nicolaou, K.C., Bulger, P.G., Sarlah, D.: Angew. Chem. Int. Ed. **44**, 4442 (2005)
4. Negishi, E.-I.: Anastasia. L. Chem. Rev. 103, 1979 (2003)
5. Faweett, C.H., Firu, R.D., Spencer, D.M.: Physiol. Plant Pathol **1**, 163 (1971)
6. Imai, K.J.: Pharm. Soc. Jpn **76**, 405 (1956)
7. Quesnelle, C.A., Gill, P., Dodier, M., St. Laurent, D., Serrano-Wu, M., Marinier, A., Martel, A., Mazzucco, C.E., Stickle, T.M., Barrett, J.F., Vyas, D.M., Balasubramanian, B.N.: Bioorg. Med. Chem. Lett. 13, 519 (2003)
8. Karpov, A.S., Merkul, E., Rominger, F., Müller, T.J.J.: Angew. Chem. Int. Ed. **44**, 6951 (2005)
9. D'Souza, D.M., Müller, T.J.J.: Nat. Protoc. **3**, 1660 (2008)
10. Marco-Contelles, J., de Opazo, E.J.: Org. Chem **67**, 3705 (2002)
11. Forsyth, C.J., Xu, J., Nguyen, S.T., Samdai, I.A., Briggs, L.R., Rundberget, T., Sandvik, M., Miles, C.O.J.: Am. Chem. Soc **128**, 15114 (2006)
12. Tietze, L.F., Singidi, R.R., Gericke, K.M., Bockemeier, H., Laatsch, H.: Eur. J. Org. Chem. 5875 (2007)
13. Willy, B., Müller, T.J.J.: Arkivoc 195 (2008)
14. Aradi, A., Aschi, M., Marinelli, F., Verdecchia, M.: Tetrahedron **64**, 5354 (2008)
15. Bannwarth, P., Valleix, A., Gree, D., Gree, R.: J. Org. Chem **74**, 4646 (2009)
16. Lee, K.Y., Lee, M.J., Kim, J.N.: Tetrahedron **61**, 8705 (2005)
17. Stefani, H.A., Cella, R., Dorr, F.A., de Pereira, C.M.P., Gomes, F.P., Zeni, G.: Tetrahedron Lett. **2005**, 46 (2001)
18. Palimkar, S.S., Kumar, P.H., Jogdand, N.R., Daniel, T., Lahoti, R.J., Srinivasan, K.V.: Tetrahedron Lett. **47**, 5527 (2006)
19. Yim, S.J., Kwon, C.H., An, D.K.: Tetrahedron Lett. **48**, 5393 (2007)
20. Jackson, M.M., Leverett, C., Toczko, J.F., Roberts, J.C.: J. Org. Chem **67**, 5032 (2002)
21. Alonso, D.A., Nájera, C., Pacheco, M.C.: J. Org. Chem **69**, 1615 (2004)
22. Wang, B., Bonin, M., Micouin, L.J.: Org. Chem **70**, 6126 (2005)
23. Chen, L., Li, C.: Org. Lett. **6**, 3151 (2004)
24. Kakusawa, N., Yamaguchi, K., Kurita, J., Tsuchiya, T.: Tetrahedron Lett. **41**, 4143 (2000)
25. Kobayashi, T, Tanaka, M.: J.C.S. Chem. Comm. 333 (1981)
26. Huang, Y., Alper, H.J.: Org. Chem **56**, 4534 (1991)
27. Kiji, J., Okano, T., Kimura, H., Saiki, K.: J. Mol. Catal. A Chem **130**, 95 (1998)
28. Ciattini, P.G., Morera, E., Ortar, G.: Tetrahedron Lett. **32**, 6449 (1991)
29. Delaude, L., Masdeu, A.M., Alper, H.: Synthesis 1149 (1994)
30. Areadi, A., Cacchi, S., Marinelli, F., Pace, P., Sanzi, G.: Synlett 823 (1995)
31. Kang, S.-K., Lim, K.-H., Ho, P.-S., Kim, W-Y.: Synthesis 874 (1997)
32. Luo, S.-L., Liang, Y.-M., Liu, C.-M., Ma, Y.-X.: Synth. Comm **31**, 343 (2001)
33. Ahmed, M.S.M., Mori, A.: Org. Lett. **5**, 3057 (2003)
34. Ahmed, M.S.M., Sekiguchi, A., Masui, K., Mori, A.: Bull. Chem. Soc. Ja **78**, 160 (2005)
35. Bishop, B.C., Brands, K.M.J., Gibb, A.D., Kennedy, D.J.: Synthesis 43 (2004)

36. Liang, B., Huang, M., You, Z., Xiong, Z., Lu, K., Fathi, R., Chen, J., Yang, Z.J.: Org. Chem **70**, 6097 (2005)
37. Kakusawa, N., Kurita, J.: Chem. Pharm. Bull. **54**, 699 (2006)
38. Rahman, Md.T., Fukuyama, T., Kamata, N., Sato, M., Ryu, I.: Chem. Comm. 2236 (2006)
39. Fukuyama, T., Yamaura, R., Ryu, I.: Can. J. Chem. **83**, 711 (2005)
40. Ma, W., Li, X., Yang, J., Liu, Z., Chen, B., Pan, X.: Synthesis 2489 (2006)
41. Feher, C., Kuik, A., Mark, L., Kollar, L., Skoda-Foldes, R.J.: Organomet. Chem. **694**, 4036 (2009)
42. Li, C., Li, X., Zhu, Q., Cheng, H., Lv, Q., Chen, B.: Catal. Lett. **127**, 152 (2009)
43. Sans, V., Trzeciak, A.M., Luis, S., Ziolkowski, J.J.: Catal. Lett. **109**, 37 (2006)
44. Iizuka, M., Kondo, Y.: Eur. J. Org. Chem. 5180 (2007)
45. Liu, J., Chen, J., Xia, C.J.: Catal **253**, 50 (2008)
46. Liu, J., Peng, X., Sun, W., Zhao, Y., Xia, C.: Org. Lett. **10**, 3933 (2008)
47. Hao, W., Sha, J., Sheng, S., Cai, M.J.: Mol. Catal. A: Chem **298**, 94 (2009)
48. Doi, T., Inous, H., Tokita, M., Watanabe, J., Takahashi, T.J.: Comb. Chem. **10**, 135 (2008)
49. Wu, X.-F., Neumann, H., Beller, M.: Chem. Eur. J. **16**, 12104 (2010)
50. Wu, X.-F., Sundararaju, B., Neumann, H., Dixneuf, P.H., Beller, M.: Chem. Eur. J. **17**, 106 (2011)
51. Wu, X.-F., Neumann, H., Beller, M.: Angew. Chem. Int. Ed. **50**, 11142 (2011)
52. Wu, X.-F., Neumann, H., Beller, M.: Org. Biomol. Chem. **9**, 8003 (2011)
53. Wu, X.-F., Sundararaju, B., Neumann, H., Dixneuf, P.H., Beller, M.: Chem. Eur. J. **17**, 8014 (2011)
54. Wu, X.-F., Jiao, H., Neumann, H., Beller, M.: Chem. Eur. J. **18**, 16177 (2012)
55. Fusano, A., Fukuyama, T., Nishitani, S., Inouye, T., Ryu, I.: Org. Lett. **12**, 2410 (2010)
56. Frisch, A.C., Beller, M.: Angew. Chem. Int. Ed. **44**, 674 (2005)
57. An, Z.-W., Catellani, M., Chiusoli, G.P.J.: Organometa. Chem **397**, C31 (1990)
58. Torii, S., Okumoto, H., Xu, L.H.: Tetrahedron Lett. **32**, 237 (1991)
59. Torii, S., Okumoto, H., Xu, L.H., Sadkane, M., Shostakovsky, M.V., Ponomaryov, A.B., Kalinin, V.N.: Tetrahedron **49**, 6773 (1993)
60. Kalinin, V.N., Shostakovsky, M.V., Ponomaryov, A.B.: Tetrahedron Lett. **33**, 373 (1992)
61. Haddad, N., Tan, J., Farina, V.J.: Org. Chem **71**, 5031 (2006)
62. Genelot, M., Bendjeriou, A., Dufaud, V., Djakovitch, L.: Applied Catal. A General **369**, 125 (2009)
63. Brocato, E., Cstagnoli, C., Catellani, M., Chiusoli, G.P.: Tetrahedron Lett. **33**, 7433 (1992)
64. Miao, H., Yang, Z.: Org. Lett. **2**, 1765 (2000)
65. Awuah, E., Capretta, A.: Org. Lett. **11**, 3210 (2009)
66. Yang, Q., Alper, H.J.: Org. Chem **75**, 948 (2010)
67. Karpov, A.S., Merkul, E., Rominger, F., Müller, T.J.J.: Angew. Chem. Int. Ed. **44**, 6951 (2005)
68. Tambade, P.J., Patil, Y.P., Nandurkar, N.S., Bhanage, B.M.: Synlett 886 (2008)
69. del Moral, D., Ricart, S., Moretó, J.M.: Chem. Eur. J. **16**, 9193 (2010)

Chapter 6
Carbonylative C–H Activations

Transition metal-catalyzed carbonylation reactions represent an enormous toolbox for CO–X bond formation (X = C, N, O, etc.). While most coupling reactions take place with heteronucleophiles nowadays, carbonylations including C–H activation are attracting more and more attention because the use of stoichiometric amounts of organometallic reagents can be avoided.

The first report on a palladium-catalyzed carbonylative C–H activation was published in 1986 by Kobayashi and Tanaka [1]. They reported that the carbonylation of organic halides with activated methylene compounds in the presence of NEt_3 under 20 bar of CO produces various ketones in good yields (Scheme 6.1). Aryl iodides, bromobenzene and one example of a vinyl bromide were used as starting materials. But relatively high pressure and high pressure are needed, and tri-ethylamine was used both as a base and solvent.

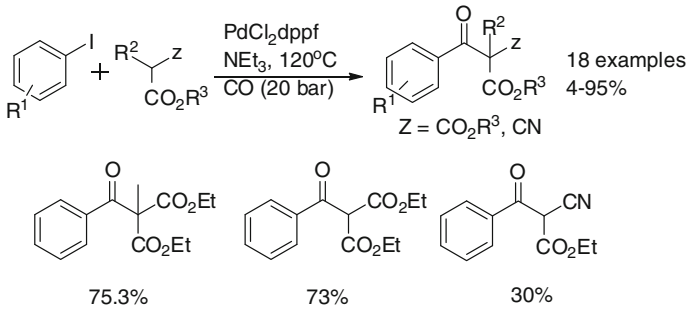
Later on, intramolecular coupling reactions of internal enolates were reported by Negishi and colleagues [2, 3], and 5- or 6-membered rings were synthesized by using the carbonylative C–H activation methodology (Scheme 6.2). In 1998 this group proved that the same reaction can also be catalyzed by $Cl_2Ni(PPh_3)_2$, $Ni(COD)_2$ or Li_2CuCl_4 [4].

In 2002 Larock and Campo reported the palladium-catalyzed cyclocarbonylation of *o*-halobiaryls [5, 6], giving various substituted fluorenones in high yields (Scheme 6.3). The cyclocarbonylation of 4′-substituted 2-iodobiphenyls generates 2-substituted fluorenones, incorporating either electron-donating or electron-withdrawing substituents. Similarly, 3′-substituted 2-iodobiphenyls afforded 3-substituted fluorenones in excellent yields with good regioselectivity. The authors also succeeded in extending the reaction to polycyclic fluorenones, fused isoquinoline, indole, pyrrole, thiophene, benzothiophene, and benzofuran rings.

In 2007 the palladium-catalyzed coupling of aryl or vinyl iodides with ethyl diazoacetate was published by Wang and his team [7]. It was the first example of using α-diazocarbonyl compounds as a coupling partner in a palladium-catalyzed carbonylation reaction (Scheme 6.4).

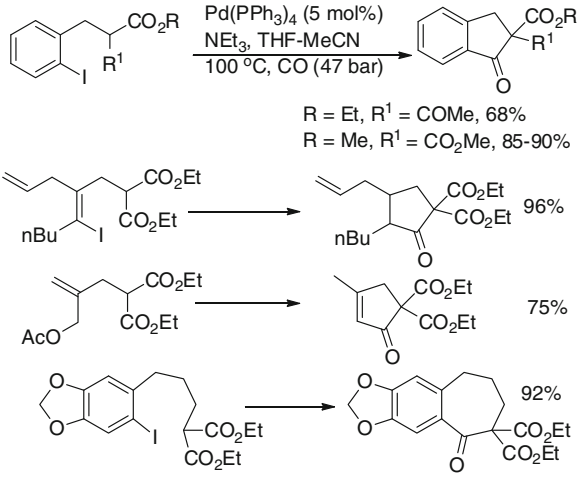
In 2010 Beller' group developed a general yet efficient methodology for the carbonylative coupling between aryl iodides and heteroarenes [8]. This represented the first carbonylative C–H activation reactions of heteroarenes to form diarylketones.

M. Beller and X.-F. Wu, *Transition Metal Catalyzed Carbonylation Reactions*,
DOI: 10.1007/978-3-642-39016-6_6, © Springer-Verlag Berlin Heidelberg 2013



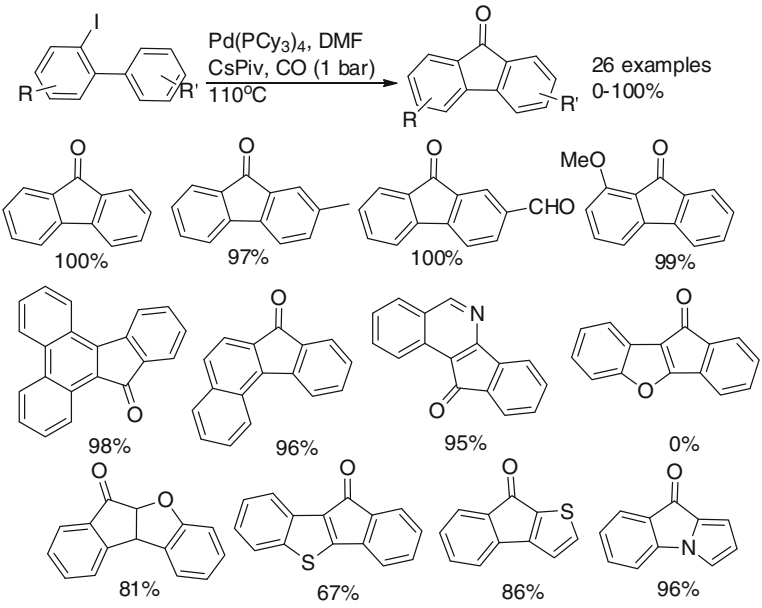
Scheme 6.1 Pd-catalyzed carbonylative coupling with activated methylene compounds

Scheme 6.2 Pd-catalyzed intramolecular carbonlative C–H activations

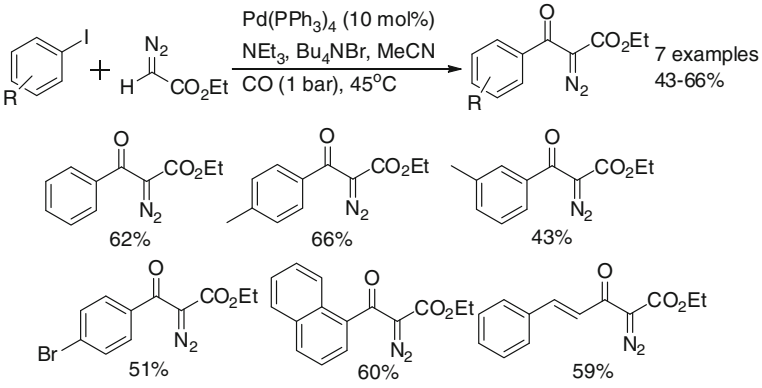


Applying various aryl iodides and different heterocycles, such as oxazoles, thiazoles, and imidazole in the presence of a Pd/Cu system, the corresponding coupling products are obtained in a straightforward manner in moderate to good yields (Scheme 6.5). Compared with established carbonylative cross-coupling reactions for the synthesis of ketones, no additional organometallic reagents are needed, making the protocol as an useful extension of palladium-catalyzed coupling reactions.

Above we mentioned the palladium-catalyzed carbonylative coupling of organohalides with C–H nucleophiles. Compared with their version of carbonylative coupling with organometallic reagents, the pre-activation of C–H bonds was not needed. The other pathway in carbonylative C–H activation is the reaction between two nucleophiles in the presence of an additional oxidant; sometimes these types of reactions are also called oxidative carbonylations. Only the reaction between Ar–H and nucleophiles will be discussed in the following; the other oxidative carbonylation reactions will be summarized in Chap. 8.

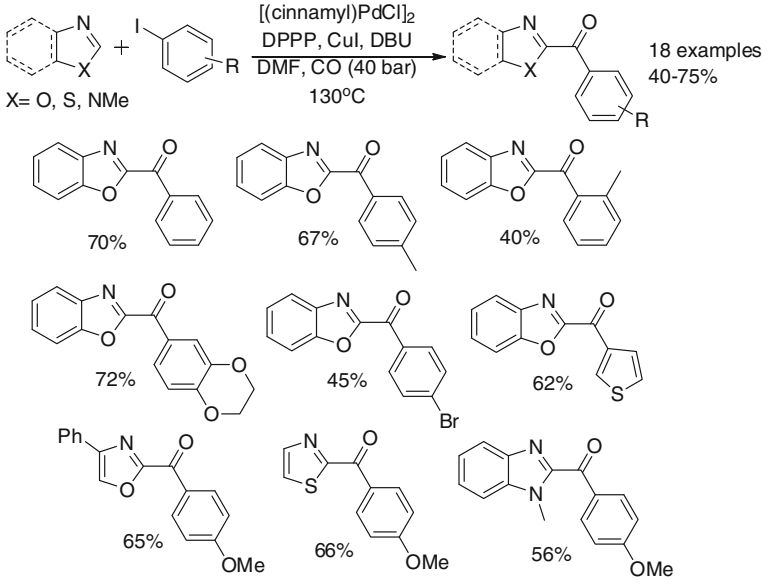


Scheme 6.3 Pd-catalyzed carbonylative synthesis of fluorenones



Scheme 6.4 Pd-catalyzed carbonylative coupling reactions of aryl iodides with α-diazocarbonyl compound

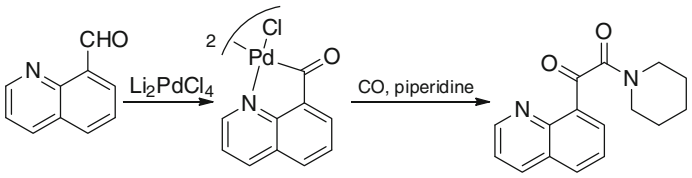
In 1980 Fujiwara and colleagues described for the first time a palladium-mediated oxidative carbonylation of arenes to benzoic acids [9–11]. The direct carboxylations of benzene, toluene, anisole, chlorobenzene, furan, and thiophene were carried out under CO and in the presence of $Pd(OAc)_2$. 2–43 % of the corresponding benzoic acids were formed as the terminal products. Later on, the reaction was performed with a catalytic amount of palladium salts using *tert*-



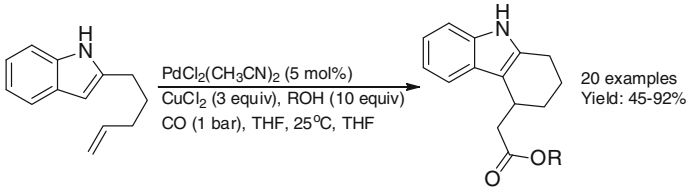
Scheme 6.5 Pd-catalyzed carbonylative coupling of ArI with heteroarenes

BuOOH, or $K_2S_2O_8$ as an additional oxidant. After the original work of Fujiwara, the C–H functionalization of simple arenes was investigated by other groups, too. In this respect, Itahara reported on the palladium-promoted oxidative carbonylation of 1-acylindoles, thiophenes, and 1,3-dimethyluracils to produce the corresponding carboxylic acids under atmospheric pressure of CO in 1982 [12, 13]. Palladium-catalyzed carbonylation of aromatic aldehydes and hydrocarbons to α-keto amides were developed by Yamamoto and his team [14]. Aromatic aldehydes were allowed to react with tertachloropalladate (II) via C–H activation to produce the corresponding aroylpalladium complexes, which afford α-keto amides after subsequent quenching with CO and piperidine in high yields (Scheme 6.6). A similar procedure was also described using 2-*tert*-butyl-4,4-dimethyl-2-oxazoline [15].

Dixneuf's group developed an interesting synthesis of heteroaromatic esters by a palladium-promoted oxidative carbonylation of thiophene, furan, benzofuran,



Scheme 6.6 Palladium-mediated carbonylation of C–H bonds



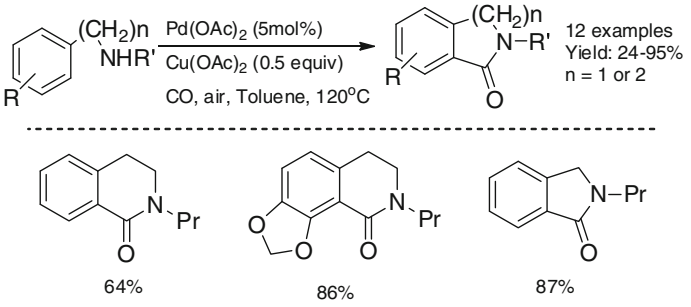
Scheme 6.7 Palladium-catalyzed cyclization/alkoxycarbonylation of alkenyl indoles

and pyrrole in the presence of alcohol [16]. The reaction proceeded at room temperature, but 50 bar of CO was required. The presence of mercury salt and copper(II) salt to reoxidize the Pd(0) species was also necessary. Later on, Ugo and colleagues succeeded in improving this methodology and described the reaction under 1 bar of CO [17]. In 2004, Nozaki and his team studied the hydroxycarbonylation of biphenyls via C–H activation processes. Using formic acid as a carbonyl source to avoid the management of CO gas, the palladium-catalyzed oxidative carbonylation was carried out in trifluoroacetatic acid in the presence of $K_2S_2O_8$ as an oxidant. Moderate yields of carboxylic acids were achieved, but the regioselectivity was problematic [18]. Phosphenium salts as strong electron-withdrawing ligands[19–21] proved to be effective in this catalytic system [22].

Tetrahydrocarbazoles and related compounds constitute heterocycles occurring both in pharmaceuticals and agrochemicals. Hence, it is interesting that Widenhoefer and Liu succeeded with palladium-catalyzed oxidative carbonylations for the synthesis of tetrahydrocarbazoles [23, 24]. Starting from alkenyl indoles in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%) and $CuCl_2$ (3 equiv) under 1 bar of CO in THF, the corresponding products were obtained in good yields with high regioselectivity (Scheme 6.7). A possible reaction pathway has also been given for this cyclization.

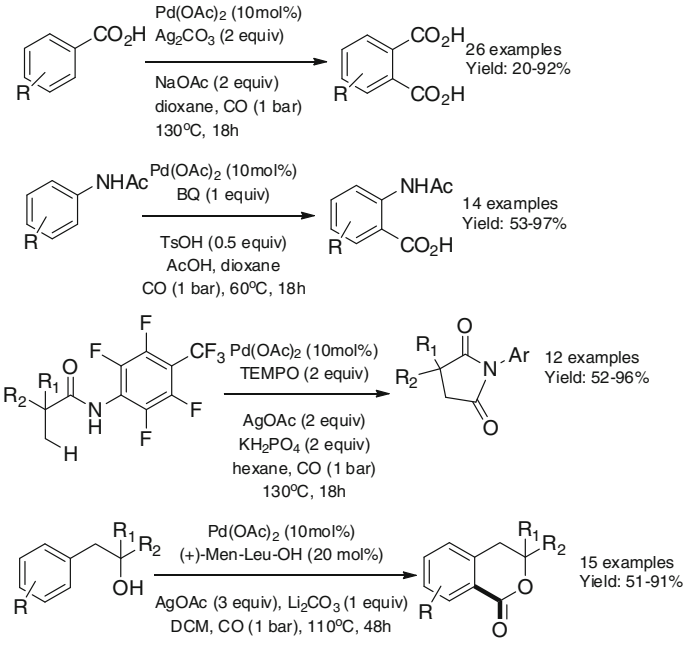
The group working with Orito reported on the synthesis of benzolactams via carbonylative C–H activation [25–27]. The assistance of $Cu(OAc)_2$ and the presence of CO (1 bar) and air were important for this transformation. The direct carbonylation reaction proceeded in a phosphine-free catalytic system with remarkable site selectivity to afford a variety of five- or six-membered benzolactams from secondary *w*-phenylalkylamines (Scheme 6.8). In the case of primary amines, the corresponding ureas were produced. With regard to the mechanism, the ortho-palladation of methyl L-phenylalanate and the depalladation with CO forming tetrahydroisoquinoline were carried out in a step-by-step study by Vicente and his colleagues [28].

In a series of papers, Ishii's group described their developments for the carboxylation of anisoles, biphenyls, and benzenes [29–31]. Applying a combination of $Pd(OAc)_2$ (5 mol%) and HPMoV (molybdovanadophosphates, 2 mol%) under pressure of CO (0.5 bar) and O_2 (0.5 bar), carboxylic acids were formed in AcOH in fairly good yields with fair to good selectivity.

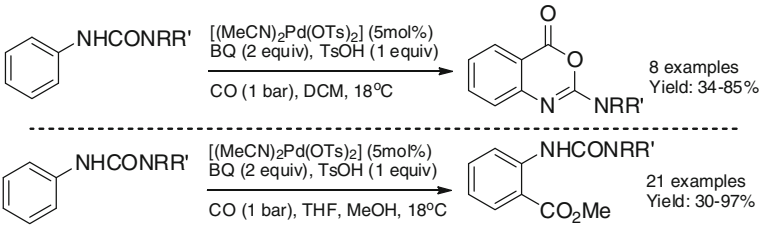


Scheme 6.8 Palladium-catalyzed carbonylative synthesis of benzolactams

Also, Yu and colleagues described several novel methodologies for the palladium-catalyzed oxidative carbonylative C–H activation of arenes. 1,2- and 1,3-dicarboxylic acids have been selectively produced from the corresponding benzoic acids under the assistance of $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv) and NaOAc (2 equiv) in the presence of CO (1 bar) at 130 °C [32]. Anthranilic acids, oxazolinones, and quinazolinones were synthesized from corresponding anilindes by applying BQ as an oxidant and TsOH as an additive [33–35]. Interestingly, they used amino acids as ligands to promote the oxidative carbonylation of phenethyl



Scheme 6.9 Palladium-catalyzed oxidative carbonylation of arenes



Scheme 6.10 Palladium-catalyzed oxidative carbonylation of aniline derivatives

alcohols to 1-isochromanones (Scheme 6.9). Recently, this group also succeeded in applying sulfonamide as a directing group in palladium-catalyzed oxidative carbonylative C–H activations [36].

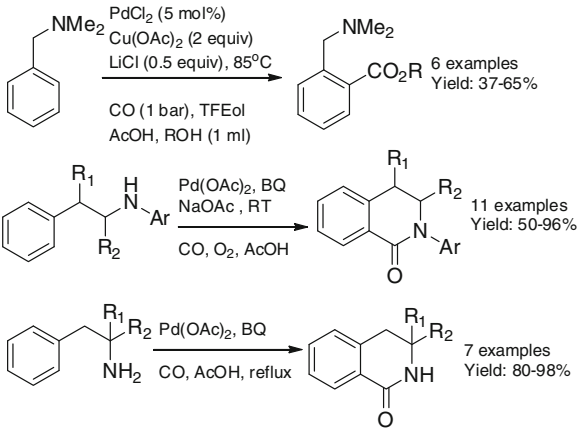
An interesting oxidative carbonylation of aniline derivatives was published in 2009 [37]. The reaction proceeded under 1 bar of CO at room temperature with 5 mol% of $[Pd(OTs)_2(MeCN)_2]$ as the precatalyst. Either cyclic imidates or methyl anthranilates can be easily generated, depending on the reaction conditions. The use of *N*-aryl urea derivatives with a terminal N–H moiety allowed for the generation of quinazolinones (Scheme 6.10).

The oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acids has been described by Bell and Zakzeski [38]. By using a Pd(II) catalyst in combination with a carboxylic acid, ammonium metavanadate, CO, and O_2, trifluoromethylbenzoic acid was achieved in good selectivity. Shi and his colleagues performed LiCl-promoted Pd(II)-catalyzed oxidative carbonylation of *N,N*-dimethylbenzylamines [39]. This reaction is highly regioselective and the product can be further transformed into *ortho*-methyl benzoate under mild conditions.

At the same time, Gaunt's group published a method in which they started from secondary *β*-arylethylamines to obtain dihydro-2-quinolones [40], and Granell's and Garcia's group developed a procedure for the carbonylation of *N*-unprotected arylethylamines (Scheme 6.11) [41].

Finally, oxidative carbonylations of simple ketones, such as hexanone and pentanone, were reported to give diesters [42, 43]. In the presence of $PdCl_2$, $CuCl_2$, CO, and in methanol, various diesters have been produced in good yields from corresponding cyclic ketones.

Zhu and his team developed an unprecedented C–H aminocarbonylation reaction using unprotected aniline NH_2 as a directing group [44]. Various free (NH)-phenanthridinone derivatives were efficiently synthesized in the presence of $Pd(TFA)_2$ as a catalyst and $Cu(TFA)_2$ as a stoichiometric oxidant under an atmospheric pressure of CO starting from *o*-arylanilines (Scheme 6.12). The resulting free (NH)-phenanthridinone skeleton can be readily diversified following known methods, including *N*-alkylation, *N*-arylation, Suzuki coupling of the chloride, or triflate intermediates. Some *ortho*-heteroarene substituted anilines can also be applied in this C–H aminocarbonylation reaction, giving polyheterocycles



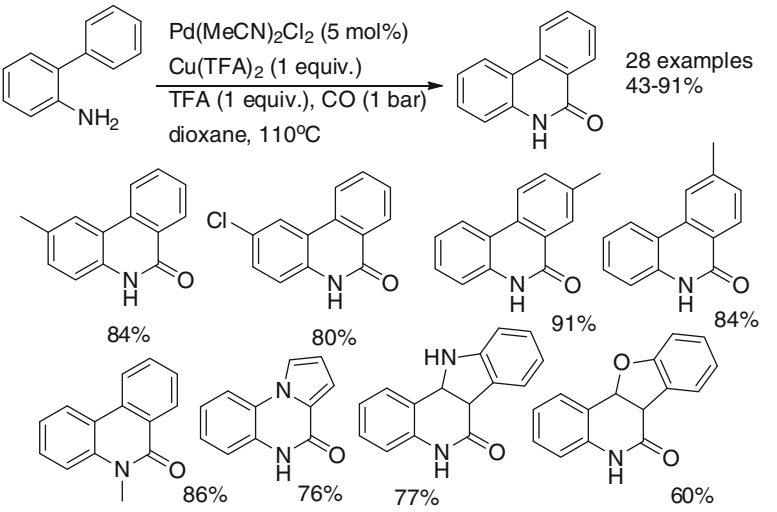
Scheme 6.11 Palladium-catalyzed oxidative carbonylation of anilines

containing a free (NH)-lactam moiety, which exists in many bioactive relevant molecules.

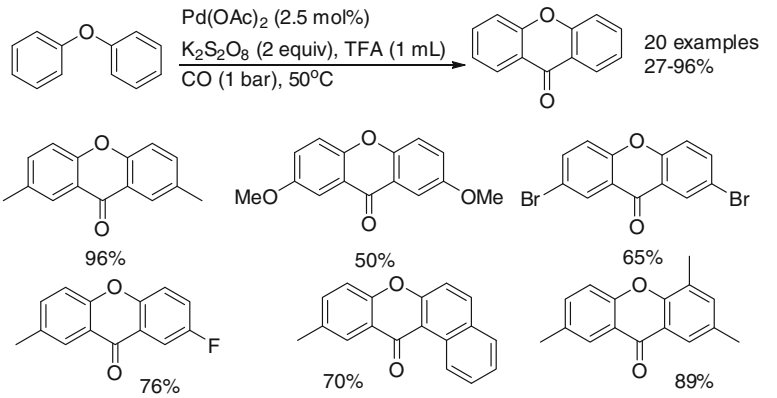
Lei and his associates developed a Pd-catalyzed double C–H functionalization/carbonylation of diaryl ethers to form xanthones [45]. By using a simple catalytic system consisting of $Pd(OAc)_2$, $K_2S_2O_8$, and TFA, a variety of diaryl ethers could be directly carbonylated to xanthones in moderate to good yields (Scheme 6.13). Moreover, various functional groups were tolerated under the optimized conditions. Notably, this transformation provides an effective and practical protocol for the syntheses of bioactive xanthones.

Huang's group succeeded in developing an efficient Pd-catalyzed carbonylation of benzylic C–H bonds with CO through nondirected $C(sp^3)$-H bond activation [46]. This carbonylation process represents a practical and effective methodology for the synthesis of substituted phenylacetic acid esters from simple toluenes. The new strategy for the generation of such a benzylpalladium intermediate should pave the way to some new classes of C–H functionalization reactions, complementary to the classical synthetic methods with organic halides. At the same time, Guan and colleagues developed a novel palladium-catalyzed C–H bond carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides [47]. The mechanism was investigated, and a key intermediate was isolated and characterized. This novel palladium-catalyzed carbonylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available *N*-alkyl anilines into a variety of substituted isatoic anhydrides under mild conditions (Scheme 6.14).

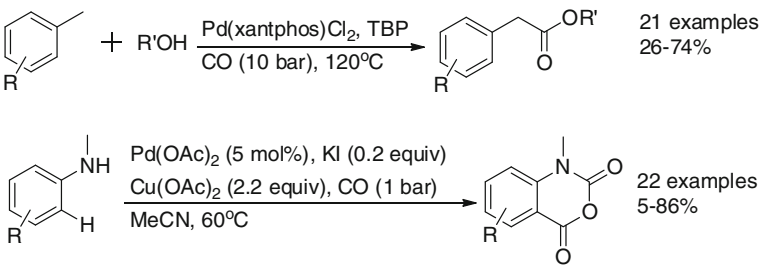
Indoles as an important class of heterocycles were studied in carbonylations as well. In 2011, Lei's team developed an interesting procedure for the carbonylative transformation of indoles to the corresponding esters [48]. High regioselectivity was obtained and an electrophilic palladation mechanism was proposed. More recently, Lei's group developed some novel methodologies for the carbonylation of indoles [49–51]. Amides, α-ketoamides, esters, and alkynones were produced in good yields with I_2 as an oxidant (Scheme 6.15).



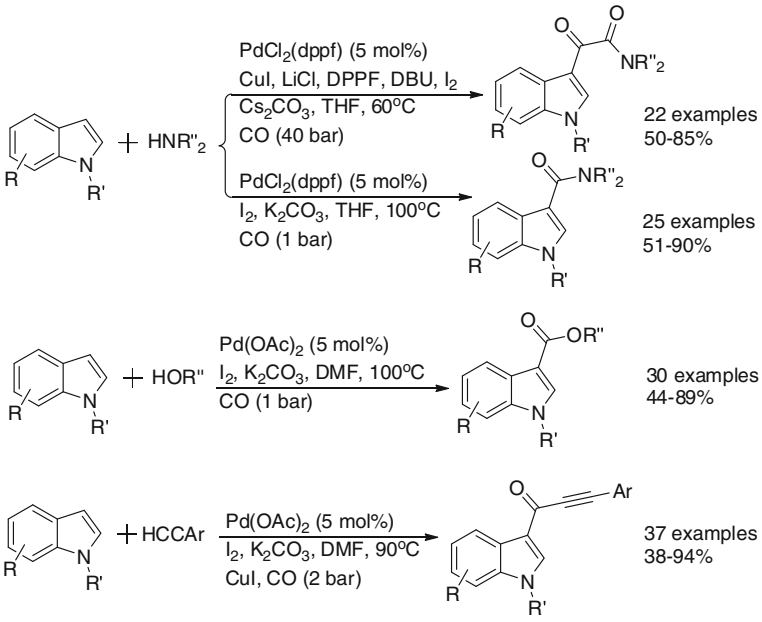
Scheme 6.12 Palladium-catalyzed oxidative carbonylation of *o*-arylanilines



Scheme 6.13 Palladium-catalyzed carbonylation of diaryl ethers



Scheme 6.14 Palladium-catalyzed carbonylative activation of Csp^3-H

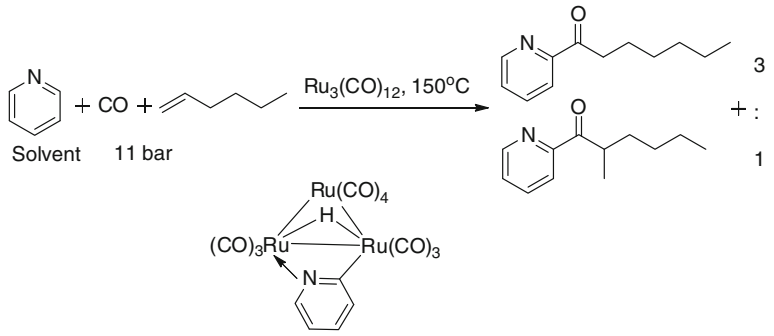


Scheme 6.15 Carbonylative transformation of indoles

In addition to palladium catalysts, ruthenium catalysts were applied in carbonylative C–H activation reactions as well. Moore and colleagues described the first ruthenium-catalyzed carbonylative C–H activation reaction in 1992 [52]. O*rtho*-acylation of pyridine and other nitrogen-containing aromatic compounds can be carried out with olefins and CO, using $Ru_3(CO)_{12}$ as the catalyst (Scheme 6.16). Interestingly, internal olefins, such as *cis*- and *trans*-2-hexene, yield the same linear/branched product ratio as terminal olefins.

Some other transition metal carbonyl compounds were also investigated instead of $Ru_3(CO)_{12}$, such as $Os_3(CO)_{12}$, $Rh_4(CO)_{12}$, $Re_2(CO)_{10}$, but none of them showed any activity in this reaction. The mechanism behind this reaction was most likely the fact that a coordinatively unsaturated metal center of the trinuclear cluster is attacked and coordinated by pyridine, and subsequent *ortho*-metalation gives the key intermediate. Olefin insertion into a linear and branched alkyl species, followed by CO coordination and insertion, produces the acyl species, which reacts further to the acylated product by reductive elimination.

One main issue for Moore's procedure is that the reaction needs a substrate as solvent. In 1996, Murai and his researchers solved this challenge [53, 54] by carrying out the coupling reaction with imidazoles in toluene, under 20 bar of CO, at 160 °C. After 20 h, various substituted imidazoles were acylated under the assistant of 4 mol% of $Ru_3(CO)_{12}$. The reaction proceeded with excellent linear selectivity. Besides imidazoles, 1-methylpyrazoles were also acylated in good



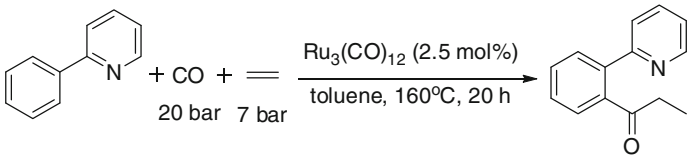
Scheme 6.16 $Ru_3(CO)_{12}$ catalyzed carbonylation of pyridine

yields. Not only aliphatic alkenes, but styrenes were successfully applied as coupling partners as well.

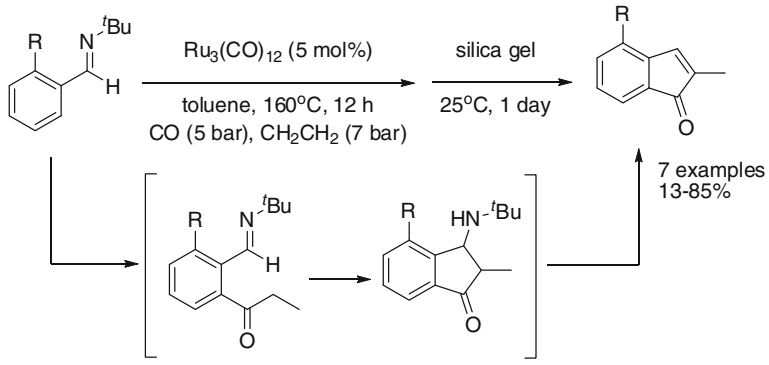
Later, Murai's group described the ruthenium-catalyzed carbonylation of pyridylbenzenes (Scheme 6.17) [55]. Pyridylbenzenes were acylated with ethylene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ in toluene at 160 °C under 20 bar of CO. This reaction was also successful in using naphthyl and thienyl rings. Other effective directing groups for carbonylation at a C–H bond in the benzene ring are six-membered heterocycles, such as 2-pyrimidine and 4-pyrimidine. Besides ethylene, trimethylvinylsilane and *tert*-butylethylene can also be used as coupling partners for this reaction. However, this procedure failed with substrates as 1-hexene, cyclohexene, allyltrimethylsilane, styrene, methyl methacrylate, vinyl acetate, triethoxyvinylsilane, and isopropenyltrimethylsilane.

In 1997 Murai's group developed a two-step procedure for the synthesis of 2-substituted inden-1-ones [56]. The reaction pathway comprised a carbonylation at a C–H bond and subsequent intramolecular aldolcondensation. Aromatic imines were applied as starting materials and coupled with both ethylene and trimethylvinylsilane to yield indenones in moderate to good yields (Scheme 6.18).

$Ru_3(CO)_{12}$-catalyzed carbonylation at an olefinic C–H bond was also reported in 1998 by Murai's group [57]. The propionylation of pyridylolefins at an olefinic C–H bond with CO and ethylene proceeds with a catalytic amount of $Ru_3(CO)_{12}$ in toluene. The carbonylation occurs regioselectively at the γ-position to the pyridine nitrogen and ethylene serves as the only olefin, which can be used successfully.



Scheme 6.17 $Ru_3(CO)_{12}$ catalyzed carbonylation of pyridylbenzene



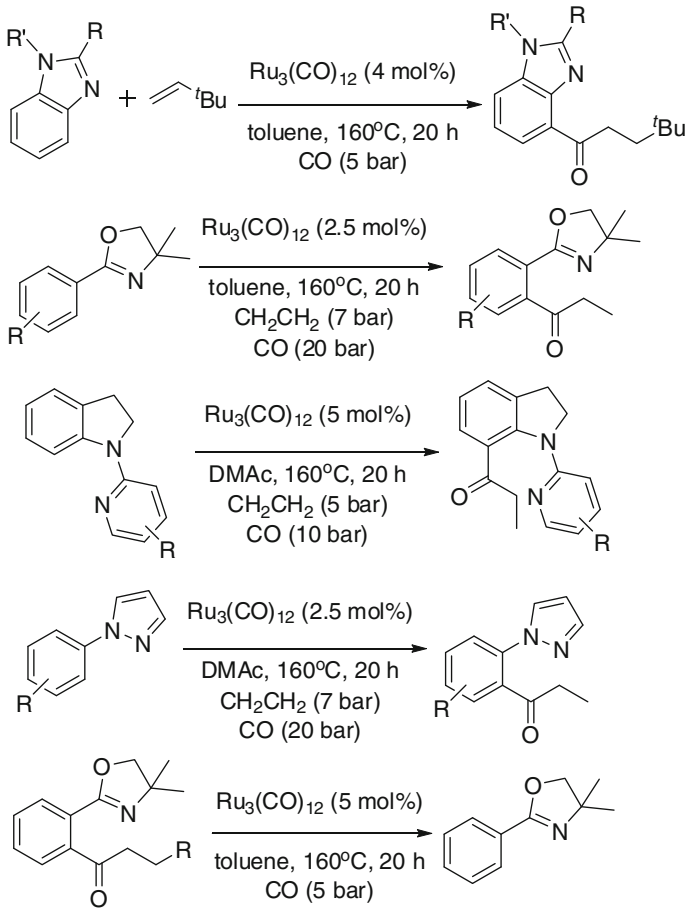
Scheme 6.18 $Ru_3(CO)_{12}$ catalyzed carbonylative synthesis of indenones

Using transition-metal complexes other than $Ru_3(CO)_{12}$, no catalytic activity has been exhibited so far. This reaction can also be extended to *N*-(2-pyridyl)enamines, giving the corresponding ethyl ketones as the coupling products. Here the pyridine ring is separated from an olefin unit by a sp^3-nitrogen atom. Interestingly, this reaction also shows high catalytic activity using $Rh_4(CO)_{12}$. In addition, other olefins, such as propene, 1-hexene, 3,3-dimethyl-1-butene, styrene, cyclopentene, acryl acid methyl ester, ethyl vinyl ether, and trimethylvinylsilane can also be used as a coupling partner.

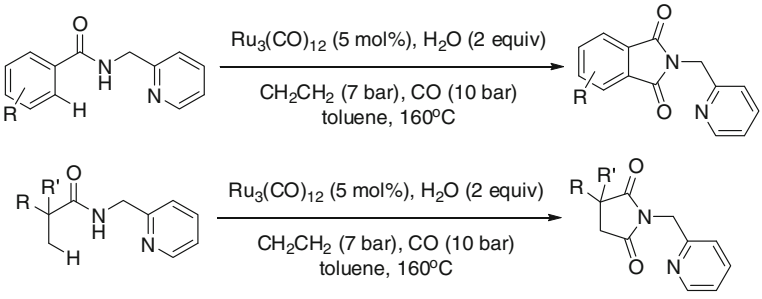
In addition to the above-mentioned reactions, Murai's group developed several other ruthenium-catalyzed carbonylations of arenes with similar reaction conditions (Scheme 6.19). Here, aza-heterocycle [58], 2-phenyloxazolines [59], *N*-pyridylindolines [60], *N*-arylpyrazoles [61, 62], and 2-phenylpyridines [63], were carbonylated into the corresponding products with $Ru_3(CO)_{12}$ or Ru/C as the catalyst. Besides these novel carbonylation reactions, ruthenium-catalyzed decarbonylative cleavage of alkyl phenyl ketones producing phenyl derivatives were also discovered by this group [64].

More recently, Chatani and his researchers developed the ruthenium-catalyzed carbonylation at the *ortho*-C–H bonds of aromatic amides [65] to give phthalimides as their products. Analogously, this reaction can also be transferred to even inactivated $C(sp^3)$-H bonds and yield the corresponding succinimides. (Scheme 6.20) [66] In both cases, the presence of 2-pyridinylmethylamino moiety is necessary for these transformations, because it plays an important role as a *N*,*N*-bidentate ligand to form a dinuclear ruthenium complex with $Ru_3(CO)_{12}$. Interestingly, in the absence of ethylene, no carbonylation product could be detected while the efficiency of the reaction decreased in the absence of water. In the latter case, a long reaction time (5 days) is still needed.

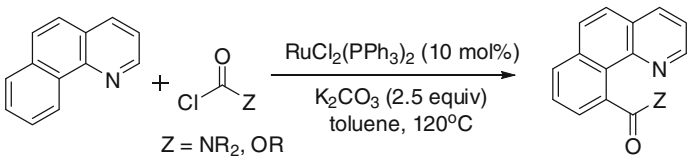
A CO-free acylation of arylpyridines was developed by Kakiuchi and colleagues (Scheme 6.21) [67, 68]. In the presence of a catalytic amount of ruthenium catalyst, arylpyridines were coupled with acyl chlorides, carbamoyl chlorides, and alkyl chloroformates in moderate to good yields. This procedure offers an alternate



Scheme 6.19 Ruthenium-catalyzed carbonylative C–H activations

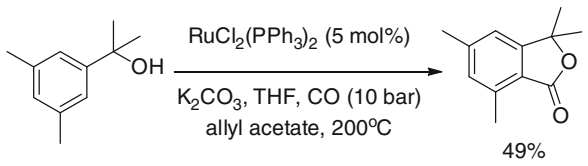


Scheme 6.20 Ruthenium-catalyzed carbonylation of amides



Scheme 6.21 Ruthenium-catalyzed acylation of arenes

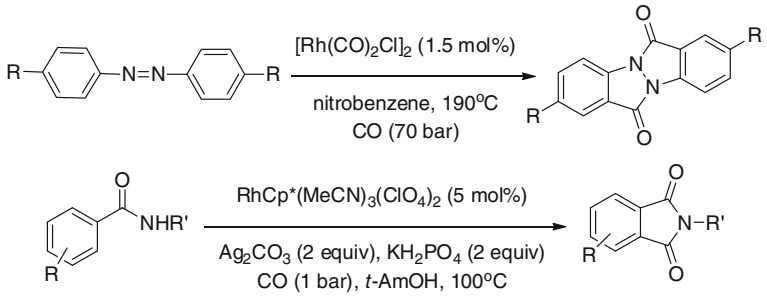
Scheme 6.22 Ruthenium-catalyzed oxidative carbonylation of allylic alcohols



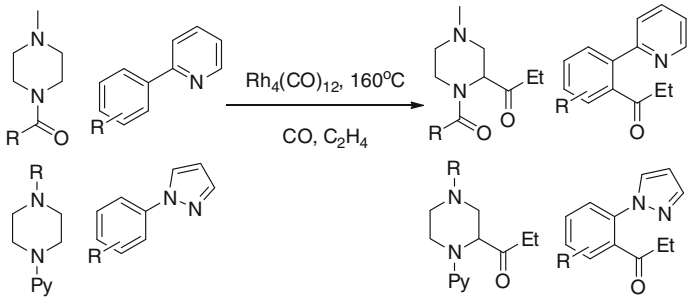
method for the direct alkoxy and amido carbonylation of arenes, even in those cases where the usual Friedel–Crafts methods are difficult.

Lactones are heterocyclic rings that commonly occur in natural compounds, which exhibit potential biological activities. The first ruthenium-catalyzed carbonylative synthesis of 2-furanones was developed by Watanabe and colleagues in 1994 [69]. In the presence of catalytic amounts of ruthenium catalyst, 2-furanones were prepared in moderate to high yields from corresponding allylic alcohols. Since this oxidative cyclocarbonylation reaction releases one equivalent of hydrogen, and a hydrogen acceptor was used. While allyl acetate works well, other acceptors, such as acetone, cyclohexene, and diphenylacetylene were not useful for this transformation. A combination of $Ru_3(CO)_{12}$ and $RuCl_3{\cdot}nH_2O$ with triaryl- or trialkyl-phosphines can also promote this reaction, but a considerable amount of saturated lactones was obtained. No carbonylation was observed by using other transition metals, such as $NiBr_2(PPh_3)_2$, $RhCl(PPh_3)_3$, $PdCl_2(PPh_3)_2$ and $PtCl_2(PPh_3)_2$, demonstrating the superior activity of ruthenium in this reaction. Notably, the same catalytic system was also applied for the oxidative cyclization of 4-penten-1-ols (Scheme 6.22) [70]. The reaction proceeded at 160 °C in the presence of $Ru_3(CO)_{12}$ and PPh_3 under 5 bar of CO.

Additionally, rhodium catalysts were explored in this area as well. Takahashi's group reported a rhodium-catalyzed cyclocarbonylation of azobenzenes in 2004 [71]. With the assistance of this rhodium catalyst, indazolo[2,1-a]indazole-6,12-diones were achieved in good yields using nitrobenzene as a hydrogen acceptor (Scheme 6.23). In contrast, performing the carbonylation of azobenzene via a cobalt catalysis, quinazoline was obtained as the final product. More recently, Rovis's group reported rhodium-catalyzed carbonylative C–H activation of benzamides [72]. This novel strategy allows preparing phthalimides via C–H/N–H activation from corresponding aromatic amides. This reaction tolerates a variety of functional groups in which the C–H bonds of electron-rich aromatic amides are favored.



Scheme 6.23 Rhodium-catalyzed carbonylative C–H activation



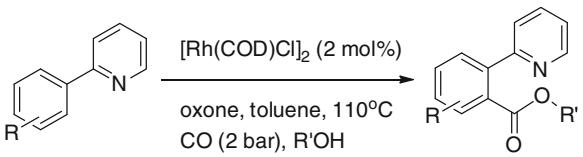
Scheme 6.24 Rhodium-catalyzed C–H activations

Over the past decades, Murai's and Chatani's groups developed a series of methodologies for the rhodium-catalyzed carbonylations initiated by C–H activation [73–76]. A range of heterocyclic compounds, such as *N*-acylpiperazines, *N*-(2-pyridinyl)piperazines, 2-arylpyridines, and *N*-arylpyrazoles, were acylated with CO and ethylene (Scheme 6.24).

Zhang and colleagues described a rhodium-catalyzed oxidative carbonylation of aromatic C–H bond with CO and alcohols in 2009 (Scheme 6.25) [77]. A broad substrate scope of electron-rich, electron-poor, and heterocyclic arenes were carbonylated under their conditions and produced the corresponding esters in good yields. The reaction is tolerant with many functional groups, and excellent regioselectivities and yields up to 96 % of *o*-substituted aryl or heteroaryl carboxylic esters were achieved by this method. A possible mechanism for the rhodium-catalyzed oxidative carbonylation reaction was also proposed by the authors. Among all the oxidants evaluated, oxone provided the best results in this reaction.

In this chapter, the transition of metal catalyzed carbonylative activation of C–H bonds has been discussed. This area is dominated by Pd, Ru and Rh catalysts, whereas the ability of other metals, such as Cu and Fe, have still not been explored. From the reaction mechanism point of view, the first step is the palladation of arene to produce an Ar-Pd bond, and then be followed by CO insertion.

Scheme 6.25 Rhodium-catalyzed C–H activation of phenylpyridines



In the next chapter we will discuss the carbonylative Heck reaction. Again, the reaction mechanism is different from those in the preceding chapters.

References

1. Kobayashi, T., Tanaka, M.: Tetrahedron Lett. **27**, 4745 (1986)
2. Negishi, E.-I., Zhang, Y., Shimyama, I., Wu, G.: J. Am. Chem. Soc. **111**, 8018 (1989)
3. Negishi, E.-I., Coperet, C., Sugihara, T., Shimoyama, I., Zhang, Y., Wu, G., Tour, J.M.: Tetrahedron **30**, 425 (1994)
4. Negishi, E.-I., Nakabe, H., Shimoyama, I., Wu, G., Zhang, Y.: Tetrahedron, **54**, 1095 (1998)
5. Campo, M.A., Larock, R.C.J.: Org. Chem. **67**, 5616 (2002)
6. Campo, M.A., Larock, R.C.: Org. Lett. **2**, 3675 (2000)
7. Peng, C., Cheng, J., Wang, J.J.: Am. Chem. Soc. **129**, 8708 (2007)
8. Wu, X.-F., Anbarasan, P., Neumann, H., Beller, M.: Angew. Chem. Int. Ed. **49**, 7316 (2010)
9. Fujiwara, Y., Kawauchi, T., Taniguchi, H.: J. C. S. Chem. Comm. 220 (1980)
10. Fujiwara, Y., Takaki, K., Taniguchi, Y.: Synlett 591 (1996)
11. Jia, C., Kitamura, T., Fujiwara, Y.: Acc. Chem. Res. **34**, 633 (2001)
12. Itahara, T.: Chem. Lett. 1151 (1982)
13. Itahara, T.: Chem. Lett. 127 (1983)
14. Ozawa, F., Yamagami, I., Nakano, M., Fujisawa, F., Yamamoto, A.: Chem. Lett. 125 (1989)
15. Balavoine, G., Clinet, J.C.J.: Organomet. Chem. **390**, C84 (1990)
16. Jaouhari, R., Dixneuf, P.H., Lécolier, S.: Tetrahedron Lett. **27**, 6315 (1986)
17. Ugo, R., Chiesa, A., Nardi, P.J.: Mol. Catal. **59**, 23 (1990)
18. Shibahara, F., Kinoshita, S., Nozaki, K.: Org. Lett. **6**, 2437 (2004)
19. Cowley, A.H., Kemp, R.A.: Chem. Rev. **85**, 367 (1985)
20. Gudat, D.: Coord. Chem. Rev. **163**, 71 (1997)
21. Abrams, M.B., Scott, B.L., Baker, R.T.: Organometallics **19**, 4944 (2000)
22. Sakakibara, K., Yamashita, M., Nozaki, K.: Tetrahedron Lett. **46**, 959 (2005)
23. Liu, C., Widenhoefer, R.A.J.: Am. Chem. Soc. **126**, 10250 (2004)
24. Liu, C., Widenhoefer, R.A.: Chem. Eur. J. **12**, 2371 (2006)
25. Orito, K., Horibata, A., Nakamura, T., Ushito, H., Nagasaki, H., Yuguchi, M., Yamashita, S., Tokuda, M.J.: Am. Chem. Soc. **126**, 14342 (2004)
26. Orito, K., Miyazawa, M., Nakamura, T., Horibata, A., Ushito, H., Nagasaki, H., Yuguchi, M., Yamashita, S., Yamazaki, T., Tokuda, M.J.: Org. Chem. **71**, 5951 (2006)
27. Yamashita, S., Kurono, N., Senboku, H., Tokuda, M., Orito, K.: Eur. J. Org. Chem. 1173 (2009)
28. Vicente, J., Saura-Llamas, I., Garcia-López, J.-A., Calmuschi-Cula, B.: Organometallics **26**, 2768 (2007)
29. Ohashi, S., Sakaguchi, S., Ishii, Y.: Chem. Commun. 486 (2005)
30. Yamada, S., Sakaguchi, S., Ishii, Y.J.: Mol. Catal. A: Chem. **262**, 48 (2007)
31. Yamada, S., Ohashi, S.-I., Obora, Y., Sakaguchi, S., Ishii, Y.: J. Mol. Catal. A: Chem. **282**, 22 (2008)

32. Giri, R., Yu, J.-Q.J.: Am. Chem. Soc. **130**, 14082 (2008)
33. Giri, R., Lam, J.K., Yu, J.-Q.J.: Am. Chem. Soc. **132**, 686 (2010)
34. Yoo, E.J., Wasa, M., Yu, J.-Q.J.: Am. Chem. Soc. **132**, 17378 (2010)
35. Lu, Y., Leow, D., Wang, X., Engle, K.M., Yu, J.-Q.: Chem. Sci. **2**, 967 (2011)
36. Dai, H.-X., Stepan, A.F., Plummer, M.S., Zhang, Y.-H., Yu, J.-Q.J.: Am. Chem. Soc. **133**, 7222 (2011)
37. Houlden, C.E., Hutchby, M., Bailey, C.D., Ford, J.G., Tyler, S.N.G., Gagné, M.R., Lloyd-Jones, G.C., Booker-Milburn, K.I.: Angew. Chem. Int. Ed. **1830**, 48 (2009)
38. Zakzeski, J., Bell, A.T.J.: Mol. Catal. A: Chem. **302**, 59 (2009)
39. Li, H., Cai, G.-X., Shi, Z.-J.: Dalton Trans. **39**, 10442 (2010)
40. Haffemayer, B., Gulias, M., Gaunt, M.J.: Chem. Sci. **2**, 312 (2011)
41. López, B., Rodriguez, A., Santos, D., Albert, J., Ariza, X., Garcia, J., Granell, J.: Chem. Commun. **47**, 1054 (2011)
42. Hamed, O., El-Qisairi, A., Henry, P.M.: Tetrahedron Lett. **41**, 3021 (2000)
43. Hamed, O., El-Qisairi, A., Henry, P.M.J.: Org. Chem. **66**, 180 (2001)
44. Liang, D., Hu, Z., Peng, J., Huang, J., Zhu, Q.: Chem. Commun. **49**, 173 (2013)
45. Zhang, H., Shi, R., Gan, P., Liu, C., Ding, A., Wang, Q., Lei, A.: Angew. Chem. Int. Ed. **51**, 5204 (2012)
46. Xie, P., Xie, Y., Qian, B., Zhou, H., Xia, C., Huang, H.J.: Am. Chem. Soc. **134**, 9902 (2012)
47. Guan, Z.H., Chen, M., Ren, Z.-H.J.: Am. Chem. Soc. **134**, 17490 (2012)
48. Zhang, H., Liu, D., Chen, C., Liu, C., Lei, A.: Chem. Eur. J. **17**, 9581 (2011)
49. Xing, Q., Shi, L., Lang, R., Xia, C., Li, F.: Chem. Commun. **48**, 11023 (2012)
50. Lang, R., Shi, L., Li, D., Xia, C., Li, F.: Org. Lett. **14**, 4130 (2012)
51. Li, D., Shan, S., Shi, L., Lang, R., Xia, C., Li, F.: Chin. J. Catal. **34**, 185 (2013)
52. Moore, E.J., Pretzer, W.R., O'Connell, T.J., Harris, J., La Bounty, L., Chou, L., Grimmer, S.S.J.: Am. Chem. Soc. **114**, 5888 (1992)
53. Chatani, N., Fukuyama, T., Kakiuchi, F., Murai, S.J.: Am. Chem. Soc. **118**, 493 (1996)
54. Chatani, N., Fukuyama, T., Tatamidani, H., Kakiuchi, F., Murai, S.J.: Org. Chem. **65**, 4093 (2000)
55. Chatani, N., Ie, Y., Kakiuchi, F., Murai, S.J.: Org. Chem. **62**, 2604 (1997)
56. Fukuyama, T., Chatani, N., Kakiuchi, F., Murai, S.J.: Org. Chem. **62**, 5647 (1997)
57. Chatani, N., Ishii, Y., Ie, Y., Kakiuchi, F., Murai, S.J.: Org. Chem. **63**, 5129 (1998)
58. Fukuyama, T., Chatani, N., Tatsumi, J., Kakiuchi, F., Murai, S.J.: Am. Chem. Soc. **120**, 11522 (1998)
59. Ie, Y., Chatani, N., Ogo, T., Marshall, D.R., Fukuyama, T., Kakiuchi, F., Murai, S.J.: Org. Chem. **65**, 1475 (2000)
60. Chatani, N., Yorimitsu, S., Asaumi, T., Kakiuchi, F., Murai, S.J.: Org. Chem. **67**, 7557 (2002)
61. Asaumi, T., Chatani, N., Matsuo, T., Kakiuchi, F., Murai, S.J.: Org. Chem. **68**, 7538 (2003)
62. Asaumi, T., Matsuo, T., Fukuyama, T., Ie, Y., Kakiuchi, F., Chatani, N.J.: Org. Chem. **69**, 4433 (2004)
63. Imoto, S., Uemura, T., Kakiuchi, F., Chatani, N. Synlett 170 (2007)
64. Chatani, N., Ie, Y., Kakiuchi, F., Murai, S.J.: Am. Chem. Soc. **121**, 8645 (1999)
65. Inoue, S., Shiota, H., Fukumoto, Y., Chatani, N.J.: Am. Chem. Soc. **131**, 6898 (2009)
66. Hasegawa, N., Charra, V., Inoue, S., Fukumoto, Y., Chatani, N.J.: Am. Chem. Soc. **133**, 8070 (2011)
67. Kochi, T., Urano, S., Seki, H., Mizushima, E., Sato, M., Kakiuchi, F.J.: Am. Chem. Soc. **131**, 2792 (2009)
68. Kochi, T., Tazawa, A., Honda, K., Kakiuchi, F.: Chem. Lett. **40**, 1018 (2011)
69. Kondo, T., Kodoi, K., Mitsudo, T., Watanabe, Y.: J. Chem. Soc. Chem. Commun. 755 (1994)
70. Kondo, T., Tsunawaki, F., Sato, R., Ura, Y., Wada, K., Mitsudo, T.: Chem. Lett. **32**, 24 (2003)
71. Zhou, D.-Y., Kioke, T., Suetsugu, S., Onitsuka, K., Takahashi, S.: Inorg. Chim. Acta **357**, 3057 (2004)
72. Du, Y., Hyster, T.K., Rovis, T.: Chem. Commun. **47**, 12074 (2011)

73. Ishii, Y., Chatani, N., Kakiuchi, F., Murai, S.: Tetrahedron Lett. **38**, 7565 (1997)
74. Ishii, Y., Chatani, N., Kakiuchi, F., Murai, S.: Organometallics **16**, 3615 (1997)
75. Chatani, N., Uemura, T., Asaumi, T., Le, Y., Kakiuchi, F., Murai, S.: Can. J. Chem. **83**, 755 (2005)
76. Asaumi, T., Matsuo, T., Fukuyama, T., Le, Y., Kakiuchi, F., Chatani, N.J.: Org. Chem. **69**, 4433 (2004)
77. Guan, Z., Ren, Z., Spinella, S.M., Yu, S., Liang, Y., Zhang, X.J.: Am. Chem. Soc. **131**, 729 (2009)

Chapter 7
Carbonylative Heck Reactions

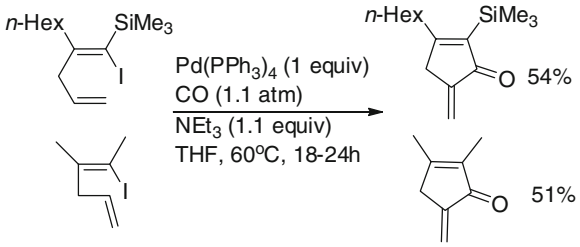
The "Carbonylative Heck Reaction" is not the same as those that were traditionally called "Heck carbonylations". Heck carbonylations normally include alkoxycarbonylation, aminocarbonylation and hydroxycarbonylation, while a carbonylative Heck reaction is more related to a Heck reaction. In the late 1960s, Richard Heck developed several coupling reactions of arylmercury compounds in the presence of either stoichiometric or catalytic amounts of palladium salts [1–7]. Based on this work in 1972, he described a protocol for the coupling of iodobenzene with styrene, which today is known as the "Heck reaction" [8]. In contrast to this, the catalytic insertion of olefins into acylpalladium complexes is called a "Carbonylative Heck reaction". Here the acylpalladium complexes can either by CO insertion or by the oxidative addition of benzoyl precursors [9, 10].

The first palladium-catalyzed copolymerization of carbon monoxide (CO) with olefins was described in 1982 [11], and as a consequence, carbonylative coupling reactions with alkenes were reported soon after. Notably, it was Negishi and Miller who discovered the first two examples of intramolecular carbonylative Heck reactions of 1-iodopenta-1,4-dienes by applying stoichiometric amounts of palladium [12]. 5-Methylenecyclopent-2-enones as the products were produced in moderate yields (Scheme 7.1).

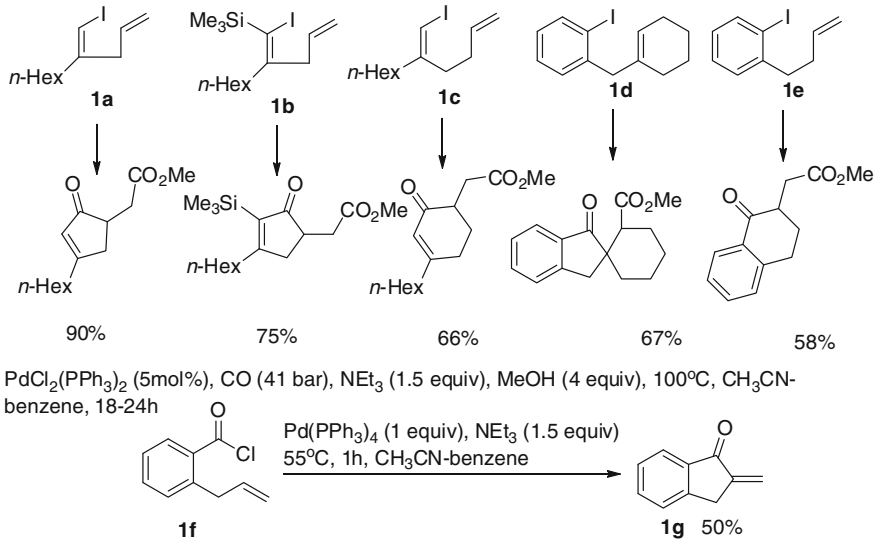
However, using **1a–1e** as substrates, no desired carbonylation products were detected, although the complete conversion of starting material occurred. Presumably, the polymerization of **1a–1e** (Scheme 7.2) took place [13]. Negishi and Miller's group improved the methodology two years later [14]. In their new methodology, **1a–1e** were applied as starting materials and the corresponding products were obtained in moderate to excellent yields using catalytic amounts of palladium salts in the presence of MeOH. A possible reaction mechanism was proposed, and "CO-free" carbonylative Heck reactions were realized. 2-Methylene-2,3-dihydro-inden-1-one **1g** was produced from the corresponding acid chloride **1f** in a 50 % yield under "CO-free" conditions.

Negishi et al. continued their interest in this topic by synthesizing various quinones using *o*-iodoaryl cyclohexyl ketones as the starting materials [15]. In the presence of $Pd(dba)_2$ as a catalyst (5 mol %) and under CO pressure (41 bar), quinones were produced in good yields with 100 % regioselectivity (Scheme 7.3).

M. Beller and X.-F. Wu, *Transition Metal Catalyzed Carbonylation Reactions*,
DOI: 10.1007/978-3-642-39016-6_7,



Scheme 7.1 The first examples of palladium-mediated intramolecular carbonylative Heck reactions

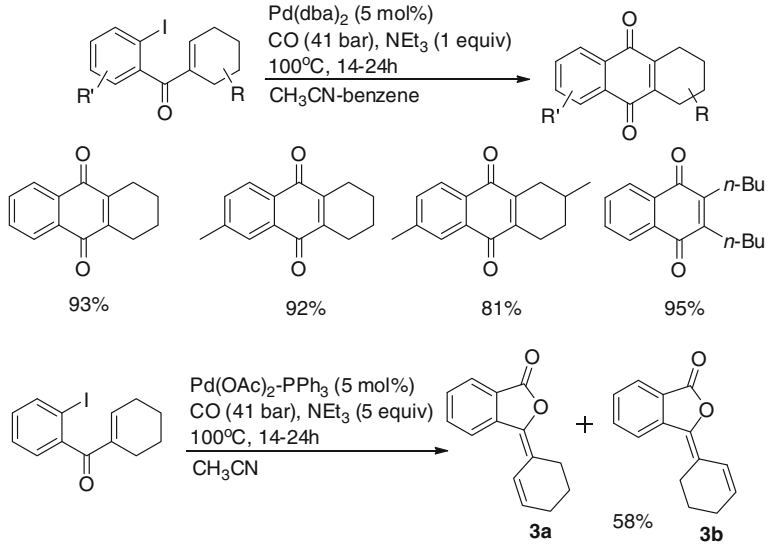


Scheme 7.2 Palladium-catalyzed intramolecular carbonylative Heck reaction

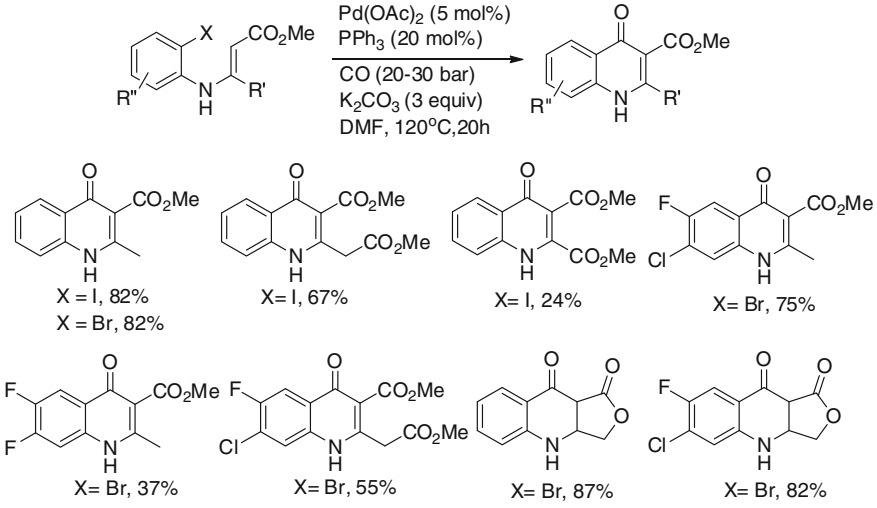
In this catalytic system, 58 % of furanones were formed instead of quinones if $Pd(OAc)_2/PPh_3$ was used. This latter work can be considered to be the first real palladium-catalyzed intramolecular carbonylative Heck reaction. In 1996, a full account using various vinyliodides was published by the same group [16–18].

In 2002 Ryu and colleagues reported on similar work that was catalyzed by Pd in the presence of light [19]. Similar products are obtained by the palladium-catalyzed carbonylative coupling of allyl acetate with benzynes [20].

Notably, Torii and colleagues reported the intramolecular carbonylative Heck coupling of 3-(2-haloarylamino)prop-2-enoates to the corresponding quinolinone derivatives [21]. In the presence of a catalytic amount of $Pd(OAc)_2$ under 20 bar of CO at 120 °C, quinolinones were synthesized in good yields (Scheme 7.4). A related carbonylative cross-coupling of aryl iodides with alkynones was reported

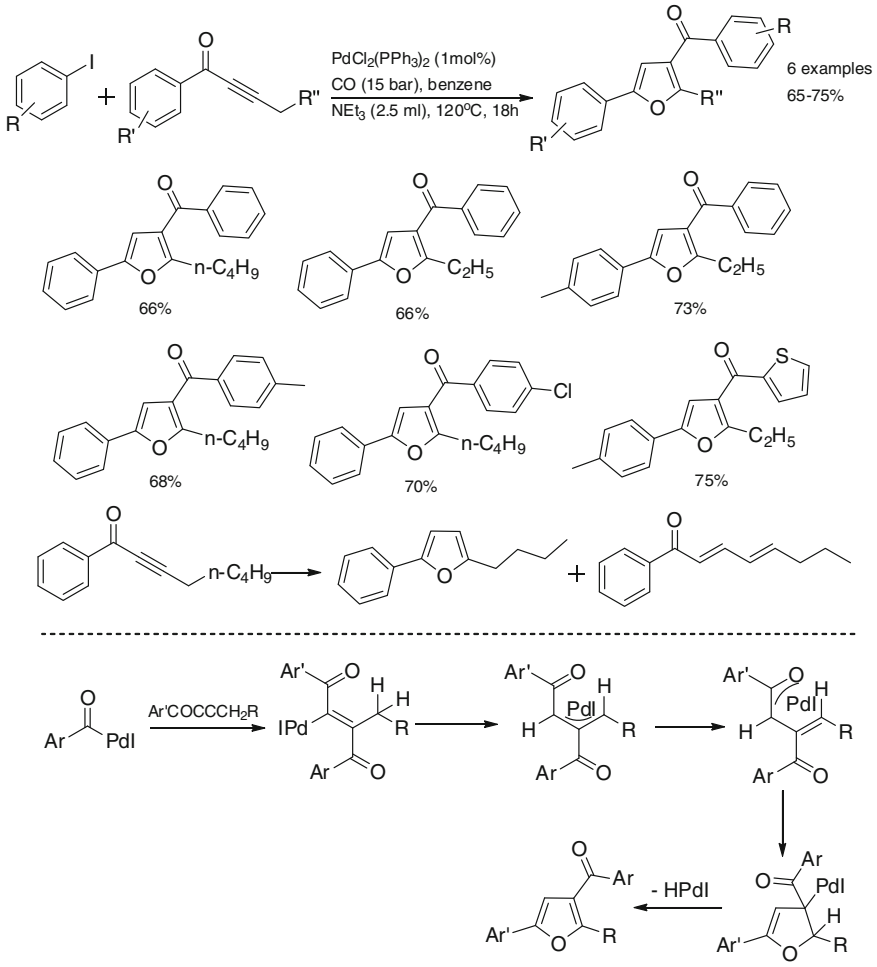


Scheme 7.3 First palladium-catalyzed intramolecular carbonylative Heck reaction



Scheme 7.4 Palladium-catalyzed carbonylative Heck reaction to quinolinones

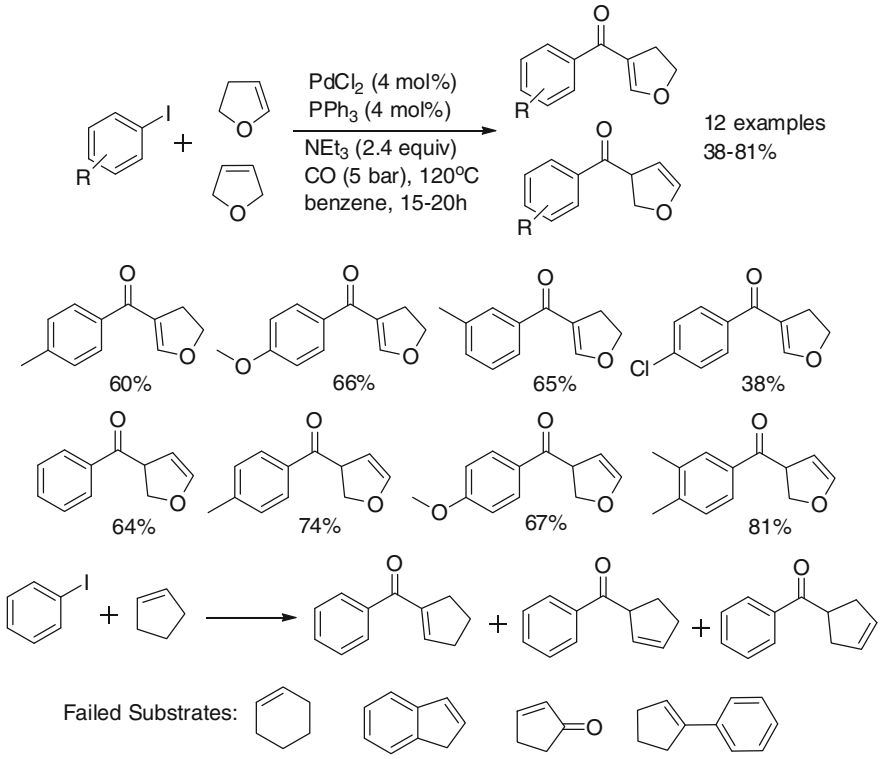
by Miura's team [22]. They showed that in the presence of CO and a palladium catalyst, various furans were produced in good yields (Scheme 7.5). Recently, Beller, Wu and colleagues succeeded in extending the reaction to aryl bromides and terminal alkynes. The reaction was believed to go through alkynone as the intermediate [23].



Scheme 7.5 Palladiumd-catalyzed carbonylative cross-coupling reactions of aryl iodides with alkynones to furans

In 1995 Miura and colleagues described a palladium-catalyzed carbonylative cross-coupling of aryl iodides with five-membered cyclic olefins [24]. This represents the first palladium-catalyzed *intermolecular* carbonylative cross-coupling of aryl iodides with olefins. Various benzoylated cyclic olefins were isolated in good yields (Scheme 7.6). Unfortunately, the reaction with cyclopentene led to a mixture of three regioisomers of benzoylcyclopentene. During their investigations, Miura's group found that the amount of PPh_3 added to the reaction mixture markedly influenced the product yields.

In 1997, Alper and colleagues applied allenes as a special family of alkenes in palladium-catalyzed carbonylative reactions with *o*-iodophenols [25]. Remarkably,



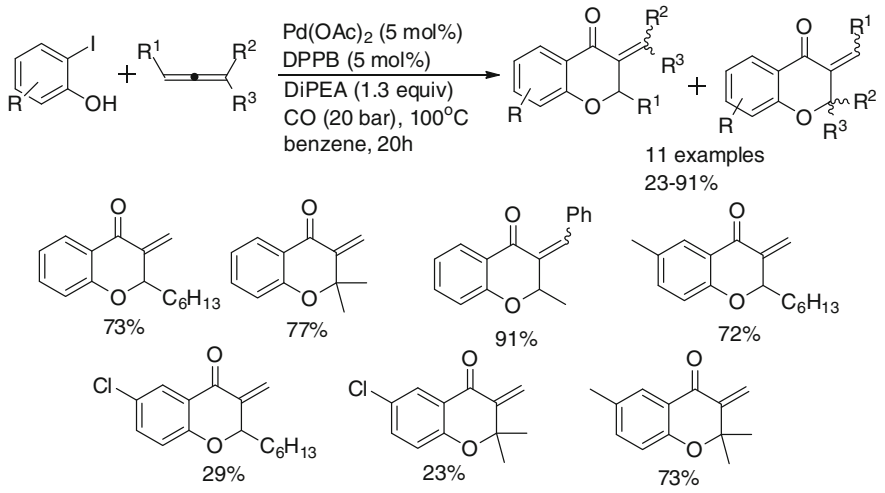
Scheme 7.6 Palladiumd-catalyzed carbonylative cross-coupling of ArI with cyclic olefins

the reaction works in a highly regioselective manner and only one single benzopyranone isomer was obtained in good yields (Scheme 7.7). That same year, Grigg and Pratt reported another carbonylative cascade reaction. Starting from 2-methallyliodobenzene, allenes were incorporated during the cascade process [26].

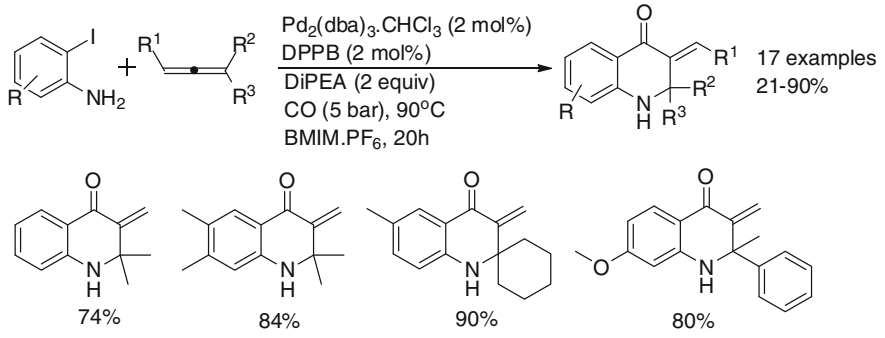
Similar to their previous work, Alper and colleagues succeeded in describing a palladium-catalyzed carbonylative coupling of *o*-iodoanilines with allenes in 2007 [27]. Quinolinones were synthesized in moderate to good yields under low CO pressure (5 bar) (Scheme 7.8). Here, an ionic liquid was used as solvent and promoter to enhance the efficacy of the cyclization protocol. Interestingly, the recyclability of the system was also demonstrated.

In 1999, Iwasawa and Satoh reported a new Heck-type coupling for the synthesis of 4,5-didehydrotropone-$Co_2(CO)_4$dppm complexes [28]. The palladium-catalyzed carbonylation was promoted by a diphenylacetylene cobalt complex **A** and gave the desired complexes in high yields (Scheme 7.9).

The same year, Hayashi and colleagues described an enantioselective palladium-catalyzed intramolecular carbonylative coupling of aryl and alkenyl triflates [29]. Enantiomerically enriched cyclopentenones were prepared in high yields



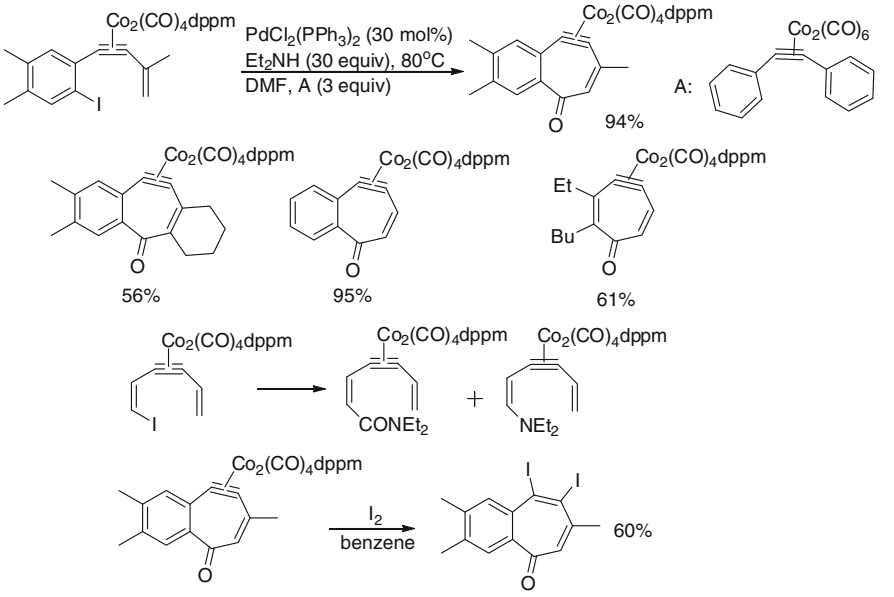
Scheme 7.7 Palladium-catalyzed carbonylative coupling of *o*-iodophenols with allenes



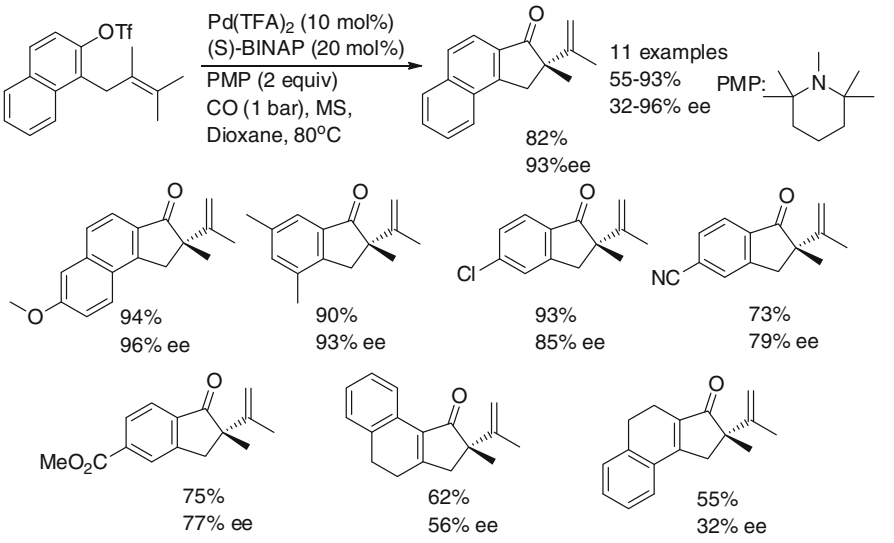
Scheme 7.8 Palladiumd-catalyzed carbonylative coupling of *o*-iodoanilines with allenes

from prochiral *o*-allylaryl triflates and 2-allylalkenyl triflates using $Pd(TFA)_2$/(*S*)-Binap as the catalyst (Scheme 7.10). In this system, PMP as a kind of special base was applied.

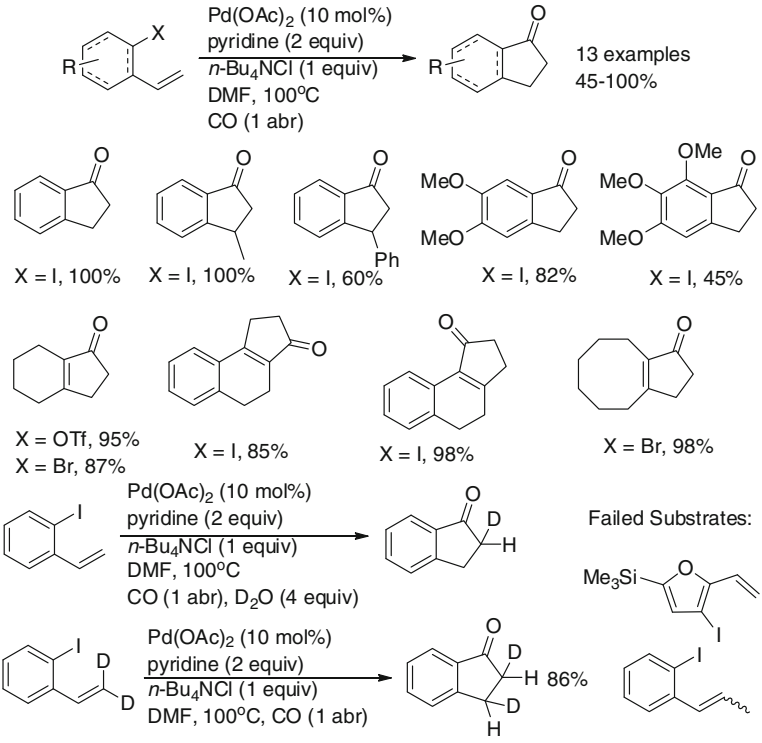
Larock and Gagnier discovered a general and efficient methodology for the synthesis of indanones and 2-cyclopentenones in 2003. Using *o*-halogen styrenes as their substrates, the desired products were prepared in good to excellent yields (Scheme 7.11) [30]. In the same way, Negishi and colleagues described the synthesis of indenones from *o*-iodostyrene. Afterwards, they extended this methodology to dienyl triflates, iodides, and bromides. All products were isolated in good yields. Regarding the mechanism, a trace of water in the solvent may serve as a proton source to favor the formation of indanone instead of indenone.



Scheme 7.9 Palladium-catalyzed cyclization of 4,5-didehydrotropone-$Co_2(CO)_4$.dppm complexes via carbonylative Heck reaction



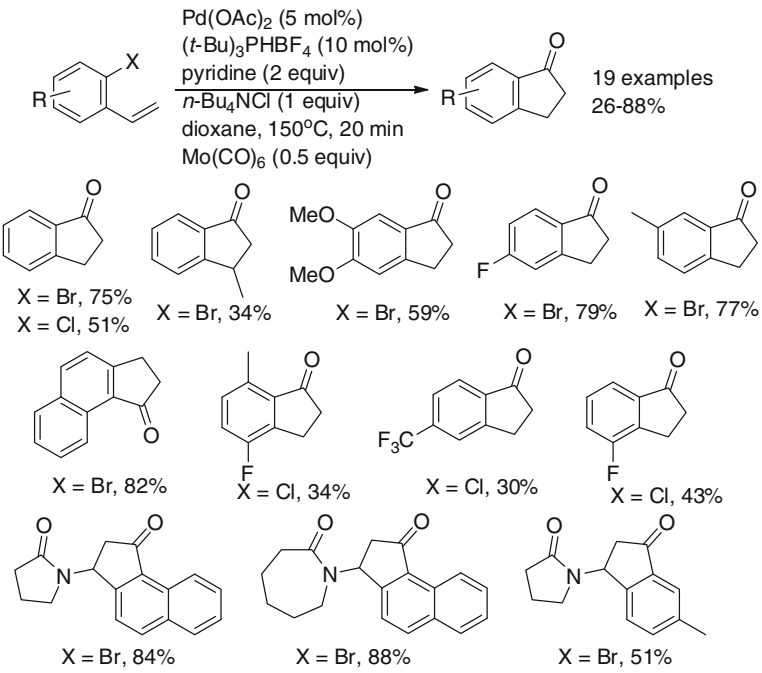
Scheme 7.10 Palladium-catalyzed intramolecular carbonylative coupling of aryl and alkenyl triflates to cyclopentenones



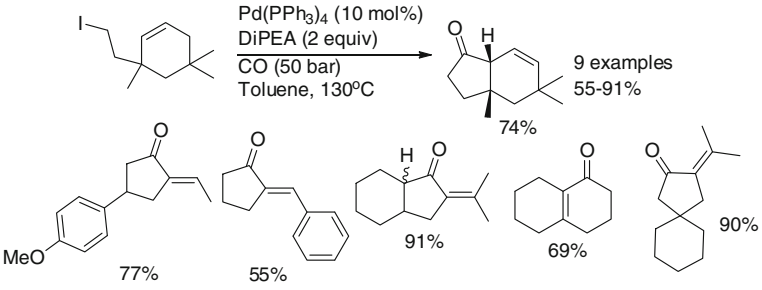
Scheme 7.11 Palladium-catalyzed carbonylative indanone synthesis

More recently, Larhed and his team developed a metal carbonyl-mediated and microwave supported intramolecular carbonylative coupling reaction of *o*-bromostyrenes [31]. Indanones and 3-acylaminoindanones were produced in good yields. In the presence of $Pd(OAc)_2/(t\text{-}Bu)_3PHBF_4$ with $Mo(CO)_6$ as a CO source, and under the irradiation of MW, indanones were achieved in 20 min from the corresponding aryl bromides and chlorides. Both electron-withdrawing and electron-donating groups are tolerated on the arene part, but electron-poor *o*-bromocinnamic acid derivatives furnished only the corresponding lactones via a hydroxycarbonylation-Michael addition sequence (Scheme 7.12).

Last year, Alexanian and Bloome described a palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides [32]. The treatment of a range of primary and secondary alkyl iodides in the presence of a palladium catalyst under CO pressure yielded a variety of synthetically versatile enone products. This novel palladium-catalyzed Heck-type cyclization is a rare example where inactivated alkyl halides with β-hydrogens are involved. Various substituted alkenes were well tolerated, and mono- as well as bicyclic carbocycles are easily accessed (Scheme 7.13).

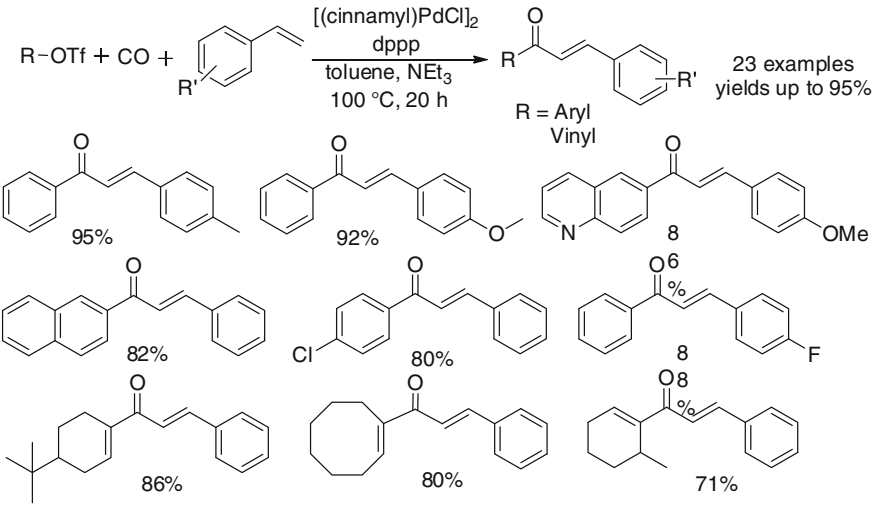


Scheme 7.12 Palladium-catalyzed carbonylative synthesis of indanones using MW



Scheme 7.13 Palladium-catalyzed carbonylative Heck-type cyclization of alkyl halides

It is clear that the main efforts in this area have so far focused on intramolecular carbonylative Heck reactions. A general intermolecular carbonylative coupling of aryl halides or triflates with terminal olefines was not known until the recent work of our group. Initially, we succeeded in carbonylative Heck couplings of aryl triflates with styrenes [33]. Starting from easily available aryl and alkenyl triflates, the corresponding unsaturated ketones are obtained in good yields (Scheme 7.14). The resulting products represent useful building blocks for the synthesis of a variety of biologically active compounds.

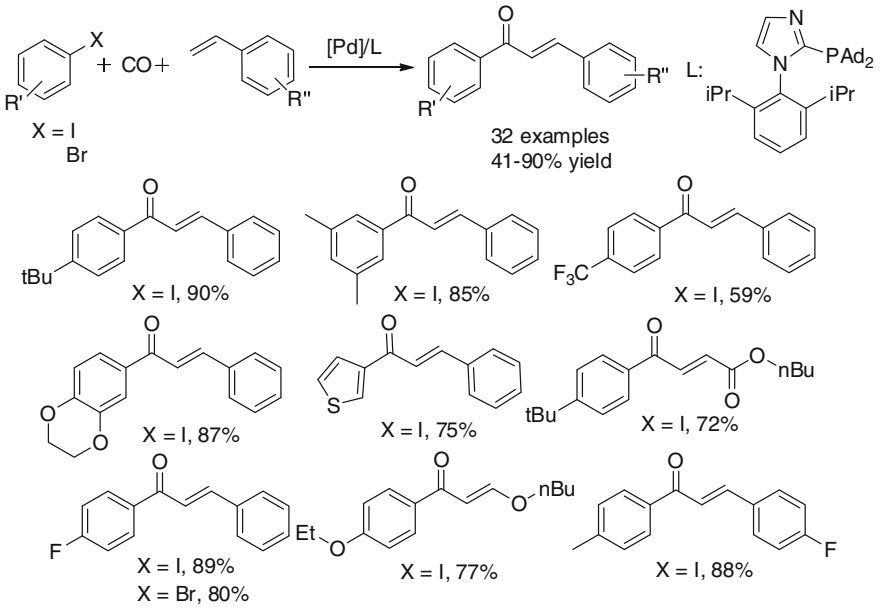


Scheme 7.14 Palladiumd-catalyzed carbonylative Heck reaction of ArOTf with styrenes

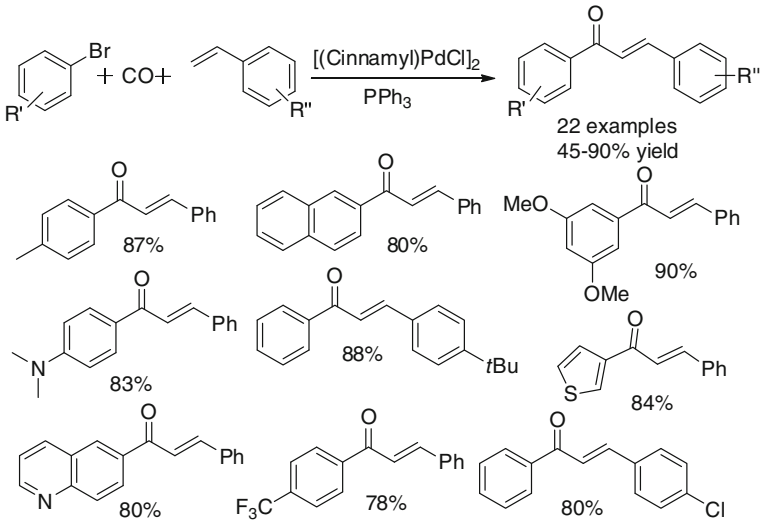
Shortly thereafter, a more general palladium-catalyzed carbonylative Heck reaction of aryl halides was able to be developed by our group [34]. For the first time, various aromatic and aliphatic alkenes were used successfully in this system, and good yields of the corresponding α,β-unsaturated ketones were obtained (41–90 %). Starting from easily available aryl iodides and bromides, interesting building blocks were obtained under mild conditions (Scheme 7.15). With respect to the reaction mechanism, the aryl palladium complex and acyl palladium complex were characterized by X-ray, and the mechanism was studied step by step. The results fit well with DFT calculations.

Most recently, the synthesis of chalcones from aryl bromides in the presence of PPh_3 as a ligand was achieved (Scheme 7.16) [35]. Later on, this group extended our methodology to vinyl ethers [36]. Based on both experimental results and DFT calculations, a proposed mechanism for this reaction is shown in Scheme 7.17. It begins with the oxidative addition of ArX to the Pd^0 center to form the corresponding aryl palladium complex. Followed by the coordination and insertion of CO, the respective acyl palladium complex is produced. After coordination, addition, and elimination processes, the desired chalcone is produced. Under the assistant of the base, Pd^0 is regenerated and starts the next reaction cycle.

The group of Skrydstrup developed a two-chamber technology for the carbonylations. Using this two-chamber technology, CO was generated ex situ. By applying near-stoichiometric amounts of the carbon monoxide precursor, an effective exploitation of the hazardous CO gas is obtained affording chalcone derivatives in good yields from the corresponding aryl iodides and styrenes and vinyl ethers [37, 38]. Application to isotope labeling, incorporating ^{13}CO, was further established.

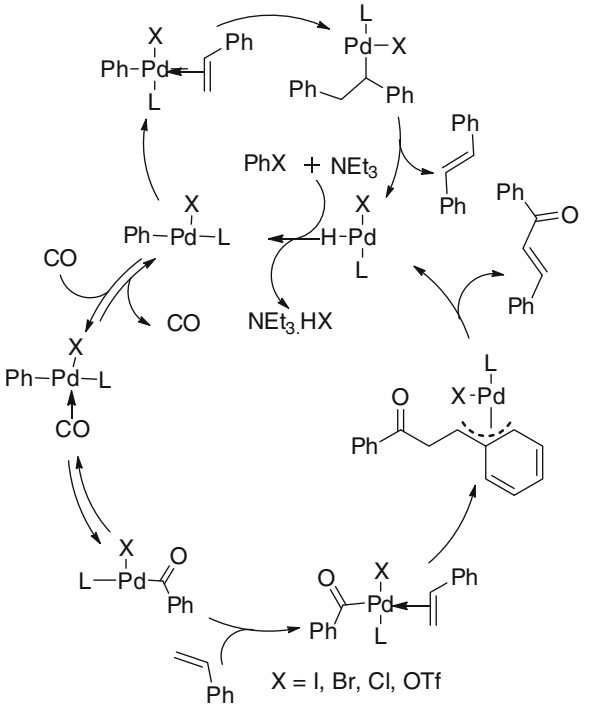


Scheme 7.15 Palladium-catalyzed carbonylative Heck reaction of aryl halides

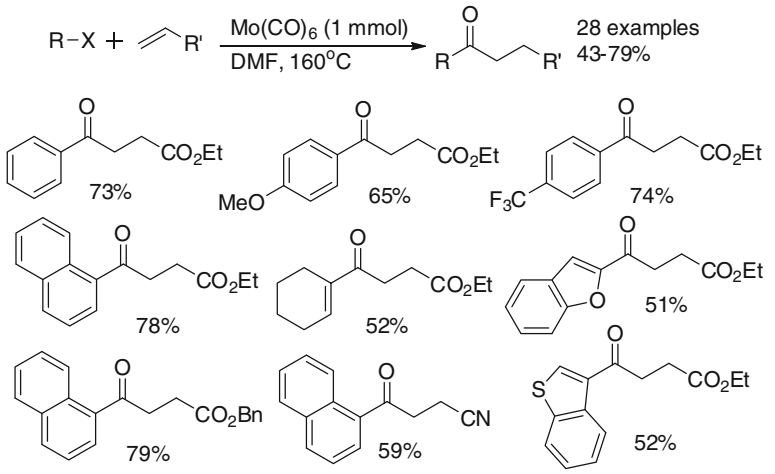


Scheme 7.16 Palladium-catalyzed carbonylative Heck reaction of aryl bromides

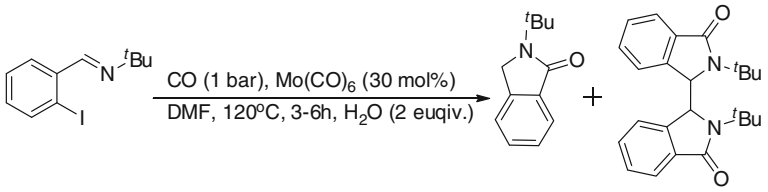
A molybdenum carbonyl complex was used as a promoter in carbonylation reactions as well [39]. Iwasawa and colleagues developed an intermolecular addition reaction of an acylmetal species generated by the oxidative addition of



Scheme 7.17 General reaction mechanism for carbonylative Heck reaction



Scheme 7.18 $Mo(CO)_6$-promoted carbonylation of alkenes



Scheme 7.19 $Mo(CO)_6$-Promoted carbonylative cyclization of *o*-haloaryl and *β*-haloalkenylimines

aryl or alkenyl halides to $Mo(CO)_6$. The reaction needed a stoichiometric amount of $Mo(CO)_6$, and a variety of substituted ketones were produced from readily available materials (Scheme 7.18).

A molybdenum carbonyl complex that promoted the carbonylative cyclization of *o*-haloaryl and *β*-haloalkenylimines was also developed by this group (Scheme 7.19) [40]. *γ*-Lactams were produced in good yields; the two kinds of products can be obtained selectively by changing the reaction conditions.

In this chapter, we discussed carbonylative Heck reactions, or the reaction of C–X with alkenes. *β*-hydride elimination is the step that distinguishes this type of carbonylation reaction from the other carbonylation reactions, from a mechanism point of view.

In the next chapter, oxidative carbonylation reactions will be summarized.

References

1. Heck, R.F. J. Am. Chem. Soc. **90**, 5518 (1968)
2. Heck, R.F. J. Am. Chem. Soc. **90**, 5526 (1968)
3. Heck, R.F. J. Am. Chem. Soc. **90**, 5531 (1968)
4. Heck, R.F. J. Am. Chem. Soc. **90**, 5535 (1968)
5. Heck, R.F. J. Am. Chem. Soc. **90**, 5538 (1968)
6. Heck, R.F. J. Am. Chem. Soc. **90**, 5542 (1968)
7. Heck, R.F. J. Am. Chem. Soc. **90**, 5546 (1968)
8. Heck, R.F., Nolley, J.P. J. Org. Chem. **37**, 2320 (1972)
9. Andersson, C., Hallberg, A. J. Org. Chem. 53, 4257 (1988)
10. Hori, K., Ando, M., Takaishi, N., Inamoto, Y. Tetrahedron Lett. **28**, 5883 (1987)
11. Sen, A., Lai, T.-W. J. Am. Chem. Soc. **104**, 3520 (1982)
12. Negishi, E.-i., Miller, J.A. J. Am. Chem. Soc. **105**, 6761 (1983)
13. Tour, J.M., Negishi, E.-i. J. Am. Chem. Soc. **107**, 8289 (1985)
14. Negishi, E.-i., Wu, G., Tour, J.M. Tetrahedron Lett. **29**, 6745 (1988)
15. Negishi, E.-i., Tour, J.M. Tetrahedron Lett. **27**, 4869 (1986)
16. Negishi, E.-i., Ma, S., Amanfu, J., Copéret, C., Miller, J.A., Tour, J.M. J. Am. Chem. Soc. **118**, 5919 (1996)
17. Negishi, E.-i., Copéret, C., Ma, S., Mita, T., Sugihara, T., Tour, J.M. J. Am. Chem. Soc. **118**, 5904 (1996)
18. Copéret, C., Ma, S., Negishi, E.-i. Angew. Chem. Int. Ed. Engl. **35**, 2125 (1996)

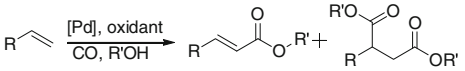
19. Ryu, I., Kreimerman, S., Araki, F., Nishitani, S., Oderaotoshi, Y., Minakata, S., Komatsu, M. J. Am. Chem. Soc. **124**, 3812 (2002)
20. Chatani, N., Kamitani, A., Oshita, M., Fukumoto, Y., Murai, S. J. Am. Chem. Soc. **123**, 12686 (2001)
21. Torii, S., Okumoto, H., Xu, L.H. Tetrahedron Lett. **31**, 7175 (1990)
22. Okuro, K., Furuune, M., Miura, M., Nomura, M. J. Org. Chem. **57**, 4754 (1992)
23. Wu, X. -F., Zhang, M., Jiao, H., Neumann, H., Beller, M. Asian J. Org. Chem. **2**, 135 (2013)
24. Satoh, T., Itaya, T., Okuro, K., Miura, M., Nomura, M. J. Org. Chem. **60**, 7267 (1995)
25. Okuro, K., Alper, H. J. Org. Chem. **62**, 1566 (1997)
26. Grigg, R., Pratt, R. Tetrahedron Lett. **38**, 4489 (1997)
27. Ye, F., Alper, H. J. Org. Chem. **72**, 3218 (2007)
28. Iwasawa, N., Satoh, H. J. Am. Chem. Soc. **121**, 7951 (1999)
29. Hayashi, T., Tang, J., Kato, K. Org. Lett. **1**, 1487 (1999)
30. Gagnier, S.V., Larock, R.C. J. Am. Chem. Soc. **125**, 4804 (2003)
31. Wu, X., Nilsson, P., Larhed, M. J. Org. Chem. **70**, 346 (2005)
32. Bloome, K.S., Alexanian, E.J. J. Am. Chem. Soc. **132**, 12823 (2010)
33. Wu, X.-F., Neumann, H., Beller, M. Angew. Chem. Int. Ed. **49**, 5284 (2010)
34. Wu, X.-F., Neumann, H., Spannenberg, A., Schulz, T., Jiao, H., Beller, M. J. Am. Chem. Soc. **132**, 14596 (2010)
35. Wu, X.-F., Jiao, H., Neumann, H., Beller, M. ChemCatChem. **3**, 726 (2011)
36. Schranck, J., Wu, X.-F., Neumann, H., Beller, M. Chem. Eur. J. **18**, 4827 (2012)
37. Hermange, P., Gogsig, T.M., Lindhardt, A.T., Taaning, R.H., Skrydstrup, T. Org. Lett. **13**, 2444 (2011)
38. Gogsig, T.M., Nielsen, D.U., Lindhardt, A.T., Skrydstrup, T. Org. Lett. **14**, 2536 (2012)
39. Sanga, K., Watanabe, J., Takaya, J., Iwasawa, N. Synlett. 929 (2007)
40. Takaya, J., Sangu, K., Iwasawa, N. Angew. Chem. Int. Ed. **48**, 7090 (2009)

Chapter 8
Oxidative Carbonylation Reactions

In the last six chapters we discussed the transition metal catalyzed carbonylative activation of organohalogen (C-X, X = I, Br, Cl, OTf, etc.) compounds. They all have one common point in their reaction mechanism; taking a palladium catalyst, for example, the reactions start with Pd(0) and then go to Pd(II) after an oxidative addition. To summarize, the reactions all go through Pd(0) to Pd(II) and a Pd(0) cycle. But for oxidative carbonylation reactions, the reactions go through Pd(II) to Pd(0) and a Pd(II) cycle. Clearly, oxidative carbonylations need additional oxidants to reoxidize the Pd(0) to Pd(II), and various organic nucleophiles were applied as substrates in the presence of CO. One of the most obvious advantages for oxidative carbonylation reactions is the oxidative addition step can be avoid which is more reluctant under CO atmosphere.

The prototype for today's palladium-catalyzed oxidative carbonylations is the well-known "Wacker Process," which was developed already in the late 1950s. Here, ethylene is oxidized to acetaldehyde using a combination of palladium(II) and copper(II) salts. Although no CO was used in this process, all the basic elementary steps for regenerating the catalyst under oxidative conditions are included. Obviously, the mechanism is different from carbonylative coupling reactions, such as reductive carbonylation, alkoxycarbonylation, Suzuki and Sonagashira carbonylations. In the Wacker process, coordination of the olefin onto the electrophilic palladium(II) center allows for a reaction of the double bond with water, alcohols or acetic acid to produce aldehydes, vinylethers or vinylacetates, respectively. Until now, the Wacker process is still the most important route for obtaining acetaldehyde from ethylene. In order to run the reaction catalytic in palladium, the formed Pd(0) species has to be regenerated to Pd(II). This is achieved by adding cupric chloride ($CuCl_2$) to the reaction mixture. Notably, the resulting Cu(I) is regenerated to Cu(II) by molecular oxygen, making the process catalytic in both palladium and copper. This crucial discovery of regenerating the Pd(II) species by $CuCl_2$ was adopted by many palladium-catalyzed oxidative carbonylations of alkenes, which resulted in unsaturated esters or diesters, depending on the catalyst system and the conditions (Scheme 8.1). Nowadays, besides $CuCl_2$, other oxidant reagents, such as direct O_2 or BQ (*p*-benzoquinone), etc., can be used to reoxidize Pd(0) to regenerate the catalytic cycle.

M. Beller and X.-F. Wu, *Transition Metal Catalyzed Carbonylation Reactions*,
DOI: 10.1007/978-3-642-39016-6_8,



Scheme 8.1 Palladium-catalyzed oxidative carbonylation of olefins

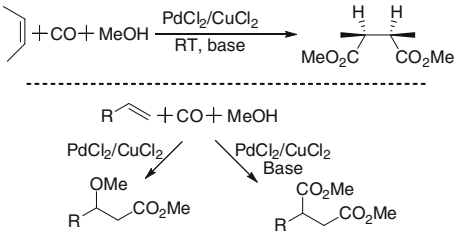
As early as 1963, Tsuji and colleagues described the reaction of olefin-palladium chloride complexes with CO to produce β-chloroacyl chlorides [1, 2]. Both internal and terminal aliphatic olefins were transformed into the corresponding chloroesters when the reaction was conducted in alcohols. Later on, in 1969, Yukawa and Tsutsumi reported on the reaction of a styrene-palladium complex with CO in alcohols [3]. Here, various cinnamates and phenylsuccinates were synthesized. Compared with Tsuji's work, they proposed a different reaction mechanism. They assumed that the oxidative addition of the alkyloxycarbonyl groups into styrenes is the key step, but a stoichiometric amount of palladium was still necessary to perform the reaction. Another version of a dialkoxycarbonylation of olefins was reported by Heck [4], using mercuric chloride as additive.

While these initial examples were performed in the presence of stoichiometric amounts of palladium, the first catalytic dialkoxycarbonylation of olefins was independently described by Fenton [5] and Medema [6] in 1969 and 1970. More specifically, a catalytic amount of palladium was used together with an equivalent of $CuCl_2$, and the reactions were run at high pressure of CO and comparatively high reaction temperatures (140–150 °C). Heck demonstrated that $CuCl_2$ is not able to efficiently reoxidize Pd(0) at low temperatures [7–9]. In 1972 Fenton and Steinwand reported on the oxidative carbonylation of olefins to succinates [10]. For the reoxidation of palladium, iron and copper chlorides were used, but oxygen should also have been present—otherwise only low yields of succinates were obtained. A related study of the hydroxycarbonylation of olefins was described by the same group [11]. Nowadays, this type of reaction is efficiently performed in the presence of protic acids.[1]

In order to elucidate the mechanism in more detail, the stereospecific oxidative carbonylation of *cis*- and *trans*-2-butene in methanol was carried out by Stille and colleagues [16]. $PdCl_2$ and $CuCl_2$ were applied as the catalytic system, resulting in a stereospecific *trans*-methoxypalladation. The addition of equimolar amounts of NaOAc changed the course of the reaction completely and led to stereospecific *cis*-carboxymethylpalladation as the exclusive reaction pathway. The authors also investigated the mechanism by means of ^{13}C NMR [17, 18]. Apart from internal and terminal olefins, they extended their methodology to reactions of diolefins [19], vinyl ketones, unsaturated alcohols, and unsaturated esters. All these substrates were dicarboxylated in high yields (Scheme 8.2).

In 1979 Cometti and Chiusoli published their results on the synthesis of methyl cinnamates from styrene [20]. Using a mixture of $PdCl_2$, $CuCl_2$, $MgCl_2$ and

[1] For selected examples, see [12–15].



Scheme 8.2 Palladium-catalyzed oxidative carbonylation of olefins to diesters

NaOAc, the reaction was run in methanol at room temperature under atmospheric pressure of CO to produce methyl cinnamate together with dimethyl phenylsuccinate as the products (Scheme 8.3).

Alper and his group reported on another protocol for the hydroxycarbonylation of alkenes in 1983 [21]. Here, $PdCl_2$ and $CuCl_2$ were applied as the catalytic system. Alkenes were transformed into branched propionic acids in good yields in the presence of water, oxygen, and HCl. Later on, they extended their protocol to monohydroesterification of diols [22–24]. As shown in Scheme 8.4, the reactions could be conducted under mild conditions (room temperature, 1 bar of CO).

Consiglio and colleagues described the enantioselective version of bis-alkoxycarbonylations of alkenes [25–27]. Here, BQ was applied to reoxidize the palladium centre. As chiral ligands, DIOP, BINAP, and some other chiral phosphine ligands were tested. More recently, Chan's group succeeded in using modified dipyridylphosphine cationic Pd(II) complexes to obtain both good *ee* and chemoselectivity.[2]

Instead of using $CuCl_2$ and BQ, butyl nitrite was also applied in the oxidative carbonylation of alkenes by Chauvin and colleagues.[3] When $PdCl_2(PhCN)_2$ and PPh_3 were used as the catalyst system, $PdCl_2(CO_2Bu)NO(PPh_3)$ was isolated and proved to be one of the reaction intermediates. In the gas phase of the reaction, CO_2, N_2O, NO and N_2 were found, but no N_2O.

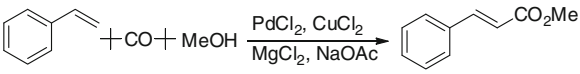
In 1996 Castanet et al. developed a CO-free procedure for the oxidative carbonylation of alkenes [32]. Instead of a MeOH/CO mixture, methyl formate was used in the presence of a Pd^{II}/Cu system and unsaturated esters were produced in one step. During the reaction, methyl formate acted as the source of both alcohol and CO, but an initial partial pressure of CO was required in order to obtain high yields. Moreover, they demonstrated that by the addition of lithium methoxide, the handling of CO could be avoided.

Inomata and his team described the Pd/C-catalyzed oxidative carbonylation of terminal olefins [33]. The reaction proceeded selectively to mono- or diesters under 1 bar of CO at room temperature in good yields, in the presence of $CuCl_2$ or CuCl as the additive. Interestingly, mainly monoesters were observed when $CuCl_2$

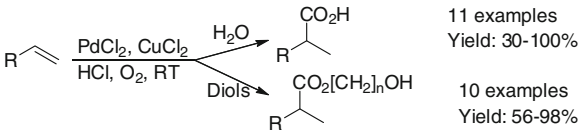
[2] For a summary on the Pd-catalyzed asymmetric alkoxycarbonylation of vinylarenes, see: [28, 29].

[3] For a review on the application of alkyl nitrites as oxidant, see: [30, 31].

Scheme 8.3 Palladium-catalyzed synthesis of methyl cinnamate



Scheme 8.4 Palladium-catalyzed oxidative carbonylation of alkenes to branched products



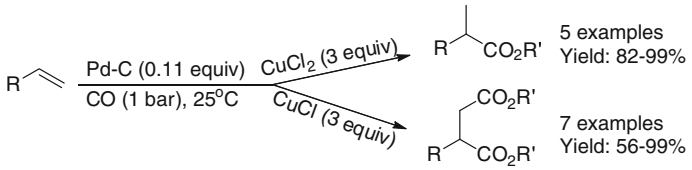
was applied as oxidant, while diesters were formed in good yields by using CuCl as the oxidant reagent (Scheme 8.5). By using $PdCl_2$ (0.1 equiv) instead of Pd/C, in the presence of CuCl (1.5 equiv) and O_2, they were also able to transform 3-buten-1-ols into the corresponding γ-butyrolactones and 2-oxotetrahydrofuran-3-acetic acid esters in high yields [34].

An asymmetric version for the synthesis of diesters was published by the same group in 2001 [35]. By using a chiral bisoxazoline ligand in the presence of copper(I) triflate at 25 °C, terminal olefins were carbonylated to enantiomerically enriched diesters in good yields with up to 66 % *ee* (Scheme 8.6).

Previously, this catalyst system was also used for the oxidative carbonylation of homoallylic alcohols to synthesize lactones with 19–65 % *ee* [36]. In 1998, Saigo and colleagues reported on the use of phosphine sulfides as ligands for the oxidative carbonylation of olefins [37]. Diesters were produced in high yields starting from the corresponding alkenes (Scheme 8.7). Enantioselectivity can be obtained by applying chiral biphosphine sulfides as ligands. Notably, their model system gave 36 and 60 % yield in the absence of ligand and with triphenylphosphine oxide, respectively. However, no reaction took place in the presence of PPh_3.

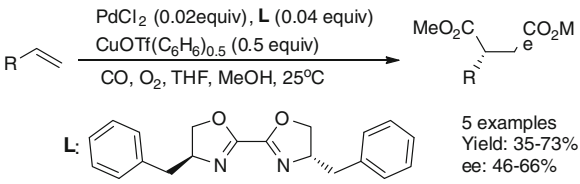
Yang and his team developed a procedure for the oxidative carbonylation of terminal olefins to phenylsuccinate esters by using thioureas as ligands [38]. It was claimed that these ligands can prevent both palladium precipitation and double bond isomerization. Later on, the same authors synthesized a set of thiourea-oxazolines (*S*,*N*-bidentate ligand) which also allowed for enantioselective reactions (Scheme 8.8) [39, 40].

In 2001 Bianchini's group described the oxidative carbonylation of styrene to methyl cinnamate and dimethyl phenylsuccinate. Methyl cinnamate was synthesized starting from styrene with a good yield with excellent selectivity by applying a modified diphosphine as ligand [41], while dimethyl phenylsuccinate was produced by using pyridinimine as the ligand [42]. Jiang and Zhu succeeded in applying the phosphate-based ligand [(*S*)-(+)-BNPPA] in the palladium-catalyzed alkoxycarbonylation of *N*-vinylphalimide [43]. The effects of solvent, temperature, promoters, and other parameters were studied. Good yields and high regioselectivities of either branched or linear products were obtained under optimum conditions.



Scheme 8.5 Pd/C-catalyzed oxidative carbonylation of alkenes

Scheme 8.6 Palladium-catalyzed oxidative carbonylation of olefins



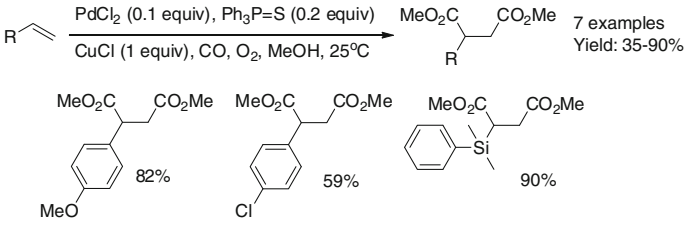
Besides efforts on the development of ligands for oxidative carbonylation of alkenes, Jiang and colleagues performed the oxidative carbonylation of norbornene in supercritical carbon dioxide ($scCO_2$) [44]. Ishii and colleagues were able to develop copper-free reaction conditions by using catalytic amounts of $Pd(OAc)_2$ and molybdovanadophosphate (NPMoV) [45]. With CO and air, cyclopentene was oxidatively carbonylated into dimethyl *cis*-1,2-cyclopentanedicarboxylate and dimethyl *cis*-1,3-cyclopentanedicarboxylate in good yields. The addition of NH_4Cl can improve the yield of this reaction.

The oxidative carbonylation of hydroxy-substituted alkenes can lead to synthetically interesting tetrahydrofurans and pyrans.[4] As early as 1984, Semmelhack and his group developed a methodology for the synthesis of furans and pyrans using a palladium-catalyzed oxidative carbonylation of hydroxyalkenes. In the presence of $CuCl_2$ (3 equiv), $PdCl_2$ (0.1 equiv) and CO (1.1 bar) at 25 °C, the heterocycles were isolated in good yields (Scheme 8.9) [50]. In another study, they performed the carbonylative synthesis of tetrahydrofurans [51, 52], and this procedure was applied to the synthesis of pyran-lactones [53], racemic frenolicin [54], and also plakortones [55–58].

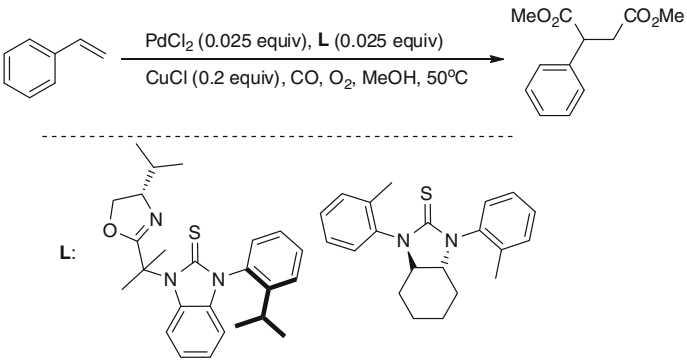
In 1985 Alper and Leonard applied their previously reported reaction conditions [14, 15] in the oxidative carbonylation of alkenones to produce five- and six-membered lactones. The reaction was conducted in THF, in the presence of a $PdCl_2/CuCl_2$ catalyst system yielding lactones in 42–80 % (Scheme 8.10).

That same year, Yoshida and colleagues demonstrated the oxidative carbonylation of 4-penten-1,3-diols. In the presence of $PdCl_2$ (0.1 equiv), $CuCl_2$ (3 equiv), NaOAc (3 equiv) and under CO (1 bar) at room temperature, lactones were achieved stereoselectively [59]. They also succeeded in finding optimal conditions for the oxidative carbonylation of 3-hydroxypent-4-enylamides to produce the

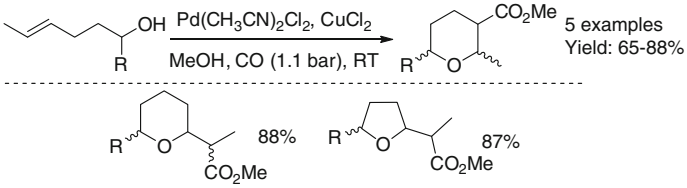
[4] For related reviews on this topic, see: [46–49].



Scheme 8.7 Palladium-catalyzed oxidative carbonylation of olefins using triphenylphosphine sulfide as ligand



Scheme 8.8 Palladium-catalyzed oxidative carbonylation of olefins using thioureas as ligand

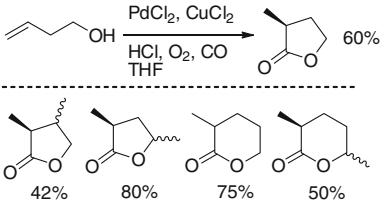


Scheme 8.9 Palladium-catalyzed oxidative carbonylation of hydroxyalkenes

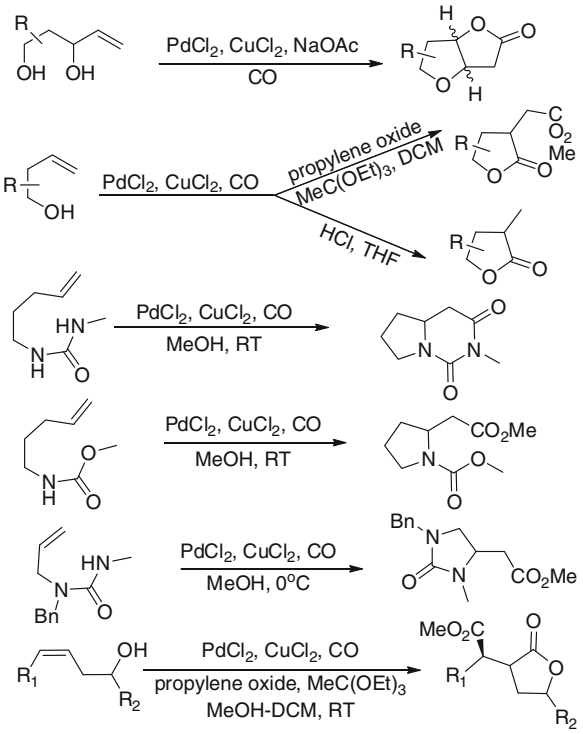
corresponding 3-hydroxy pyrrolidine 2-acetic acid lactones in 66–90 % of yields [60]. The same group also used substituted ureas, 3-hydroxy-4-pentenylamines, 4-hydroxy-5-hexenylamines, 3-buten-1-ols, 3-butyn-1-ols, unsaturated carbamates, unsaturated amides, and even dienyl carbamates as substrates (Scheme 8.11) [61–68]. The related oxidative carbonylation of allenic amides/amines for the synthesis of heterocyclic acrylates was described by Gallagher and colleagues [69].

In 2008 Gracza and Kapitan reported the stereocontrolled oxidative carbonylation of diols [70, 71]. Performing the reaction in AcOH at room temperature,

Scheme 8.10 Palladium-catalyzed oxidative carbonylation of alkenones



Scheme 8.11 Palladium-catalyzed oxidative carbonylation of functionalized alkenes

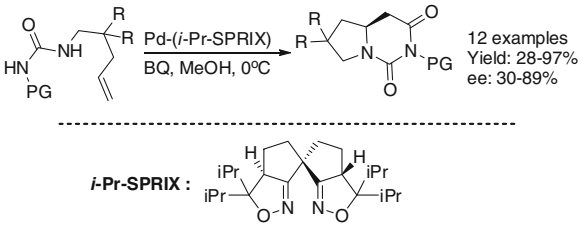


applying $Pd(OAc)_2$, a chiral bis(oxazoline) ligand and BQ as oxidant, the corresponding lactones were produced in good yields.

Recently, Sasai's group published the enantioselective oxidative carbonylation of alkenylureas. By using the palladium-spiro bis(isoxazoline) system, the desired products were produced in good yields and with moderate to good *ee* (Scheme 8.12) [72].

Jiang's group developed a palladium-catalyzed direct oxidative carbonylation of allylic C–H bonds with carbon monoxide [73]. This observation provides a novel route for accessing β-enoic acid esters with high regioselectivity (Scheme 8.13). Preliminary results from deuterium-labeling experiments indicated that the allylic C–H activation process is an irreversible rate-determining step.

Scheme 8.12 Palladium-catalyzed oxidative carbonylation of alkenylureas



Although a number of synthetic applications of oxidative carbonylations of alkenes were described in total synthesis, most research efforts focused on finding new ligands and catalyst systems. In general, a large excess of copper salts or other organic oxidants is still needed. Obviously, this creates problems both in the purification of the respective products as well as the environment. Therefore, using air, oxygen, or hydrogen peroxide as more "green oxidants" under mild conditions is an important goal for the future.

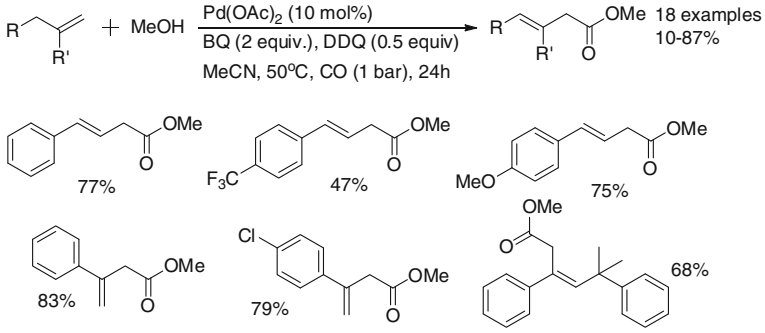
In the palladium-catalyzed oxidative carbonylation of alkynes, mixtures of products can often be formed. Nevertheless, these reactions can be valuable and have the potential to be tunable (Scheme 8.14). Costa and Salerno's group has shown that the combination of the palladium catalyst KI and oxidant is a powerful system for the oxidative carbonylation of alkynes.[5]

The examples of oxidative carbonylations of alkynes were reported on in 1964. Here, Tsuji et al. described the palladium-mediated transformation of acetylene into muconyl chloride, fumaryl and maleic acid chloride (Scheme 8.15) [77]. Later on, they used diphenylacetylene as a substrate for the synthesis of lactones in the presence of alcohol and HCl [78, 79].

For ten years, Tsuji and colleagues further developed the palladium-catalyzed oxidative carbonylation of terminal acetylenes. For example, acetylenecarboxylates were produced in high yields at room temperature under atmospheric pressure of CO, but a stoichiometric amount of $CuCl_2$ was needed to reoxidize the Pd(0) (Scheme 8.16) [80]. Temkin and colleagues investigated the mechanism of this reaction [81–84]. They found that σ-alkynylcopper(I) complexes are intermediates in the reaction, and that the addition of CuCl to the initial reaction solution caused a significant decrease in the induction period. A catalytic system consisting of $PdCl_2$, CuCl, LiCl, O_2, and CO was also successfully applied to this reaction. In 1983 Alper's group developed another method using a combination of $PdCl_2$, $CuCl_2$, HCl, and O_2. While *cis*-diesters were synthesized from terminal alkynes, *cis*-monoesters were formed, starting from internal alkynes under atmospheric pressure at room temperature [15].

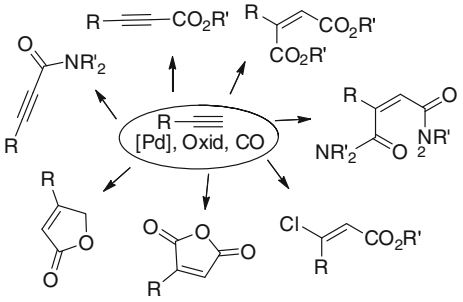
Ishii and colleagues developed a multicatalytic system for the oxidative carbonylation of terminal alkynes [85]. In the presence of $Pd(OAc)_2$, chlorohydroquinone and NPMoV, under CO and O_2, acetylenecarboxylate or phenylmaleic

[5] For reviews on PdI_2-catalyzed oxidative carbonylation reactions, see: [74–76].

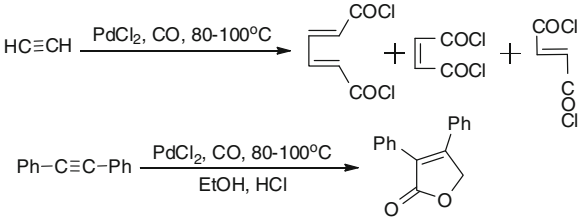


Scheme 8.13 Palladium-catalyzed carbonylation of allylic C–H

Scheme 8.14 Palladium-catalyzed oxidative carbonylations of alkynes

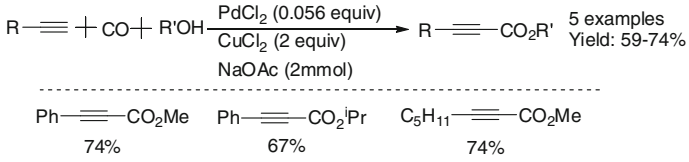


Scheme 8.15 Palladium-mediated oxidative carbonylation of alkynes

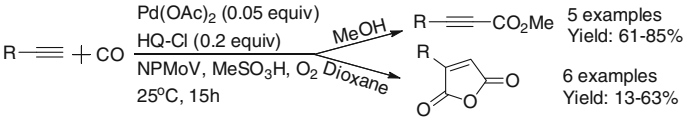


anhydride, were synthesized selectively in various solvents. Interestingly, the presence of O_2 is important; otherwise, no reaction occurred (Scheme 8.17). Notably, Jiang and his research team carried out similar work with the more common $PdCl_2/CuCl_2$-catalyst system [86].

Yamamoto and colleagues were able to develop an additive-free palladium catalyst system for the oxidative carbonylation of alkynes [87, 88]. By using their palladium-phosphine catalyst in the presence of molecular oxygen, acetylene-carboxylates were formed under atmospheric pressure of CO at room temperature. A detailed mechanistic study was also carried out proposing a reductive elimination of a palladium species with methoxycarbonyl and alkynyl residues. The oxidation of Pd(0) to Pd(II) species was confirmed to proceed cleanly with



Scheme 8.16 Palladium-catalyzed oxidative carbonylation of acetylenes



Scheme 8.17 Palladium-catalyzed oxidative carbonylation of acetylenes

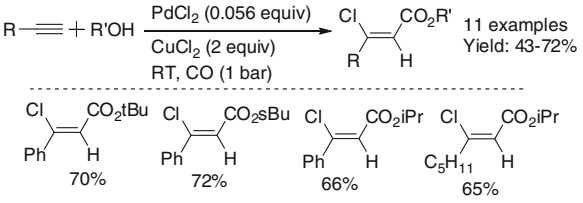
molecular oxygen as the oxidant in the presence of halide ions. On the basis of this work, a heterogeneous variant using Pd/C has also been developed.

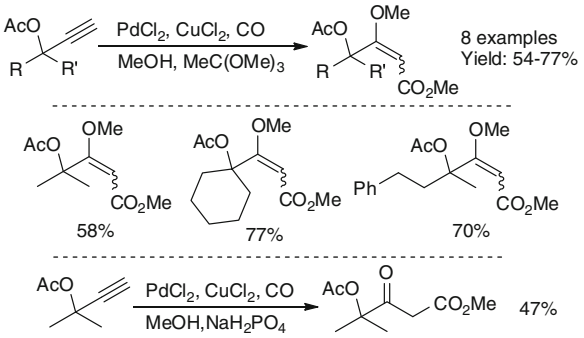
Jiang's team described the synthesis of 3-chloroacrylate esters [89]. Their reaction proceeded under 1 bar of CO at room temperature yielding 30–72 % of the desired products in a high regio- and stereoselective manner (Scheme 8.18).

The oxidative carbonylation of 1,1-disubstituted propargyl acetates to unsaturated esters was developed by Okumoto and colleagues in 1999 [90]. A stoichiometric amount of $CuCl_2$ was used as the oxidant and the reaction had to be conducted at 0 °C (Scheme 8.19).

The synthesis of lactones via palladium-catalyzed oxidative carbonylation of hydroxyalkynes was primarily reported by Tamaru and colleagues. Starting from 3-butyn-1-ols, the corresponding lactones were produced at room temperature. An access to ketopyranosides as a subunit of polyketide natural products was reported by Marshall and Yanik [91]. In the presence of 5 mol % $Pd(MeCN)_2Cl_2$ and 1.1–1.5 equivalent of BQ, methyl ketopyranosides were prepared from corresponding hydroxyalkynes with excellent stereoselectivity. A mild and efficient methodology for the palladium-catalyzed carbonylative synthesis of four-membered β-lactones has been published by Ma and colleagues [92]. In the presence of $PdCl_2$ and $CuCl_2$, β-lactones were produced from 2-alkynols in good yields (Scheme 8.20). Using readily available optically active propargylic alcohols, the corresponding β-lactones were generated with high *ee*.

Scheme 8.18 Palladium-catalyzed oxidative carbonylation of acetylenes to chloroacrylates





Scheme 8.19 Palladium-catalyzed oxidative carbonylation of propargylic acetates

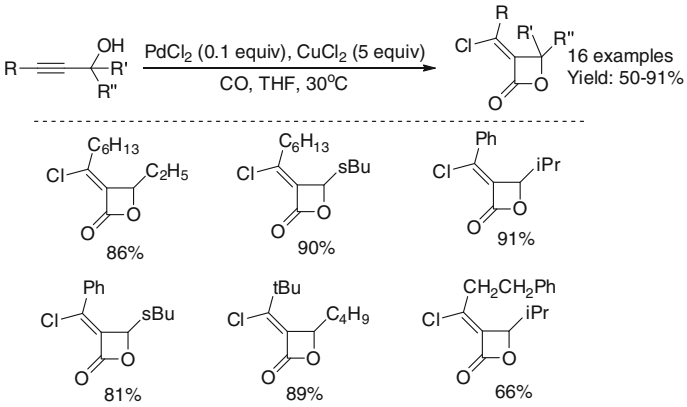
Moreover, an improved method for the oxidative carbonylation of hydroxyalkynes was developed by Kato and colleagues [93]. Applying $Pd(MeCN)_2Cl_2$ (0.05 equiv) and 1.1 equivalent of BQ in methanol at 0 °C under 1 bar of CO, the desired products were obtained from the corresponding cyclic- and acyclic-4-yn-1-ols in good yields (Scheme 8.21). Afterwards, the same group published an asymmetric version of this reaction by applying $Pd(TFA)_2$ with chiral ligands as the catalyst system at lower temperatures (−50 to −30 °C) [94, 95].

Soon afterwards, the same group developed methodologies for the oxidative carbonylation of 4-yn-1-ones and propargylic esters (Scheme 8.22). While 2-cyclopentenone carboxylates were obtained from appropriate carbonyl-substituted alkynes [96], cyclic orthoesters and furanones were successfully synthesized starting from corresponding propargylic compounds [97]. More recently, they also realized the asymmetric version of this reaction [98], which has also been applied in the total synthesis of (−)-AL-2 by Mukai and Miyakoshi [99].

In 2009 Kato and colleagues applied their palladium(II) bis(oxazoline) complexes in the intermolecular methoxycarbonylation of terminal alkynes. Here, terminal alkynes were transformed into *β*-methoxyacrylates in good yields (Scheme 8.23).

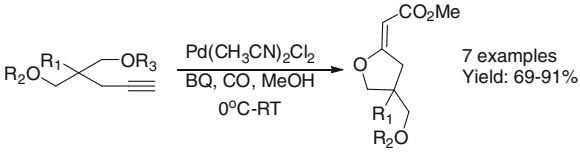
Notably, this methodology tolerates acetyl, ketal, free hydroxy and acid sensitive glycosidic groups. In the case of propargyl alcohol, (±)-dihydrokawain was produced in good yields [100]. In addition, this methodology was applied in the total synthesis of annularin G and annularin H [101].

In 1974, Stille and Wong published the first oxidative carbonylation based on organomercury compounds [102]. Using stoichiometric amount of $PdCl_2$, LiCl, and NaOAc, stereoselective carbonylation took place at room temperature. However, the desired products were obtained only in a low yield. Next, Larock and his team improved the methodology by conducting the reaction at −78 °C [103]. Here, unsaturated carboxylic acids and esters were formed in excellent yields starting from the corresponding vinylmercurials. Although stoichiometric amounts of palladium were still necessary, a catalytic version was realized by the addition of large excess of $CuCl_2$ (Scheme 8.24).



Scheme 8.20 Palladium-catalyzed oxidative carbonylation of alkynes to β-lactones

Scheme 8.21 Palladium-catalyzed oxidative carbonylation of alkynes

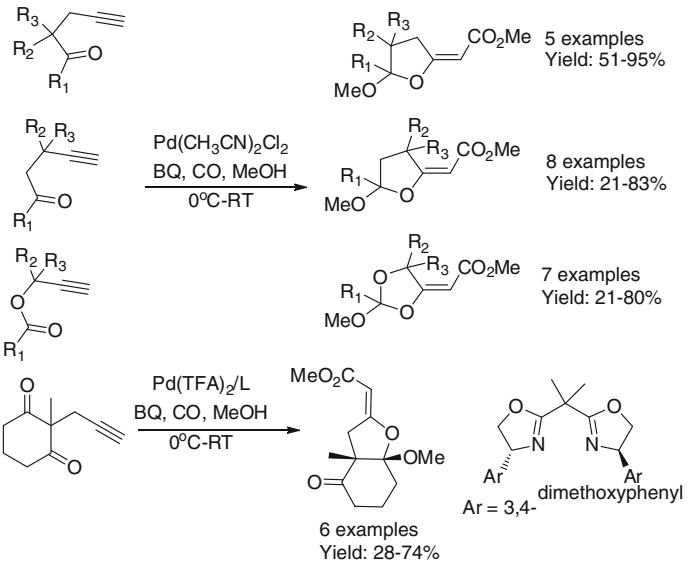


Until now, there has been only one report published concerning the oxidative carbonylation of organosilanes [104]. The reaction was carried out at room temperature and under 1 bar of CO, but a stoichiometric amount of $PdCl_2$ was required to form 61–91 % of the corresponding vinyl esters (Scheme 8.25).

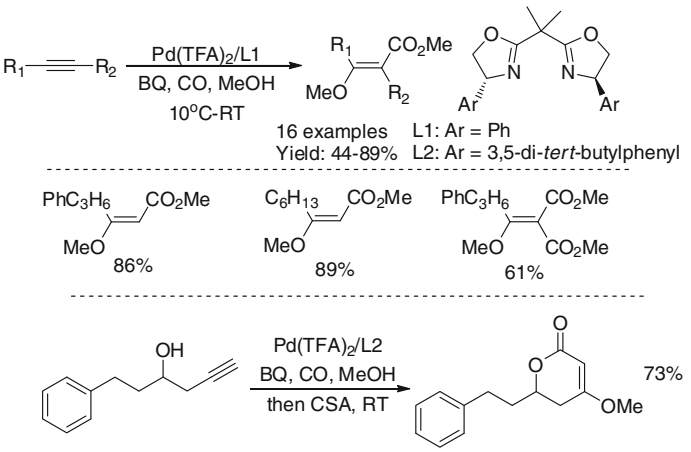
A novel palladium-catalyzed oxidative carbonylation of organoindium compounds with desyl chloride as oxidant was developed by Lei and colleagues in 2008 [105]. Primary and secondary alkyl indium reagents, as well as aryl indium reagents, were carbonylated at 60 °C in the presence of a catalytic amount of palladium catalyst. The corresponding esters were formed in good yields and the methodology showed broad functional group tolerance (Scheme 8.26). The reaction mechanism was discussed in detail.

Suzuki and colleagues described the first palladium-catalyzed oxidative carbonylation of alkenylboranes as early as 1981. They prepared 1-alkenylboranes by hydroboration of alkynes and subsequent oxidative carbonylation mediated by a catalytic amount of $PdCl_2$, in the presence of NaOAc and BQ in methanol, which provided unsaturated esters in good yields (Scheme 8.27a) [106]. Later, a stereoselective synthesis of β-mono- and β, β-disubstituted α, β-unsaturated esters was established by a stepwise cross-coupling alkylation followed by an oxidative carbonylation of 2-bromo-1-alkenylboranes (Scheme 8.27b) [107]. Good yield and excellent stereoselectivity was achieved.

Interestingly, Uemura and colleagues developed a method for the carbonylation of C–B bonds without any oxidant, using only Pd(0) as the catalyst [108, 109].

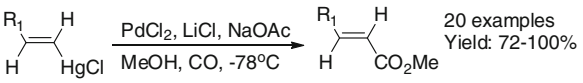


Scheme 8.22 Palladium-catalyzed oxidative carbonylation of carbonyl-substituted alkynes

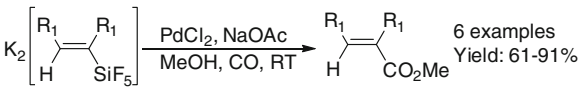


Scheme 8.23 Palladium-catalyzed oxidative carbonylation of alkynes

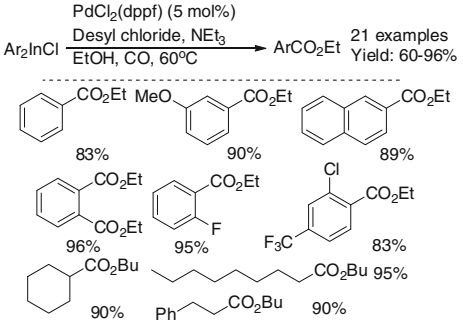
Scheme 8.24 Palladium-promoted carbonylation of organomercuries

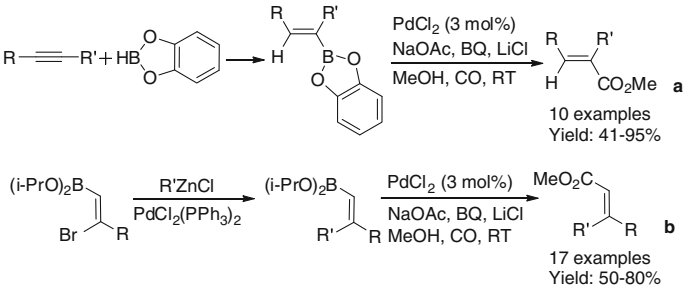


Scheme 8.25 Palladium-promoted carbonylation of organosilanes



Scheme 8.26 Palladium-catalyzed carbonylation of organoindiums

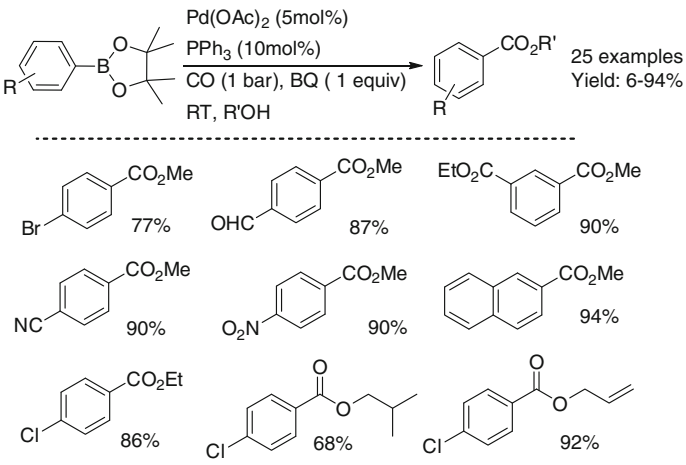




Scheme 8.27 Palladium-catalyzed oxidative carbonylation of alkenylboranes

Starting from alkenyl- and arylborates and boronic acids, corresponding esters and ketones could be synthesized under the atmospheric pressure of CO in methanol at 25 °C in moderate yields. On the other hand, Yamamoto et al. described a general and selective palladium-catalyzed oxidative carbonylation of arylboronates in alcohols [110]. In the presence of $Pd(OAc)_2/PPh_3$ and BQ, esters were produced from the corresponding arylboronates in good yields at room temperature (Scheme 8.28). A wide range of functional groups, including various carbonyl substituents, nitrile, nitro, sulfone residues, unprotected pyrrole rings and also various alcohols, was tolerated. The reaction was conducted without an acid or base additive and DFT and MP2 calculations were carried out to clarify the reaction mechanism.

Meanwhile, Lei and his colleagues discovered a novel protocol that makes use of air as an oxidant at low temperatures [111]. Using a balloon pressure of CO/air mixture, arylboronates were converted into the corresponding esters in good yields (Scheme 8.29). This was the first example that could apply simply air in the oxidative carbonylation of organoboron compounds with alcohols.



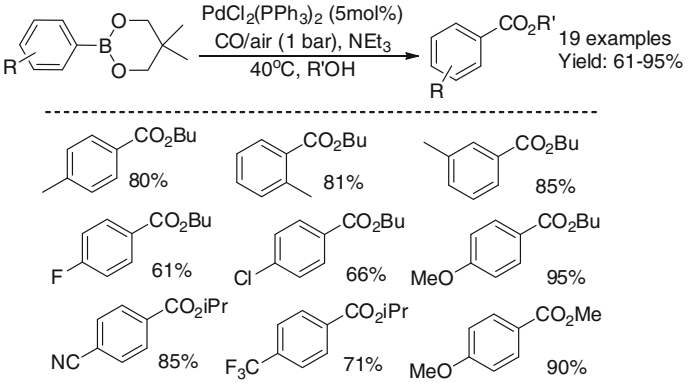
Scheme 8.28 Palladium-catalyzed oxidative carbonylation of arylboronates

The oxidative carbonylation of organoborons has also attracted the interest of Zhou and colleagues, who used 10-hydroxy-9,10-boroxarophenanthrenes in the presence of CO and stoichiometric amounts of $Pd(OAc)_2$ to form tricyclic lactones in high yields (Scheme 8.30) [112].

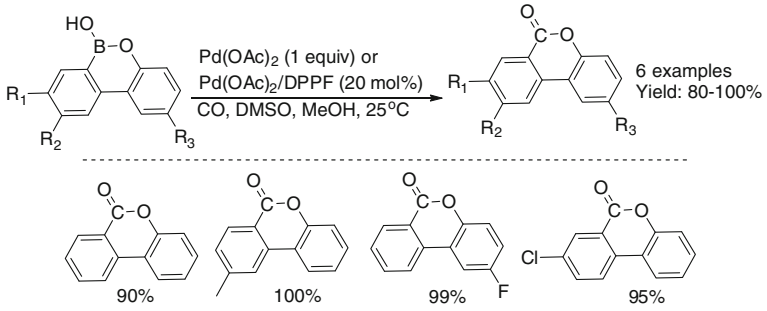
More recently, Beller's group developed a general and efficient protocol for the oxidative carbonylative coupling of arylboronic acids with styrenes [113]. Notably, air was used as a benign terminal oxidant yielding chalcones in moderate to excellent yields (Scheme 8.31). A possible mechanism for the oxidative vinylation of arylboronic acids is proposed in Scheme 8.8. Initially, a transmetalation of the arylboronic acid with the active palladium(II) complex took place. After the coordination and insertion of CO, the corresponding acyl palladium species is formed. Then, the coordination and insertion of styrene to the acyl palladium center should take place. The terminal product was produced after elimination with concomitant generation of a palladium hydride complex. This latter complex was regenerated to the active species in the presence of air, which finished the catalytic cycle.

Kang and colleagues developed a palladium-catalyzed carbonylative coupling of organolead compounds that afforded the symmetrical ketones [114]. In the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and NaOMe (5 equiv.) in CH_3CN under atmospheric pressure of carbon monoxide at room temperature, symmetrical ketones were produced in good yields (Scheme 8.32).

A palladium-catalyzed oxidative coupling of organozinc reagents were reported by Jackson and colleagues [115]. In the presence of $Pd(PPh_3)_4$ and under CO atmosphere, functionalized zinc reagents were transformed into the desired ketones in good yields. The authors also demonstrated that adventitious molecular oxygen plays a key role in the formation of the symmetrical ketones, and that rigorous exclusion of oxygen can result in substantially higher yields of ketones in the cross-coupling with some aromatic iodides. Cobalt bromide was also applied in



Scheme 8.29 Palladium-catalyzed oxidative carbonylation of arylboronates using air

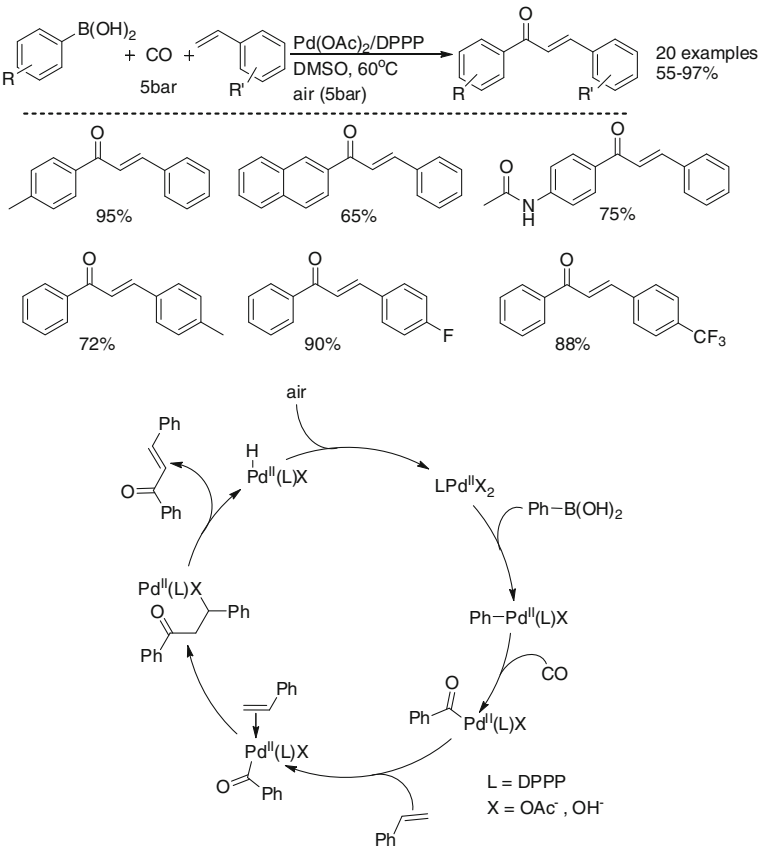


Scheme 8.30 Palladium-mediated oxidative carbonylation towards lactones

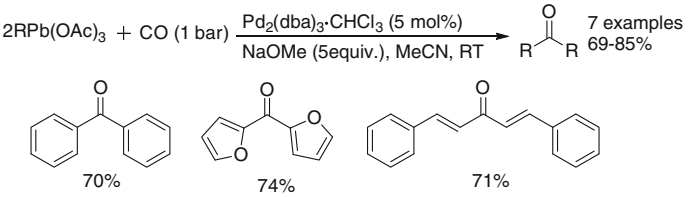
the homo-coupling of organozincs [116]. In the presence of 1.5 equivalents of $CoBr_2$ and bubbling with CO gas, ketones were formed in good yields.

More recently, a rhodium-catalyzed carbonylation of arylzinc compounds was developed by Takagi [117]. In the presence of an Rh-dppf catalyst under 1 bar of CO using 1,2-dibromoethane as the oxidant, carbonylative homo-coupling of arylzinc compounds was achieved, affording symmetrical diaryl ketones in good yields (Scheme 8.33). Under similar conditions, Pd or Ni catalysts induced oxidative homo-coupling of zinc reagents to yield diaryls instead.

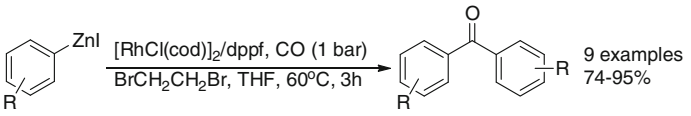
In this chapter we discussed the transition metal catalyzed oxidative carbonylation of alkenes, alkynes and organometallic reagents. In these types of reactions, an additional oxidant is needed to reoxidize the catalyst back to an active state after a reductive elimination step. The oxidants applied are normally $Cu(OAc)_2$ or BQ, air or O_2, as more green oxidants should be investigated and applied in oxidative carbonylation reactions. In contrast, carbonylative reduction reactions using CO as a reductant are also interesting. In the next chapter, the reduction of C-NO_2 with CO will be discussed.



Scheme 8.31 Palladium-catalyzed oxidative carbonylative coupling of arylboronic acids with styrenes and proposed reaction mechanism



Scheme 8.32 Pd-catalyzed carbonylative coupling of organolead compounds



Scheme 8.33 Rh-catalyzed carbonylative synthesis of ketones

References

1. Tsuji, J., Morikawa, M., Kiji, J.: Tetrahedron Lett. **1963**, 16 (1061)
2. Tsuji, J., Morikawa, M., Kiji, J.J.: Am. Chem. Soc. **86**, 4851 (1964)
3. Yukawa, T., Tsutsumi, S.J.: Org. Chem. **34**, 738 (1969)
4. Heck, R.F.J.: Am. Chem. Soc. **94**, 2712 (1972)
5. Fenton, D.M.U.S.: Patent **3**(530), 168 (1970)
6. Medema, D., Van Helden, R., Kohll, C. F.: Inorg. Chim. Acta., 255 (1969)
7. Hines, L.F., Stille, J.K.J.: Am. Chem. Soc. **94**, 485 (1972)
8. Hegedus, L.S., Darlington, W.H.J.: Am. Chem. Soc. **102**, 4980 (1980)
9. Wieber, G.M., Hegedus, L.S., Akermark, B., Michalson, E.T.J.: Org. Chem. **54**, 4649 (1989)
10. Fenton, D.M., Steinwand, P.J.J.: Org. Chem. **37**, 2034 (1972)
11. Fenton, D.M.J.: Org. Chem. **38**, 3192 (1973)
12. Bertoux, F., Tilloy, S., Monflier, E., Castanet, Y., Mortreux, A.J.: Mol. Catal. A: Chem. **138**, 53 (1999)
13. Vavasori, A., Cavinato, G., Toniolo, L.J.: Mol. Catal. A: Chem. **176**, 11 (2001)
14. Seayad, A., Jayasree, S., Damodaran, K., Toniolo, L., Chaudhari, R.V.J.: Organomet. Chem. **601**, 100 (2000)
15. Gironès, J., Duran, J., Polo, A., Real, J.: Chem. Commun., 1776 (2003)
16. James, D.E., Hines, L.F., Stille, J.K.J.: Am. Chem. Soc. **1976**, 98 (1806)
17. James, D.E., Stille, J.K.J.: Am. Chem. Soc. **1976**, 98 (1810)
18. James, D.E., Stille, J.K.J.: Org. Chem. **41**, 1504 (1976)
19. Stille, J.K., Divakaruni, R.J.: Org. Chem. **44**, 3474 (1979)
20. Cometti, G., Chiusoli, G.P.J.: Organomet. Chem. **181**, C14 (1979)
21. Alper, H., Woell, J. B., Despeyroux, B., Smith, D. J. H.: J. Chem. Soc., Chem. Commun., 1270 (1983)
22. Fergusson, S. B., Alper, H.: J. Chem. Soc., Chem. Commun.,1349 (1989)
23. Alper, H., Leonard, D. J. Chem. Soc. Chem. Commun., 511 (1985)
24. Alper, H., Despeyroux, B., Woell, J.B.: Tetrahedron Lett. **24**, 5691 (1983)
25. Pisano, C., Nefkens, S.C.A., Consiglio, G.: Organometallics **1992**, 11 (1975)
26. Nefkens, S.D.A., Sperrle, M., Consiglio, G.: Angew. Chem. Int. Ed. Engl. **32**, 1719 (1993)
27. Sperrle, M., Consiglio, G.J.: Mol. Cata. A: Chem. **143**, 263 (1999)
28. Wang, L., Kwok, W., Wu, J., Guo, R., Au-Yeung, T.T.L., Zhou, Z., Chan, A.S.C., Chan, K.-S.J.: Mol. Catal. A: Chem. **196**, 171 (2003)
29. Godard, C., Muñoz, B. K., Ruiz, A., Claver, C.: Dalton Trans., 853 (2008)
30. Bréchot, P., Chauvin, Y., Commereuc, D., Sauussine, L.: Organometallics **9**, 26 (1990)
31. Uchiumi, S., Ataka, K., Matsuzaki, T.J.: Organomet. Chem. **576**, 279 (1999)
32. Pennequin, P., Fontaine, M., Castanet, Y., Mortreux, A., Petit, F.: Appl. Catal. A: Gen **135**, 329 (1996)
33. Inomata, K., Toda, S., Kinoshita, H.: Chem. Lett., 1567 (1990)
34. Toda, S., Miyamoto, M., Kinoshita, H., Inomata, K.: Bull. Chem. Soc. Jpn. **64**, 3600 (1991)
35. Takeuchi, S., Ukaji, Y., Inomata, K.: Bull. Chem. Soc. Jpn. **74**, 955 (2001)
36. Ukaji, Y., Miyamoto, M., Mikuni, M., Takeuchi, S., Inomata, K.: Bull. Chem. Soc. Jpn. **69**, 735 (1996)
37. Hayashi, M., Takezaki, H., Hashimoto, Y., Takaoki, K., Saigo, K.: Tetrahedron Lett. **39**, 7529 (1998)
38. Dai, M., Wang, C., Dong, G., Xiang, J., Luo, T., Liang, B., Chen, J., Yang, Z.: Eur. J. Org. Chem., 4346 (2003)
39. Liang, B., Liu, J., Gao, Y.-X., Wongkham, K., Shu, D.-X., Lan, Y., Li, A., Batsanov, A.S., Howard, J.A.H., Marder, T.B., Chen, J.-H., Yang, Z.: Organometallics **26**, 4756 (2007)
40. Gao, Y.-X., Chang, L., Shi, H., Liang, B., Wongkhan, K., Chaiyaveij, D., Batsanov, A.S., Marder, T.B., Li, C–.C., Yang, Z., Huang, Y.: Adv. Synth. Catal. **2010**, 352 (1955)

41. Bianchini, C., Mantovani, G., Meli, A., Oberhauser, W., Brüggeller, P., Stampfl, T.: J. Chem. Soc., Dalton Trans., 690 (2001)
42. Bianchini, C., Lee, H.M., Mantovani, G., Meli, A., Oberhauser, W.: New J. Chem. **26**, 387 (2002)
43. Zhu, B.C., Jiang, X.Z.: Appl. Organometal. Chem. **20**, 277 (2006)
44. Jia, L., Jiang, H., Li, J.: Green Chem., 91 (1999)
45. Yokota, T., Sakaguchi, S., Ishii, Y.J.: Org. Chem. **67**, 5005 (2002)
46. Wolfe, J. P.: Eur. J. Org. Chem., 571 (2007)
47. Tamaru, Y., Kimura, M. Synlett 1997, 749 (1997)
48. Tamaru, Y.: Yoshida, Z.-i. J. Organomet. Chem. **334**, 213 (1987)
49. Muzart, J.: Tetrahedron **61**, 9423 (2005)
50. Semmelhack, M.F., Bodurow, C.J.: Am. Chem. Soc. **106**, 1496 (1984)
51. Semmelhack, M.F., Zhang, N.J.: Org. Chem. **54**, 4483 (1989)
52. Semmelhack, M.F., Kim, C., Zhang, N., Bodurow, C., Sanner, M., Dobler, W., Meler, M.: Pure Appl. Chem. **62**, 2035 (1990)
53. Semmelhack, M.F., Bodurow, C., Baum, M.: Tetrahedron Lett. **25**, 3171 (1984)
54. Semmelhack, M.F., Zask, A.J.: Am. Chem. Soc. **105**, 2034 (1983)
55. Semmelhack, M.F., Shanmugam, P.: Tetrahedron Lett. **41**, 3567 (2000)
56. Semmeihack, M.F., Epa, W.R., Cheung, A.W.-H., Gu, Y., Kim, C., Zhang, N., Lew, W.J.: Am. Chem. Soc. **116**, 7455 (1994)
57. McCormick, M., Mon ahan III, R., Soria, J., Goldsmith, D., Liotta, D.: J. Org. Chem., **54**, 4485 (1989)
58. Boukouvalas, J., Fortier, G., Radu, I.-I.J.: Org. Chem. **63**, 916 (1998)
59. Tamaru, Y., Kobayashi, T., Kawamura, S.-I., Ochiai, H., Hojo, M., Yoshida, Z.-I.: Tetrahedron Lett., **26**, 3207 (1985)
60. Tamaru, Y., Kobayashi, T., Kawamura, S.-I., Ochiai, H., Yoshida, Z.-I: Tetrahedron Lett., **26**, 4479 (1985)
61. Tamaru, Y., Hojo, M., Yoshida, Z.: i. Tetrahedron Lett. **28**, 325 (1987)
62. Tamaru, Y., Hojo, M., Higashimura, H., Yoshida, Z.: i. J. Am. Chem. Soc. **110**, 3994 (1988)
63. Tamaru, Y., Hojo, M., Yoshida, Z.-I.: J. Org. Chem. **53**, 5731 (1988)
64. Tamaru, Y., Hojo, M., Yoshida, Z.-I.: J. Org. Chem. **56**, 1099 (1991)
65. Tamaru, Y., Tanigawa, H., Itoh, S., Kimura, M., Tanaka, S., Fugami, K., Sekiyama, T., Yoshida, Z.-I.: Tetrahedron Lett., **33**, 631 (1992)
66. Kimura, M., Saeki, N., Uchida, S., Harayama, H., Tanaka, S., Gfugami, K., Tamaru, Y.: Tetrahedron Lett. **34**, 7611 (1993)
67. Harayama, H., Okuno, H., Takahashi, Y., Kimura, M., Fugami, K., Tanaka, S., Tamaru, Y.: Tetrahedron Lett. **37**, 7287 (1996)
68. Harayama, H., Abe, A., Sakado, T., Kimura, M., Fugami, K., Tanaka, S., Tamaru, Y.J.: Org. Chem. **62**, 2113 (1997)
69. Lathbury, D., Vernon, P., Gallagher, T.: Tetrahedron Lett. **27**, 6009 (1986)
70. Kapitan, P.: Gracza. T. Tetrahedron: Asymmetry **19**, 38 (2008)
71. Kapitan, P., Gracza, T.: Arkivoc 2008, **8** (2008)
72. Tsujihara, T., Shinohara, T., Takenaka, K., Takizawa, S., Onitsuka, K., Hatanaka, M., Sasai, H.J.: Org. Chem. **74**, 9274 (2009)
73. Chen, H., Cai, C., Liu, X., Li, X., Jiang, H.: Chem. Commun. **47**, 12224 (2011)
74. Gabriele, B., Salerno, G., Costa, M.: Top. Organomet. Chem. **18**, 239 (2006)
75. Gabriele, B., Salerno, G., Costa, M., Chiusoli, G.P.J.: Organomet. Chem. **687**, 219 (2003)
76. Gabriele, B., Salerno, G., Costa, M.: Synlett 2004, 2468 (2004)
77. Tsuji, J., Morikawa, M., Iwamoto, N.J.: Am. Chem. Soc. **86**, 2095 (1964)
78. Tsuji, J., Nogi, T.J.: Am. Chem. Soc. **88**, 1289 (1966)
79. Tsuji, J., Nogi, T.J.: Org. Chem. **31**, 2641 (1966)
80. Tsuji, J., Takahashi, M., Takahashi, T.: Tetrahedron Lett. **21**, 849 (1980)
81. Zung, T.T., Bruk, L.G., Temkin, O.N.: Mendeleev Commun. **4**, 2 (1994)

82. Bruk, L.G., Gorodskii, S.N., Zeigarnik, A.V., Valdés-Pérez, R.E., Temkin, O.N.J.: Mol. Catal. A: Chem. **130**, 29 (1998)
83. Bruk, L.G., Temkin, O.N.: Inorg. Chim. Acta **280**, 202 (1998)
84. Li, J., Jiang, H., Chen, M.: Synth. Comm. **31**, 199 (2001)
85. Sakurai, Y., Sakaguchi, S., Ishii, Y.: Tetrahedron Lett. **40**, 1701 (1999)
86. Li, J., Li, G., Jiang, H., Chen, M.: Tetrahedron Lett. **42**, 6923 (2001)
87. Izawa, Y., Shimizu, I., Yamamoto, A.: Bull. Chem. Soc. Jpn. **77**, 2033 (2004)
88. Izawa, Y., Shimizu, I., Yamamoto, A.: Chem. Lett. **2005**, 34 (1060)
89. Li, J., Jiang, H., Feng, A., Jia, L.J.: Org. Chem. **64**, 5984 (1999)
90. Okumoto, H., Nishihara, S., Nakagawa, H., Suzuki, A. Synlett 2000, 217 (2000)
91. Marshall, J.A., Yanik, M.M.: Tetrahedron Lett. **41**, 4717 (2000)
92. Ma, S., Wu, B., Zhao, S.: Org. Lett. **5**, 4429 (2003)
93. Kato, K., Nishimura, A., Yamamoto, Y., Akita, H.: Tetrahedron Lett. **42**, 4203 (2001)
94. Kato, K., Tanaka, M., Yamamoto, Y., Akita, H.: Tetrahedron Lett. **43**, 1511 (2002)
95. Kato, K., Matsuba, C., Kusakabe, T., Takayama, H., Yamamura, S., Mochida, T., Akita, H., Peganova, T.A., Vologdin, N.V., Gusev, O.V.: Tetrahedron **62**, 9988 (2006)
96. Kato, K., Yamamoto, Y., Akita, H.: Tetrahedron Lett. **43**, 6587 (2002)
97. Kato, K., Nouchi, H., Ishikura, K., Takaishi, S., Motodate, S., Tanaka, H., Okudaira, K., Mochida, T., Nishigaki, R., Shigenobu, K., Akita, H.: Tetrahedron **62**, 2545 (2006)
98. Kusakabe, T., Kato, K., Takaishi, S., Yamamura, S., Mochida, T., Akita, H., Peganova, T.A., Vologdin, N.V., Gusev, O.V.: Tetrahedron **64**, 319 (2008)
99. Miyakoshi, N., Mukai, C.: Org. Lett. **5**, 2335 (2003)
100. Kato, K., Motodate, S., Mochida, T., Kobayashi, T., Akita, H.: Angew. Chem. Int. Ed. **48**, 3326 (2009)
101. Motodate, S., Kobayashi, T., Fujii, M., Mochida, T., Kusakabe, T., Katoh, S., Akita, H., Kato, K.: Chem. Asian J. **5**, 2221 (2010)
102. Stille, J.K., Wong, P.K.J.: Org. Chem. **40**, 335 (1975)
103. Larock, R.C.J.: Org. Chem. **40**, 3237 (1975)
104. Tamao, K., Kakui, T., Kumada, M.: Tetrahedron Lett. **7**, 619 (1979)
105. Zhao, Y., Jin, L., Li, P., Lei, A.J.: Am. Chem. Soc. **130**, 9429 (2008)
106. Miyaura, N., Suzuki, A.: Chem. Lett., 879 (1981)
107. Yamashina, N., Hyuga, S., Hara, S., Suzuki, A.: Tetrahedron Lett. **30**, 6555 (1989)
108. Ohe, T., Ohe, K., Uemura, S., Sugita, N.J.: Organomet. Chem. **344**, C5 (1988)
109. Cho, C.S., Ohe, T., Uemura, S.J.: Organomet. Chem. **496**, 221 (1995)
110. Yamamoto, Y.: Adv. Synth. Catal. **352**, 478 (2010)
111. Liu, Q., Li, G., He, J., Liu, J., Li, P., Lei, A.: Angew. Chem. Int. Ed. **49**, 3371 (2010)
112. Zhou, Q.J., Worm, K., Dolle, R.E.J.: Org. Chem. **69**, 5147 (2004)
113. Wu, X.-F., Nemuann, H., Beller, M.: Chem. Asian J. **7**, 282 (2012)
114. Kang, S.-K., Ryu, H.-C., Choi, S.-C.: Synth. Commun. **2001**, 31 (1035)
115. Jackson, R.F.W., Turner, D., Block, M.H.J.: Chem. Soc. Perkin Trans. **1**, 865 (1997)
116. Devasagayaraj, A., Knochel, P.: Tetrahedron Lett. **36**, 8411 (1995)
117. Kobayashi, K., Nishimura, Y., Gao, F., Gotoh, K., Nishihara, Y., Takagi, K.J.: Org. Chem. **2011**, 76 (1949)

Chapter 9
The Reaction of C–NO_2 with CO

In previous chapters, the utility of CO mainly regards its application as a carbonyl source. The other interesting property of CO, used as a reductant, will be discussed in this chapter. Here, CO is used both as a carbonyl source and a reductant.

The catalytic carbonylation of nitro compounds is a field of great interest, as a number of important industrial products can be produced (Scheme 9.1), [1–4] such as the synthesis of isocyanates, carbamates, ureas, etc., which normally needed toxic phosgene as the reaction reagent and can be replaced by cheap CO in the case of carbonylation of nitro compounds. After decades' developments, several transition metals are known to be active for this transformation—for example, palladium, rhodium, ruthenium, and even iron, cobalt and selenium—all of which will be discussed in this chapter.

Palladium catalysts have been applied in the carbonylation of nitro compounds since the middle of the twentieth century; among all the reported homogeneous palladium catalysts, the combination of palladium salts with nitrogen ligands is certainly the most effective catalytic system [5–8]. A variety of reaction mechanisms was proposed, and the first isolation and characterization of a metallacyclic complex was performed in 1990 (Scheme 9.2) [9, 10]. By combining $Pd(OAc)_2$, 1,10-phenanthroline (3 equiv.), $PhNO_2$ (40 equiv.) and heating it in ethanol under CO (30 bar) at 80 °C, a yellow complex precipitated, with 80 % yield. PhNCO, $(PhNH)_2CO$, $(PhNHCO)_2NPh$, and CO_2 were produced by heating the complex in 1,2-dichlorobenzene under CO (20 bar) at 170 °C. The addition of 2,4,6-trimethylbenzoic acid can increase the production of PhNCO. Finally, a mixture of the complex, $PhNO_2$, EtOH, under CO atmosphere, together with 2,4,6-trimethylbenzoic acid heated at 135 °C, 100 % of the $PhNO_2$ was converted into $PhNHCO_2Et$ in 91 % selectivity. Based on these studies, a reaction mechanism was given that was modified afterwards for different product synthesis (Scheme 9.3).

In the reduction of nitro compounds, the addition of a nitrogen-donor ligand is necessary, and bidentate ligands are far superior to monodentate ligands. The conversion of nitrobenzene within two h rose from 14.5 to 72 % by changing 2,2′-bipyridine to 1,10-phenanthroline. The anion of palladium catalysts also plays an important role. With the $[Pd(bidentate\ ligand)_2][PF_6]_2$ complexes as a catalyst

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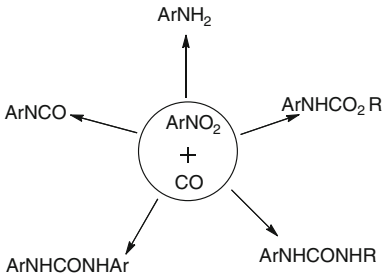
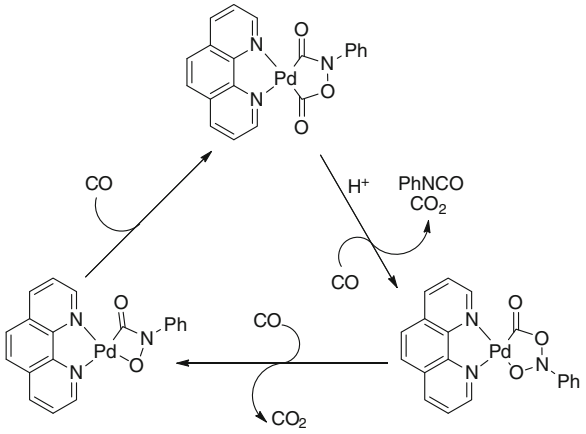
Scheme 9.1 Carbonylation of nitro compounds

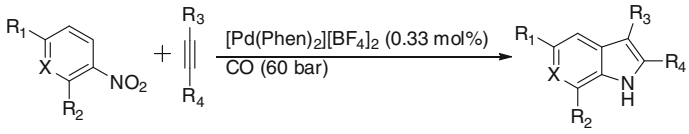


Scheme 9.2 Palladium metallacyclic complex



precursor, no co-catalyst was required. Replacing the PF_6 anions by chloride anions leads to a serious loss of activity. On the other hand, traces of chloride appear to have a positive effect on the catalytic performance. If $Pd(OAc)_2$ was used in combination with a bidentate ligand, the addition of a co-catalyst was needed. The electrophilicity of the complex must be delicately balanced in order to get efficient catalysis. With hard-base, electron-donating ligands as 2,2′-bipyridine or 1,l0-phenanthroline, anions with a relatively strong electron affinity are required. Strong acids, such as *p*-toluenesulfonic acid, can then be used as a co-catalyst, yielding non-coordinating or weakly coordinating anions by replacement of the acetates [11–13]. With this background, van Leeuwen and colleagues carried out a comprehensive study on the ligands' effect on the palladium-catalyzed carbonylation of nitrobenzene [14, 15], and Ragaini's group investigated the effects of fluoride [16].

A series of 4,4′-disubstituted-2,2′-bipyridyl ligands (R = F_3C, C1, H, Me, MeO, and Me_2N) were used to study the influence of the donating capacity of the ligand on the catalytic activity and selectivity. By way of two different types of complexes, $Pd(1ligand)_2(OTf)_2$ and Pd(ligand)Cl(OTf), the influence of the anions in the catalytic system was studied as well. Electron-withdrawing substituents on the bipyridyl ligand turned out to completely deactivate the catalyst, while only



Scheme 9.3 Reaction mechanism for Pd-catalyzed carbonylation of RNO_2

small differences were found between the ligands with electron-donating substituents. Chloride anions showed an inhibiting effect. The presence of water reduced the selectivity toward carbamate. At prolonged reaction times, the urea side product was catalytically converted into the desired carbamate. Under more severe conditions, carbamates, urea side products, and anilines were found with methoxy substituents on their phenyl rings. Based on X-ray structure elucidation, $Pd(bpy)_2(OTf)_2$ crystal was found to be monoclinic and $Pd(Me\text{-}bpy)_2(OTf)_2$ crystal was found to be triclinic. In the case of P/N ligands, the activities decreased in general. The P/N ligands containing the imine function did not yield any conversion of the nitrobenzene. Moderate activity was observed when the nitrogen was incorporated into a heterocycle, and the oxidation of the phosphorus atom by nitrobenzene decreased the activity of phosphine ligands dramatically. The flexibility and bite angle of diphosphine ligands turned out to be crucial; the highest activity was found with DPPP [1,3-bis(diphenylphosphino)propane].

Ragaini and associates found that fluorides can promote the palladium-phenanthroline catalyzed carbonylation of nitroarenes to carbamates. The effect was more evident on the rate of the reaction at short reaction times, but a positive effect on selectivity is also observed under certain conditions. The effect was observed even under conditions in which chloride inhibits the reaction. The reason for these results might be that fluoride can avoid the formation of inactivating byproducts that deactivate the catalyst. Additionally, tetraethylammonium fluoride was found to be better than sodium fluoride.

The effect of silver salts, copper acetate and mercury acetate as an additive was studied in the palladium-catalyzed carbonylation of nitrobenzene [17]. The combination of palladium acetate, sliver fluoride, 1,10-phenanthroline and *p*-toluensulfonic acid were found to be highly active and selective yielding nitrobenzene conversion up to 96 %. Copper acetate and mercury acetate are also effective as additives and gave good results. *N*-phenylcarbamate was produced in the presence of alcohol.

Nitroso compounds as a reaction intermediate for nitro compound reductions were investigated as substrates for mechanism understanding by Cenini and his colleagues [18]. The isolation of a paramagnetic complex suggested that the first step of the interaction between Pd(0) and the nitroso species is an electron transfer reaction. The palladium carbomethoxy complex from the reaction of a palladium(0) complex with PhNO under CO pressure in methanol was also isolated, which fits with the published reaction mechanism [19].

Ragaini and colleagues recently studied the influences of acid additives [20–22]. Using the palladium-phenanthroline catalyst system for the carbonylation of nitrobenzene to methyl phenylcarbamate, the addition of anthranilic acid [20] or phosphorus acids [21, 22] can accelerate the reaction. Anthranilic acid produced higher activity compared with the use of simple benzoic acid. The 4-amino isomer does not show the same increased activity. Later on, they established an improved catalytic system for the carbonylation of nitrobenzene by adding phosphorus acids as an additive, for the first time yielding activities and catalyst life in the range necessary for industrial applications. By palladium-phenanthroline complexes and phosphorus acids as promoters, nitrobenzene was carbonylated to methyl phenylcarbamate with unprecedented reaction rates (TOF up to 6,000/h) and catalyst stability (TON up to 10^5). The best promoter was phosphoric acid, which is very cheap, nontoxic and easily separable from the reaction products. The catalyst system was also applied to the economically very important dinitrotoluenes reduction.

In the case of the reduction of nitroarenes to diarylureas, the reaction normally performed with equimolar amounts of the two reagents, the use of higher concentrations of either aniline or nitrobenzene, or an increase in temperature in the 120–170 °C range, leads to the formation of higher amounts of azo- and azoxybenzene. The latter was found to exclusively contain the aryl moiety deriving from nitrobenzene, with no inclusion of that derived from aniline. The addition of a small amount of diphenylphosphinic acid doubles the conversion and improves the selectivity in diphenylurea, but the effect is attenuated for larger amounts of acid. Small amounts of chloride, to the order of 10–30 mol % with respect to palladium, improve both rate and selectivity, but only inhibiting effects are detected when chloride is added to the reaction mixture for the carbonylation of 2,4-dinitrotoluene to dimethyl 2,4-toluenedicarbamate [23].

Later on they did a comprehensive mechanistic on palladium-phenanthroline complexes catalyzed carbonylation of nitroarene and amine [24, 25]. There was evidence that the key step in both processes was the amine carbonylation. They show that when the reaction is run in methanol, the key intermediate compounds are [Pd(Phen)$(COOMe)_2$]. The kinetics of the reaction of this complex with toluidine in the presence of a carboxylic or phosphorus acid was the first order with respect to complex, acid, and toluidine. A CO atmosphere was also required for the reaction to proceed. Acid dimerization was shown not to be influential under the concentration conditions examined, but the reaction between the acid and toluidine was not negligible and a correction had to be applied. Diphenylphosphinic acid is more effective than any carboxylic acid in promoting this reaction, as also observed under catalytic conditions. Formation of an adduct between complexes and CO was spectroscopically observed when RPhen = 2,9-Me_2Phen. Several analogous complexes were also spectroscopically characterized and the X-ray structure of [Pd(2,9-Me_2Phen)Cl_2(CO)] was solved. This shows an asymmetric coordination of the nitrogen ligand. Kinetic measurements were also conducted under catalytic conditions. An Eyring plot shows that the effect of the acidic promoter is to decrease the ΔS value, whereas no positive effect was observed on ΔH. A temperature-dependent correction for the reaction between the acid and

aniline and phenanthroline present under the reaction conditions has to be applied. A comparison of the results obtained under stoichiometric and catalytic conditions strongly supports the view that the complex was involved even in the latter, and that the acid acts as a bifunctional promoter.

Besides bipyridine and phenanthroline, cheaper pyridine derivatives were also applied in the carbonylation of nitroarenes [26, 27]. The researcher synthesized a series of palladium chloride complexes with pyridines and applied the carbonylation of nitrobenzene and nitrobenzene/aniline and found that a more basic pyridine ligand gave better results.

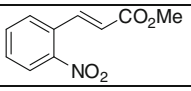
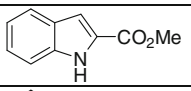
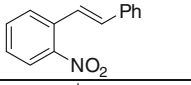
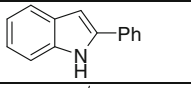
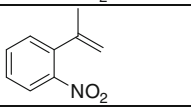
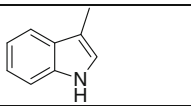
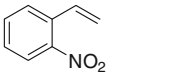
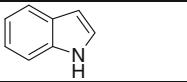
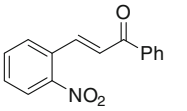
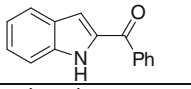
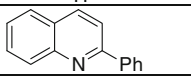
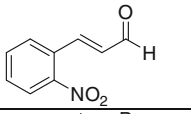
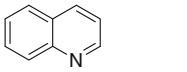
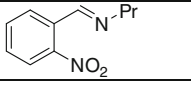
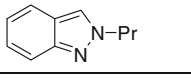
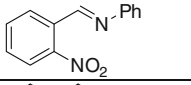
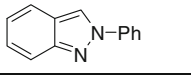
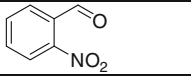
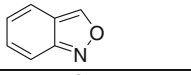
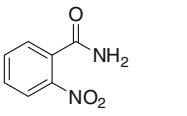
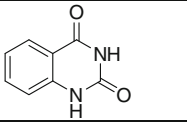
A microreaction system was developed for the carbonylation of nitrobenzene as well [28]. Under lower CO gas pressure [9.5 bar much lower than those in conventional ones (>100 bar)], phenylisocyanate was produced. A gas–liquid slug flow of the reactant mixture was formed in the microchannel for efficient mass transfer across the gas–liquid interfaces. The isocyanate yield of the microflow reaction was shown to be three to six times higher than that of the batch reaction, depending on the inner diameter (i.d.) of the microtube. A higher isocyanate yield was obtained in a narrow-bore tube (0.5 mm i.d.) than in a wide-bore tube (1.0 mm i.d.). The catalyst they applied was $Pd(py)_2Cl_2$ and pyridine system.

More recently, Bouwman carried out a detailed study on the carbonylation of nitrobenzene in methanol with palladium bidentate phosphane complexes as catalysts [29–31]. After a careful analysis of the reaction, mixtures revealed that besides the frequently reported reduction products of nitrobenzene [methyl phenyl carbamate (MPC), *N*,*N*′-diphenylurea (DPU), aniline, azobenzene (Azo) and azoxybenzene (Azoxy)], large quantities of oxidation products of methanol were co-produced (dimethyl carbonate (DMC), dimethyl oxalate (DMO), methyl formate (MF), H_2O, and CO). They proposed the Pd-imido species $P_2Pd^{II} = NPh$, which is the central key intermediate that can link together all the reduction products of nitrobenzene and all the oxidation products of methanol into one unified mechanistic scheme.

Interestingly, a palladium-catalyzed carbonylation of nitrobenzenes was applied in the synthesis of heterocycles as well.

Watanabe's group succeeded in applying carbonylation of 2-nitroarenes in the synthesis of indoles, 2*H*-indazoles, and quinazolines [32–34]. The dichlorobis(tripheny1phosphine)palladium ($PdCl_2(PPh_3)_2$-tin(II) chloride ($SnC1_2$) system was found to have high catalytic activity for the reductive *N*-heterocyclization of various 2-nitrostyrene and *N*-(2-nitrobenzy1idene)amine derivatives when used at 100 °C for 16 h under 19.6 bar of initial carbon monoxide pressure, to give the corresponding indole and 2*H*-indazole derivatives in good yields (Table 9.1). For example, 2-phenylindole was obtained in a 75 % yield from the reductive *N*-heterocyclization of 2-nitrostilbene. Similarly, 2-propyl-2*H*-indazole was readily prepared in 83 % yield by the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)propylamine. A nitrene intermediate for the present reaction was proposed on the basis of deuterium-labeling experiments and the investigation of alkyl rearrangement in the construction of the indole skeleton. Carbon monoxide effectively operates as a deoxygenating agent of the nitro group to afford a nitrene intermediate.

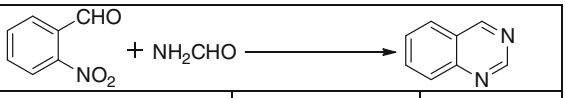
Table 9.1 Pd-catalyzed carbonylative synthesis indoles and 2*H*-indazoles

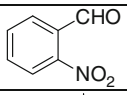
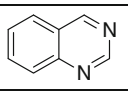
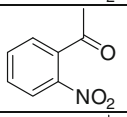
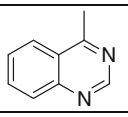
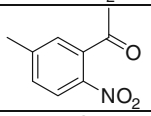
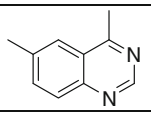
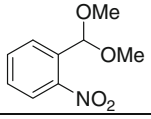
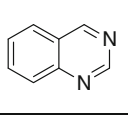
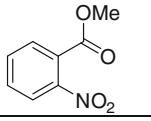
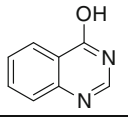
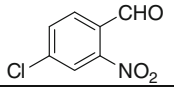
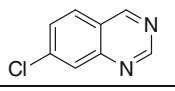
Substrate	Product	Yield[%]
		60
		74
		41
		50
		52
		34
		23
		83
		64
		37
		28

Substrate (2 mmol), $PdCl_2(PPh_3)_2$ (0.1 mmol), $SnCl_2$ (1 mmol), dioxane or THF (10 ml), CO (19.6 bar), 100 °C, 16 h

The combination of palladium complex $PdCl_2(PPh_3)_2$ with $MoCl_5$, showed a high catalytic activity for the intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehyde or 2-nitrophenyl ketones with formamide. The corresponding quinazoline derivatives were produced in moderate yields (Table 9.2). For example, in the reaction of 2-nitrobenzaldehyde with formamide, quinazoline was obtained in a 46 % yield. The reaction goes through 2-nitrobenzaldiformamide as an intermediate.

Table 9.2 Pd-catalyzed carbonylative syntheses of quinazolines



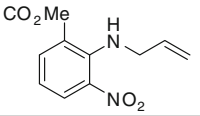
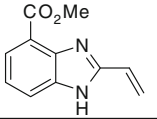
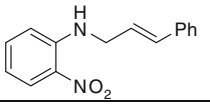
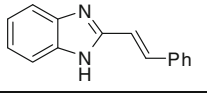
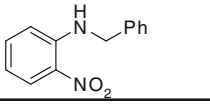
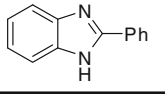
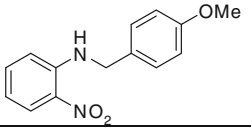
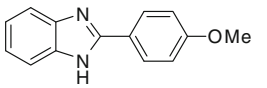
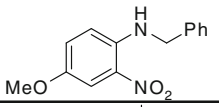
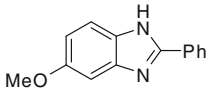
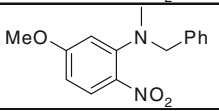
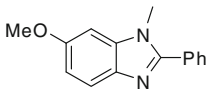
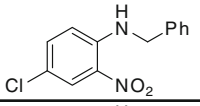
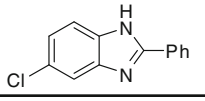
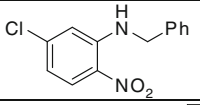
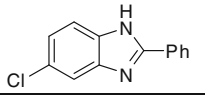
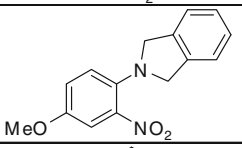
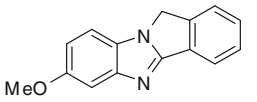
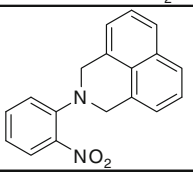
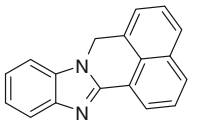
Substrate	Product	Yield[%]
		46
		44
		44
		47
		40
		18

Substrate (2 mmol), formamide (5 ml), $PdCl_2(PPh_3)_2$ (0.1 mmol), $MoCl_5$ (1 mmol), CO (19.6 bar), 100 °C, 16 h

For the carbonylation of 2-nitrostyrenes to indoles, Söderberg and Shriver found an improvement for this transformation and later on applied it in the synthesis of murrayaquinone A [35–37]. By using palladium acetate (6 mol %) together with triphenylphosphine (24 mol %) as the catalytic system, under 4 bar of carbon monoxide in acetonitrile at 70 °C, indoles were produced in moderate to good yields. Davies's group further improved the methodology [38, 39]. With 0.1 mol % palladium (II) trifluoroacetate [$Pd(TFA)_2$] and 0.7 mol % 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 1 bar of CO and 80 °C, indoles were produced in good to excellent yields.

Later on, Söderberg and his team detailed a palladium-catalyzed carbonylative *N*-heteroannulation of *N*-allyl- or *N*-benzyl-2-nitrobenzenamines to 2-substituted benzimidazoles [40]. Under 6 bar of CO in the presence of a palladium catalyst, benzimidazoles were produced in good yields with broad functional group tolerance (Table 9.3).

Table 9.3 Pd-catalyzed carbonylative synthesis of benzimidazoles

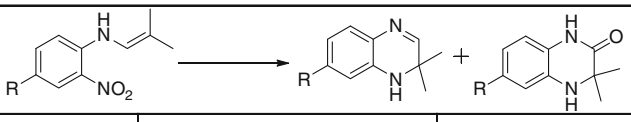
Substrate	Product	Yield[%]
		74
		54
		83
		56
		76
		60
		64
		58
		33
		61

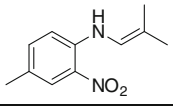
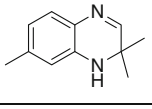
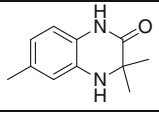
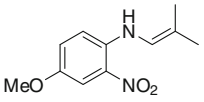
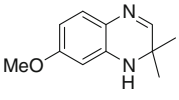
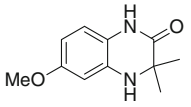
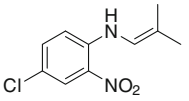
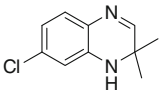
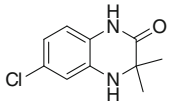
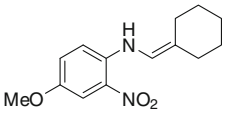
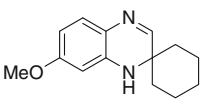
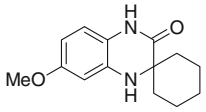
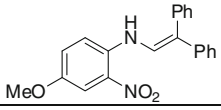
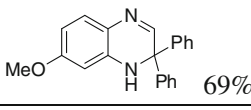
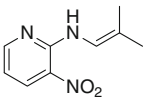
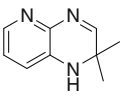
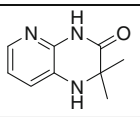
Substrate (0.405 mmol), $Pd(dba)_2$ (0.025 mmol), 1,10-phenanthroline (0.047 mmol), DMF (6 mL), CO (6 bar), 120 °C, 47 h

In 2008, this group reported the synthesis of quinoxalines [41]. The reactions were performed using bis(dibenzylideneacetone)palladium(0), 1,3-bis(diphenylphosphino)propane, and 1,10-phenanthroline in DMF under 6 bar of carbon monoxide at 70 °C. *N*-Heteroannulation of enamines derived from 2-nitrobenzenamines forming mixtures of 1,2-dihydroquinoxalines and 3,4-dihydroquinoxalin-2-ones in moderate to good yields (Table 9.4). Some mechanistic insights lent support for nitrosoarene/nitrene intermediates.

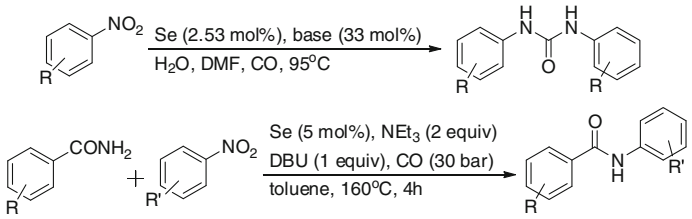
Instead of the carbonylation of 2-nitrostyrenes, Ragaini and colleagues found that indoles can be prepared from the reaction of nitroarenes with alkynes [42]. By palladium-phenanthroline complexes, 3-arylindoles were efficiently produced from nitroarenes, arylalkynes and CO by an *ortho*-C–H functionalization of the nitroarene ring (Scheme 9.4). Both electron-withdrawing and electron-donating substituents are tolerated on the nitroarene, except for bromide and activated chloride. Nitroarenes bearing electron-withdrawing substituents react faster, but

Table 9.4 Pd-catalyzed carbonylative synthesis of quinoxalines



Substrate	Product	Product
	 50%	 45%
	 88%	 1%
	 56%	 16%
	 70%	 13%
	 69%	/
	 34%	 6%

Substrate (0.49 mmol), $Pd(dba)_2$ (0.031 mmol), 1,10-phenanthroline (0.067 mmol), DPPP (0.05 mmol), DMF (5 mL), CO (6 bar), 70 °C, 2 h



Scheme 9.4 Pd-catalyzed synthesis of indoles from alkynes and nitroarenes

the selectivity of the reaction depends on both polar and radical stabilization effects. Among those tested, only arylalkynes afforded indoles under the investigated conditions. The reaction mechanism was partly investigated. The kinetics is the first order in nitroarene concentration and the rate-determining step of the cycle is the initial nitroarene reduction. No primary isotope effect is observed on either rate or selectivity, implying that the cyclization step is fast.

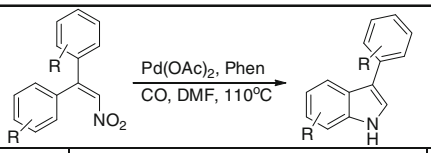
More recently, Dong's group developed a palladium-catalyzed synthesis of indoles from nitroalkenes [43]. This was the first report on transition metal-catalyzed transformation of conjugated nitroalkenes into indoles. Under mild reaction conditions (1 bar carbon monoxide, 110 °C), palladium catalyzes the reductive cyclization of nitroalkenes to form a putative nitrosoalkene intermediate, which then rearranges to provide 3-arylindoles in high yields (Table 9.5). Notably, this novel C–H bond amination takes advantage of carbon monoxide as an inexpensive stoichiometric reductant and produces carbon dioxide as the major byproduct.

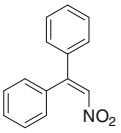
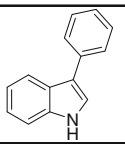
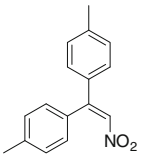
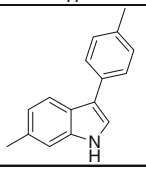
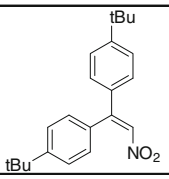
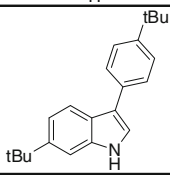
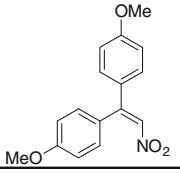
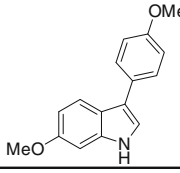
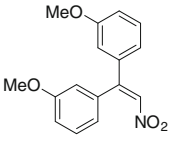
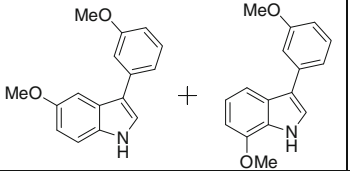
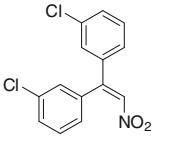
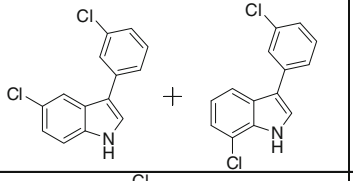
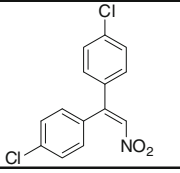
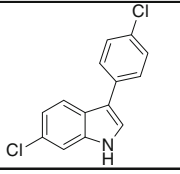
Ruthenium catalysts was explored and applied in the reduction of nitro compounds as well. But because of its high price, their large scale applications are limited. Cenini and colleagues reported a $Ru_3(CO)_{12}$ and $Ru(CO)_3(PPh_3)_2$ catalyzed carbonylation of nitroarenes [44, 45]. The corresponding carbamates are produced in high selectivity in the presence of NEt_4Cl under 82 bar of CO.

Ragaini and colleagues investigated the mechanism of the $Ru_3(CO)_{12}$/tetraalkylammonium halide catalyzed carbonylation of nitroarenes to carbamates [46, 47]. They prove that the carbonylation reaction of nitroarenes catalyzed by $Ru_3(CO)_{12}$ proceeds through the intermediate formation of aniline. Moreover, the active species is mononuclear and not a cluster [48, 49]. The effect of chloride is to accelerate the formation of $Ru(CO)_5$. This last complex forms an adduct with chloride that reacts with nitroarenes at a much higher rate than $Ru(CO)_5$ itself, but this acceleration is not kinetically relevant during most of the reaction, since the initial nitroarene activation is not rate determining. Only toward the end of the reaction is a change in rds observed and the formation of the chloride adduct may become important. [PPN][$Ru_3(CO)_{11}$(Cl)] also reacts with nitroarenes much more easily than $Ru_3(CO)_{12}$ [50].

The effect of the chloride countercation on the mechanism of the $Ru_3(CO)_{12}$/chloride catalyzed carbonylation of nitroarenes to carbamates was investigated by them afterwards. The reason for the higher activity and selectivity obtained with

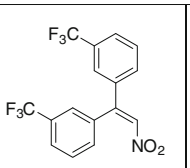
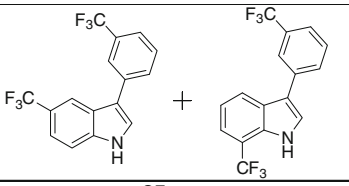
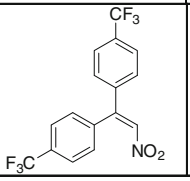
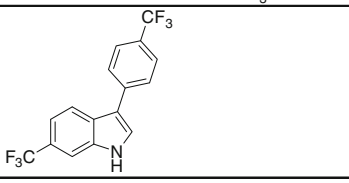
Table 9.5 Pd-catalyzed carbonylative syntheses of quinoxalines



Substrate	Product	Yield[%]
		97
		87
		92
		93
		91
		91
		98

(continued)

Table 9.5 (continued)

		86
		58

$Pd(OAc)_2$ (2 mol %), 1,10-phenanthroline (4 mol %), DMF, CO (1 bar), 110 °C

tetraethylammonium chloride with respect to [PPN][Cl] [$(PPh_3)_2NCl$] is due to the higher hygroscopicity of the former (only when no aniline is added) and to its ability to decompose to yield triethylamine. The role of this last compound is twofold. On the one hand, it accelerates the alcoholysis of the intermediately formed diarylurea. On the other, it favors a reaction pathway that consumes aniline together with nitrobenzene, thus converting a by-product into the desired product.

From a synthetic point of view, ruthenium-catalyzed carbonylation of nitroarenes were also applied in the synthesis of heterocycles. Cenini and colleagues developed a series of methodologies for the synthesis of heterocycles by carbonylation of arenes [51–56]. A metal carbonyl complexes-catalyzed carbonylation of *o*-nitrostyrenes was reported in 1986. $Fe(CO)_5$, $Ru_3(CO)_{12}$, and $Rh_6(CO)_{16}$ were found to be effective for transforming *o*-nitrostyrenes to indoles under CO pressure (Table 9.6). One year later, they did a chemometric optimization of the $Ru_3(CO)_{12}$-catalyzed deoxygenation of 2-nitrostilbene to 2-phenylindole. The effects of temperature, CO pressure, and amounts of catalyst and substrate on conversion and selectivity were examined by factorial design/response surface methods. The conversion was found to increase upon increasing the temperature and decreasing the CO pressure; it assumed a minimum value for medium amounts of catalyst and was almost independent of the amount of substrate. These results were also confirmed using a learning system and were used to develop a mechanism for the reaction. The data suggest two different mechanisms: one based on a $Ru(CO)_5$ catalyzed process and the other based on a $Ru_3(CO)_{12}$ catalyzed process, which are first and zero order with respect to the substrate, respectively. Additionally, a $Ru_3(CO)_{12}$ catalyst was applied in the carbonylation of 2-nitrochalcones to 2-substituted -4-quinolones and *o*-nitrobiphenyl to carbazoles as well.

Watanabe and colleagues reported the carbonylation of nitro compounds to heterocycles by *N*-heterocyclization [57, 58]. Quinazolines were produced from *N*-(2-nitrobenzoyl)amides in the presence of CO (40 bar) and metal carbonyl at

140 °C in excellent yields (Table 9.7). Under similar conditions, with additional 1,10-phenanthroline as ligand, 1-pyrrolines were produced from γ-nitrocarbonyl compounds in excellent yields.

Rhodium catalysts were explored in the carbonylation of nitrobenzene to phenylcarbamate or diphenylurea as well; [59–63] not only homogeneous systems, polymer-supported and silica gel immobilized systems were developed and applied in the carbonylation of nitroarenes. Moreover, rhodium-catalyzed carbonyaltion of nitro compounds were also used in the heterocyclic production. In 2011, Alper's group reported an ionic diamine rhodium complex catalyzed carbonylation of 2-nitrovinylarenes to indoles [64] and later reduction of *N*-(2-nitroarylidene)amines [65]. With this novel ionic diamine rhodium complex $[Rh(CO)_2(Me_2NCH_2CH_2NMe_2)]^+[RhCl_2(CO)_2]^-$, under 6.9 bar of CO at 100 °C, indoles and indazoles were produced in good yields (Table 9.8). Wide functional groups are tolerable, and the catalytic system also allows direct access to indoles with ester and ketone groups at the 2- or 3-position, in good yields.

Moreover, selenium was also applied in the carbonylation of nitro compounds, even its toxic. Yu, Lu and colleagues found that selenium can catalyze the carbonylation of nitroarenes to symmetrical 1,3-diarylureas under atmospheric pressure of carbon monoxide [66]. In the presence of KOH or NaOAc as base, various

Table 9.6 Ru-catalyzed carbonylative syntheses of heterocycles

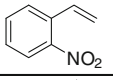
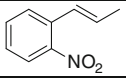
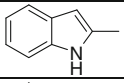
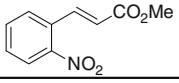
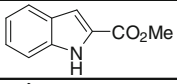
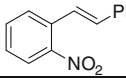
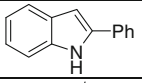
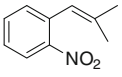
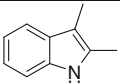
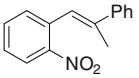
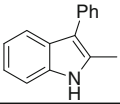
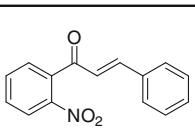
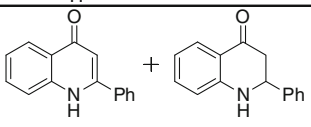
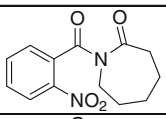
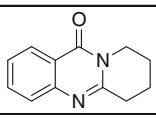
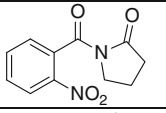
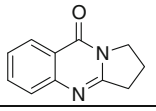
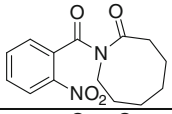
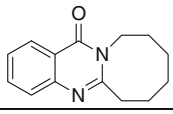
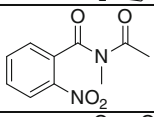
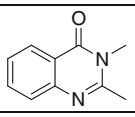
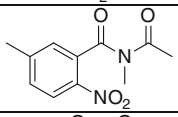
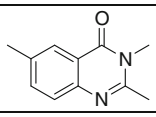
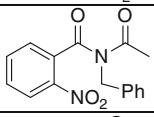
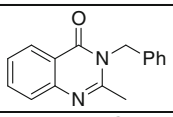
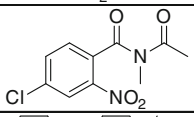
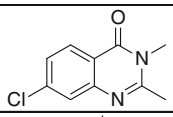
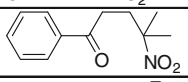
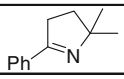
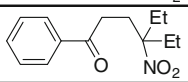
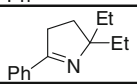
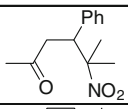
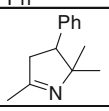
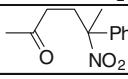
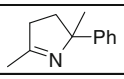
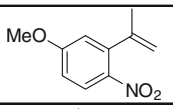
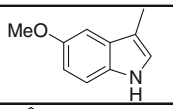
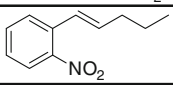
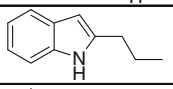
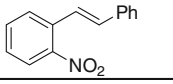
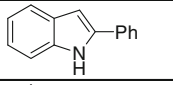
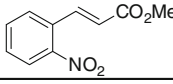
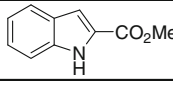
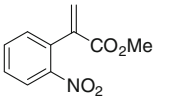
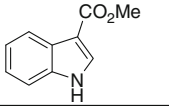
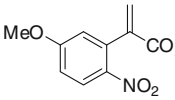
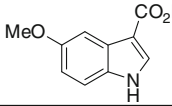
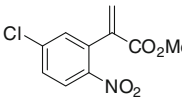
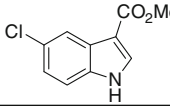
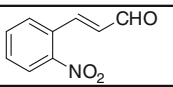
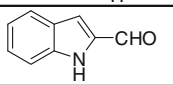
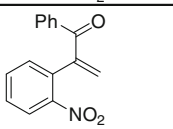
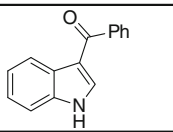
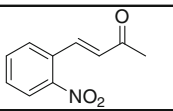
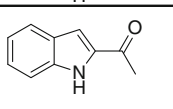
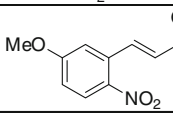
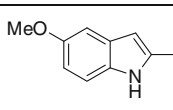
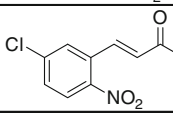
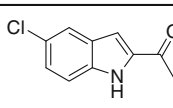
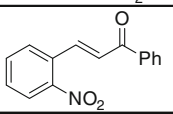
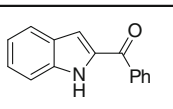
Substrate	Product	Yield[%]
		18
		68.6
		32.6
		71.5
		56.2
		57.7
	 57.3% 42.7%	/

Table 9.7 Ru-catalyzed carbonylative syntheses of quinazolines and pyrroline

Substrate	Product	Yield[%]
		88
		68
		94
		93
		92
		88
		77
		91
		81
		86
		78

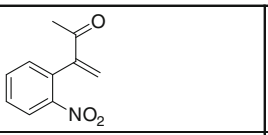
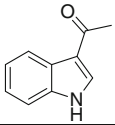
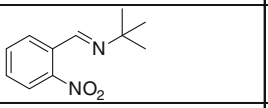
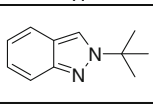
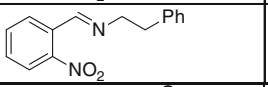
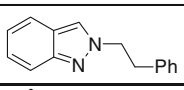
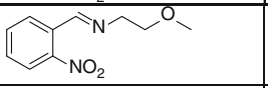
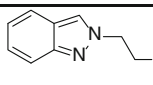
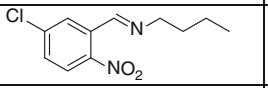
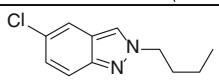
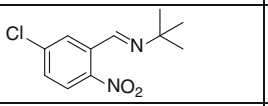
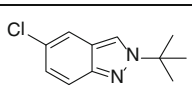
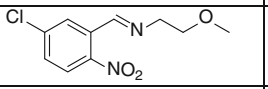
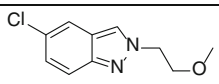
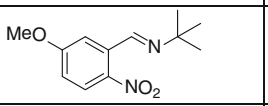
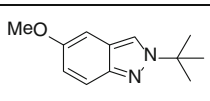
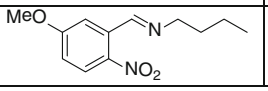
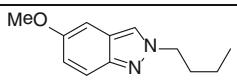
ureas were produced in good yields in DMF at 95 °C. Also in 2001, they reported a selenium-catalyzed reaction of nitroarenes and amides in the presence CO to *N*-arylamides [67]. Under the assistant of mixed organic bases NEt_3 and DBU, *N*-arylamides were produced in moderate to good yields by a selenium catalyst (Scheme 9.5).

Table 9.8 Rh-catalyzed carbonylative syntheses of heterocycles

Substrate	Product	Yield[%]
		75
		77
		100
		83
		96
		79
		83
		52
		85
		80
		82
		77
		92

(continued)

Table 9.8 (continued)

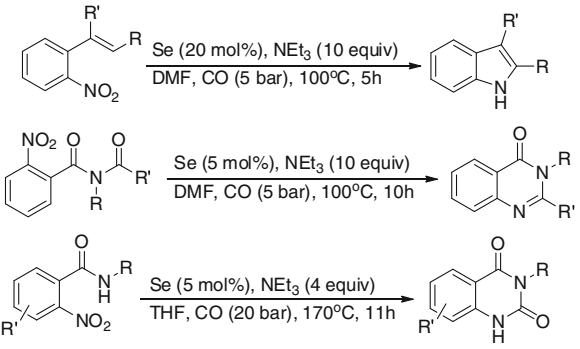
		94
		75
		85
		65
		65
		58
		56
		50
		57

As to the interests and importance of heterocycles, selenium catalysts were also applied in the carbonylation of nitro compounds for heterocycle production [68–70]. Indoles, quinazolinones, and quinazolindiones were produced from the corresponding nitro compounds in good yields (Scheme 9.6). In the presence of catalytic amounts of a selenium catalyst, under pressure of carbon monoxide, nitro compounds were reduced and heterocyclized.

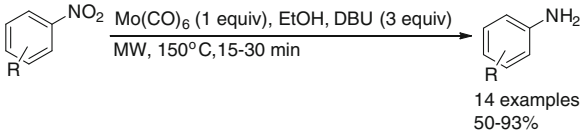
Besides the mentioned catalysts, the other transition metals were also applied in carbonylation of nitro compounds by various groups [71–79]. Such as nickel, osmium, iron, cobalt, and molybdenum. All the expected products were produced by the carbonylation of nitro compounds. Interestingly, anilines were produced from nitroarenes in the presence of $Mo(CO)_6$ and DBU under microwave irradiation in moderate to excellent yields (Scheme 9.7).

In this chapter, the carbonylation of nitro compounds has been discussed. Under the assistant of transition metal catalysts, using CO as a reductant and carbonyl

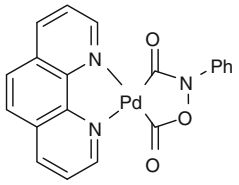
Scheme 9.5 Selenium-catalyzed amides synthesis



Scheme 9.6 Selenium-catalyzed heterocycles syntheses



Scheme 9.7 Mo(CO)6-mediated carbonylation of nitroarene to anilines



source, ureas, isocyanats, heterocycles, etc., were successfully synthesized. The reaction mechanism for this reaction has also been studied and evaluated. Until now, all types of carbonylation reactions of C–X have been addressed.

In the following chapter, the synthetic applications of carbonylation reactions in total synthesis will be summarized.

References

1. Ragaini, F.: Dalton Trans. 6251 (2009)
2. Paul, F.: Coord. Chem. Rev. **203**, 269 (2000)
3. Tafesh, A.M., Weiguny, J.: Chem. Rev. **96**, 2035 (1996)
4. Ragaini, F., Cenini, S.J.: Mol. Catal. A: Chem. **109**, 1 (1996)
5. Drent, E., van Leeuwen, P.: E. V. Patent 0086281 A1 (1983). Chem. Abs. **100**, 6109x (1984)
6. Alessio, E., Mestroni, G.J.: Mol. Catal. **26**, 337 (1984)
7. Alessio, E., Mestroni, G.J.: Organomet. Chem. **291**, 117 (1985)
8. Bontempi, A., Alessio, E., Chanos, G., Mestroni, G.J.: Mol. Catal. **42**, 67 (1987)
9. Leconte, P., Metz, F., Mortreux, A., Osborn, J.A., Paul, F., Petit, F., Pillot, A.J.: Chem. Soc. Chem. Commun. 1616 (1990)

10. Paul, F., Fischer, J., Ochsenbein, P., Osborn, J.A.: Organometallics **17**, 2199 (1998)
11. Cenini, S., Ragaini, F., Pizzotti, M., Porta, F., Mestroni, G., Alessio, E.J.: Mol. Catal. **64**, 179 (1991)
12. Gupte, S., Chaudhari, R.V.J.: Mol. Catal. **24**, 197 (1984)
13. Drent, E.: Pure Appl. Chem. **62**, 661 (1990)
14. Wehman, P., Dol. G.C., Moorman, E.R., Kamer, P.C.J., van Leeuwen, P.W.N.M., Fraanje, J., Goubitz, K.: Organometallics **13**, 4856 (1994)
15. Wehman, P., van Donge, H.M.A., Hagos, A., Kamer, P.C.J., van Leeuwen, P.W.N.M.: J. Organometal. Chem. **535**, 183 (1997)
16. Gasperini, M., Ragaini, F., Cenini, S., Gallo, E., Fantauzzi, S.: Appl. Organometal. Chem. **21**, 782 (2007)
17. Santi, R., Romano, A.M., Panella, F., Santini, C.J.: Mol. Catal. A: Chem. **127**, 95 (1997)
18. Gallo, E., Ragaini, F., Cenini, S., Demartin, F.J.: Organometal. Chem. **586**, 190 (1999)
19. Wehman, P., Borst, L., Kamer, P.C.J., van Leeuwen, P.W.N.M.: J. Mol. Catal. A **112**, 23 (1996)
20. Gasperini, M., Ragaini, F., Cenini, S., Gallo, E.J.: Mol. Catal. A: Chem. **240–205**, 107 (2003)
21. Ragaini, F., Cognolato, C., Gasperini, M., Cenini, S.: Angew. Chem. Int. Ed. **42**, 2886 (2003)
22. Ragaini, F., Gasperini, M., Cenini, S.: Adv. Synth. Catal. **346**, 63 (2004)
23. Gasperini, M., Ragaini, F., Remondini, C., Caselli, A., Cenini, S.J.: Organometal. Chem. **690**, 4517 (2005)
24. Ragaini, F., Gasperini, M., Cenini, S., Arnera, L., Caselli, A., Macchi, P., Casati, N.: Chem. Eur. J. **15**, 8064 (2009)
25. Ragaini, F., Larici, H., Rimoldi, M., Caselli, A., Ferretti, F., Macchi, P., Casati, N.: Organomtallics **30**, 2385 (2011)
26. Krogul, A., Skupinska, J., Litwinienko, G.J.: Mol. Catal. A: Chem. **337**, 9 (2011)
27. Skupinska, J., Karpinska, M.: Appl. Catal. A: General **267**, 59 (2004)
28. Takebayashi, Y., Sue, K., Yoda, S., Furuya, T., Mae, K.: Chem. Eng. J. **180**, 250 (2012)
29. Mooibroek, T.J., Schoon, L., Bouwman, E., Drent, E.: Chem. Eur. J. **17**, 13318 (2011)
30. Mooibroek, T.J., Bouwman, E., Drent, E.: Eur. J. Inorg. Chem. 1403 (2012)
31. Mooibroek, T.J., Bouwman, E., Drent, E.: Organometallics **31**, 4142 (2012)
32. Akazome, M., Kondo, T., Watanabe, Y.J.: Chem. Soc. Chem. Commun. 1466 (1991)
33. Akazome, M., Kondo, T., Watanabe, Y.J.: Org. Chem. **59**, 3375 (1994)
34. Akazome, M., Yamamoto, J., Kondo, T., Watanabe, Y.J.: Organometal. Chem. **494**, 229 (1995)
35. Söderberg, B.C., Shriver, J.A.J.: Org. Chem. **62**, 5838 (1997)
36. Scott, T.L., Söderberg, B.C.G.: Tetrahedron **59**, 6323 (2003)
37. Scott, T.L., Yu, X., Gorugantula, S.P., Carrero-Martínez, G., Söderberg, B.C.G.: Tetrahedron **62**, 10835 (2006)
38. Davies, I.W., Smitrovich, J.H., Sidler, R., Qu, C., Gresham, V., Bazaral, C.: Tetrahedron **61**, 6425 (2005)
39. Kuethe, J.T., Davies, I.W.: Tetrahedron **62**, 11381 (2006)
40. Hubbard, J.W., Piegols, A.M., Söderberg, B.C.G.: Tetrahedron **63**, 7077 (2007)
41. Wallace, J.M., Söderberg, B.C.G., Tamariz, J., Akhmedov, N.G., Hurley, M.T.: Tetrahedron **64**, 9675 (2008)
42. Ragaini, F., Rapetti, A., Visentin, E., Monzani, M., Caselli, A., Cenini, S.J.: Org. Chem. **71**, 3748 (2006)
43. Hsieh, T.H.H., Dong, V.M.: Tetrahedron **65**, 3062 (2009)
44. Cenini, S., Pizzotti, M., Crotti, C., Porta, F., La Monica, G.J.: Chem. Soc. Chem. Commun. 1286 (1984)
45. Cenini, S., Crotti, C., Pizzotti, M., Porta, F.J.: Org. Chem. **53**, 1243 (1988)
46. Ragaini, F., Ghitti, A., Cenini, S.: Organometallics **18**, 4925 (1999)
47. Ragaini, F., Cenini, S.J.: Mol. Catal. A. Chem. **161**, 31 (2000)
48. Basu, A., Bhaduri, S., Khwaja, H.J.: Organomtal. Chem. **319**, C28 (1987)

49. Han, S.-H., Song, J.-S., Macklin, P.D., Nguyen, S.T., Geoffroy, G.L.: Organomtallics **8**, 2127 (1989)
50. Bhaduri, S., Khwaja, H., Sapre, N., Sharma, K., Basu, A.J.: Chem. Soc. Dalton Trans. 1313 (1990)
51. Crotti, C., Cenini, S., Rindone, B., Tollari, S., Demartin, F.J.: Chem. Soc. Chem. Commun. 784 (1986)
52. Crotti, C., Cenini, S., Todeschini, R., Tollari, S.J.: Chem. Soc. Faraday Trans. **87**, 2811 (1991)
53. Crotti, C., Cenini, S., Ragaini, F., Porta, F., Tollari, S.J.: Mol. Catal. 283 (1992)
54. Crotti, C., Cenini, S., Bassoli, A., Rindone, B., Demartin, F.J.: Mol. Catal. 175 (1991)
55. Tollari, S., Cenini, S., Ragaini, F., Cassar, L.J.: Chem. Soc. Chem. Commun. 1741 (1994)
56. Pizzotti, M., Cenini, S., Quici, S., Tollari, S.J.: Chem. Soc. Perkin Trans 913 (1994)
57. Akazone, M., Kondo, T., Watanabe, Y.J.: Org. Chem. **58**, 310 (1993)
58. Watanabe, Y., Yamamoto, J., Akazome, M., Kondo, T., Mitsudo, T.-A.: J. Org. Chem. **60**, 8328 (1995)
59. Ragaini, F., Cenini, S., Fumagalli, A., Crotti, C.J.: Organometal. Chem. **428**, 401 (1992)
60. Mizuno, T., Alper, H.J.: Mol. Catal. A: Chem. **121**, 119 (1997)
61. Mukherjee, D.K., Saha, C.R.: J. Catal. **210**, 255 (2002)
62. Shi, F., Zhang, Q., Gu, Y., Deng, Y.: Adv. Synth. Catal. **347**, 225 (2005)
63. Kim, J.H., Kim, D.W., Cheong, M., Kim, H.S., Mukherjee, D.K.: Bull. Korean Chem. Soc. **31**, 1621 (2010)
64. Okuro, K., Gurnham, J., Alper, H.J.: Org. Chem. **76**, 4715 (2011)
65. Okuro, K., Gurnham, J., Alper, H.: Tetrahedron Lett. **53**, 620 (2012)
66. Wang, X., Lu, S., Yu, Z.: Adv. Synth. Catal. **346**, 929 (2004)
67. Chen, J., Ling, G., Yu, Z., Wu, S., Zhao, X., Wu, X., Lu, S.: Adv. Synth. Catal. **346**, 1267 (2004)
68. Nishiyama, Y., Maema, R., Ohno, K., Hirose, M., Sonoda, N.: Tetrahedron Lett. **40**, 5717 (1999)
69. Nishiyama, Y., Hirose, M., Kitagaito, W., Sonoda, N.: Tetrahedron Lett. **43**, 1855 (2002)
70. Wu, X., Yu, Z.: Tetrahedron Lett. **51**, 1500 (2010)
71. Giannoccaro, P., Pannacciulli, E.: Inorg. Chim. Acta **117**, 69 (1986)
72. Ramage, D.L., Geoffroy, G.L., Rheingold, A.L., Haggerty, B.S.: Organomtallics **11**, 1242 (1992)
73. Alper, H., Hashem, K.E.J.: Am. Chem. Soc. **103**, 6514 (1981)
74. Ragaini, F.: Organometallics **15**, 3572 (1996)
75. Alper, H., Damude, L.C.: Organometallics **1**, 579 (1982)
76. Williams, G.D., Whittle, R.R., Geoffroy, G.L., Rheingold, A.L.J.: Am. Chem. Soc. **109**, 3936 (1987)
77. Chen, L.-J., Mei, F.-M., Li, G.-X.: React. Kinet. Catal. Lett. **98**, 99 (2009)
78. Sanz, R., Escribano, J., Pedrosa, M.R., Aguado, R., Arnáiz, F.J.: Adv. Synth. Catal. **349**, 713 (2007)
79. Spence, J., Anjum, N., Patel, H., Rathnaw, R.P., Verma, J.: Synlett 2557 (2007)

Chapter 10
Applications in Total Synthesis

Several types of carbonylative transformation of C–X bonds have been discussed in previous chapters. In this chapter, the applications of carbonylation reactions in total synthesis will be summarized and discussed.

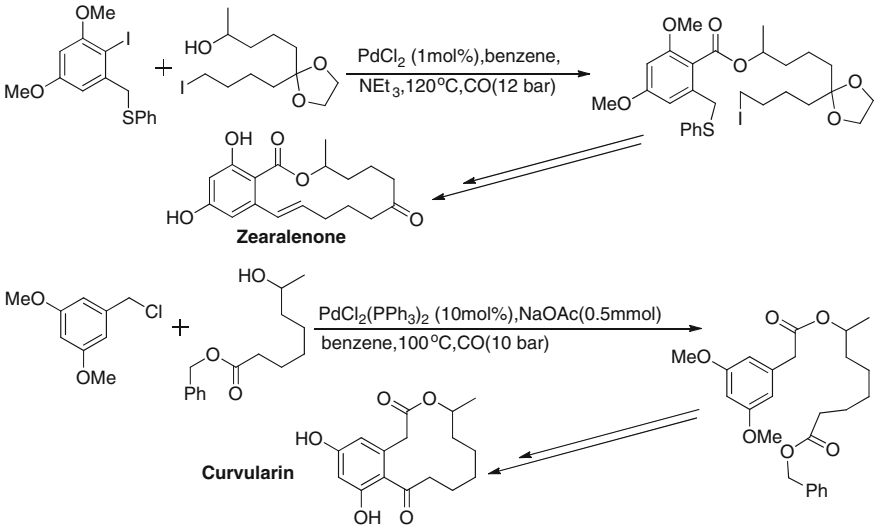
Total synthesis is, in principle, the complete chemical synthesis of complex organic molecules from simpler pieces [1, 2]. Total synthesis provides unique opportunities to discover and invent new strategies and tools for constructing organic molecules, which have experienced an explosion in their development over the last few decades [3–21]. In all synthetic methods used on organic synthesis, transition metal catalysts as a powerful tool have also been applied in the total synthesis of natural products. More specifically, transition metal-catalyzed carbonylation reactions, which are even more interesting and important, have also been applied. As carbon monoxide is inexpensive, and using cheap molecular for building high valuable compounds is interesting from both academic and industrial.

There is an impressive number of publications on the application of transition metal-catalyzed carbonylation reactions in total synthesis. In 1980 Tsuji and colleagues applied palladium-catalyzed alkoxycarbonylation in the synthesis of Zearalenone [22] and Curvularin [23]. Starting from the corresponding aryl iodides or benzyl chlorides and alcohols, the parent molecules for Zearalenone and Curvularin were prepared in good yields and finally transferred to the target products by a few more steps (Scheme 10.1).

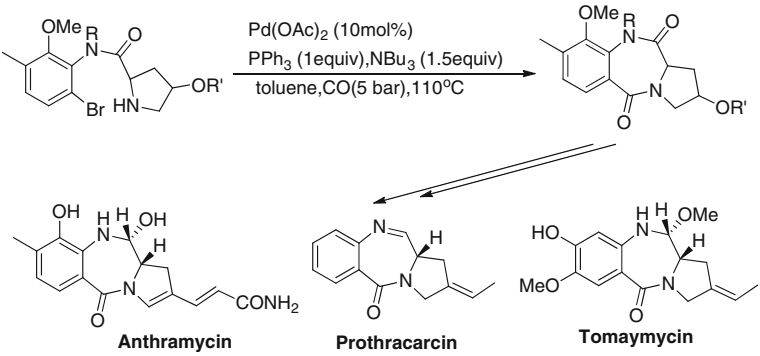
Anthramycin [24], prothracarcin and tomaymycin [25] were synthesized by Ban and colleagues by using aminocarbonylation as the key step. In the presence of a palladium catalyst under low pressure of carbon monoxide, the reaction finished with good yields of desired products (Scheme 10.2).

Stille and colleagues developed a general palladium-catalyzed carbonylative coupling of vinyl triflates with organostannanes and applied in the total synthesis of Capnellene, a naturally occurring hydrocarbon derived from Capnella imbricata as well [26]. Starting from easily available ketone, via vinyl triflate, by two times carbonylative coupling with organostannanes, the core structure for Capnellene synthesis was produced in good yield (Scheme 10.3).

M. Beller and X.-F. Wu, *Transition Metal Catalyzed Carbonylation Reactions*,
DOI: 10.1007/978-3-642-39016-6_10,



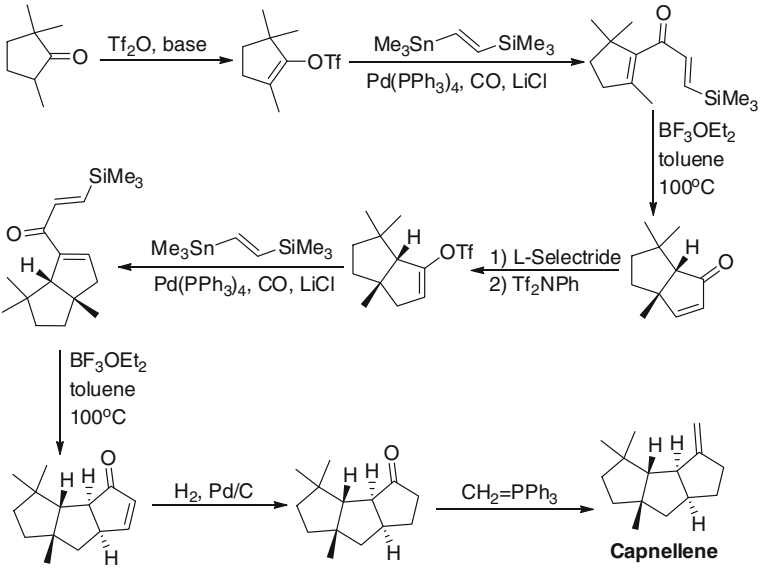
Scheme 10.1 Application in the synthesis of Zearalenone and Curvularin



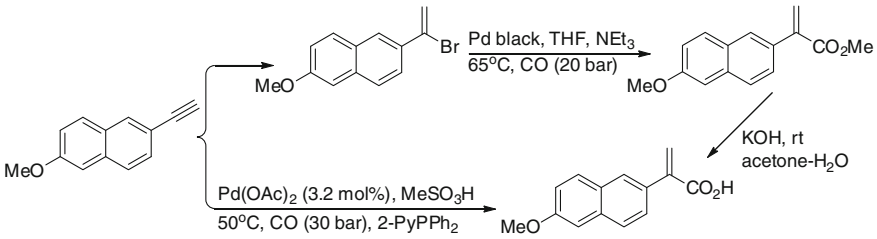
Scheme 10.2 Application in the synthesis of Anthramycin, Prothracarcin and Tomaymycin

As vinyl triflates can be easily prepared from the corresponding ketones or aldehydes, which are abundant and wildly available, the use of vinyl triflates as starting materials in total synthesis has attracted a lot of attention [27–39]. Murai's group synthesized glycinoeclepin A by palladium-catalyzed carbonylation, using vinyl triflate as the key intermediate [40, 41]. Holt and colleagues prepared bioactive steroids [42, 43], while McDonald's team prepared cephalosporins [44].

(*S*)-2-(6-Methoxy-2-naphthyl)propanoic acid is also called naproxen, an anti-inflammatory agent. Several procedures have been developed for its preparation; among them, the reduction of 2-(6-methoxy-2-naphthyl)propenoic acid is certainly one of the most direct routes. For this reason, methodologies have been developed



Scheme 10.3 Application in the synthesis of Capnellene

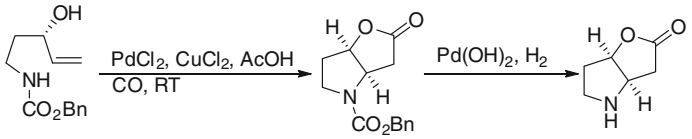


Scheme 10.4 Synthesis of 2-(6-methoxy-2-naphthyl) propenoic acid

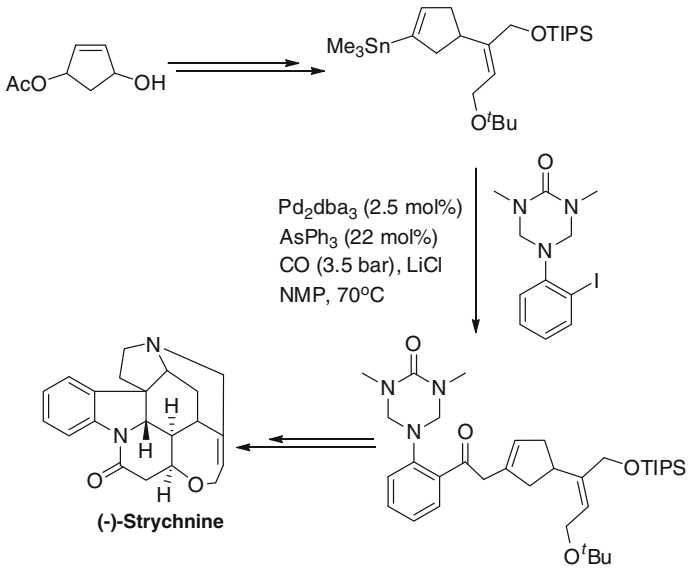
that include carbonylation reactions (Scheme 10.4). They all started from the corresponding alkyne, then transformed into vinyl halides and were followed by hydroxycarbonylation [45] or direct hydrocarbonylation of the alkynes [46].

Geissman-Weiss lactone is an important intermediate in the synthesis of a number of necine bases (pyrrolizidine alkaloids). The palladium-catalyzed carbonylative cyclization of 3-hydroxy-4-pentenylamine to the Geissman–Weiss lactone was reported in 1991 and later in 1996 (Scheme 10.5) [47–49]. This methodology was also applied in the total synthesis of C_{19} lipid diols [50].

(−)-Strychnine was first isolated in 1818 from *Strychnos ignatii* by Pelletier and Caventou. Overman and colleagues did the first asymmetric total synthesis of strychnine [51]. A palladium-catalyzed carbonylative coupling of aryl iodide with an organostannanes reagent was used for the preparation of one of the intermediates (Scheme 10.6). The entire synthesis was accomplished in 20 steps and



Scheme 10.5 Synthesis of Geissman–Weiss lactone



Scheme 10.6 Synthesis of (−)-Strychnine

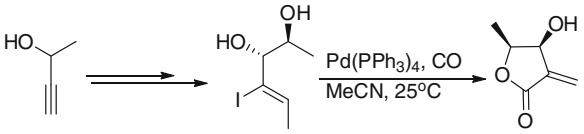
a ∼3 % overall yield from enantiopure hydroxyl cyclopentenyl acetate was successful.

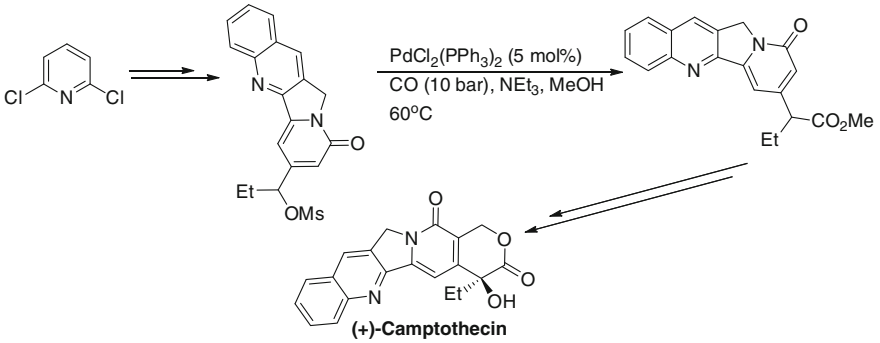
3-Alkylidene-4,5-dihydro-4-hydroxy-5-methyl-2-(3*H*)-furanones are a class of natural products isolated from plants of the *Lauraceae* family, which have interesting biological activities. In 1994 Adam and Klug reported a methodology for their preparation, and palladium-catalyzed carbonylation was applied [52]. Starting from readily available alkynes or propargylic alcohols, furanones were prepared in good yields (Scheme 10.7).

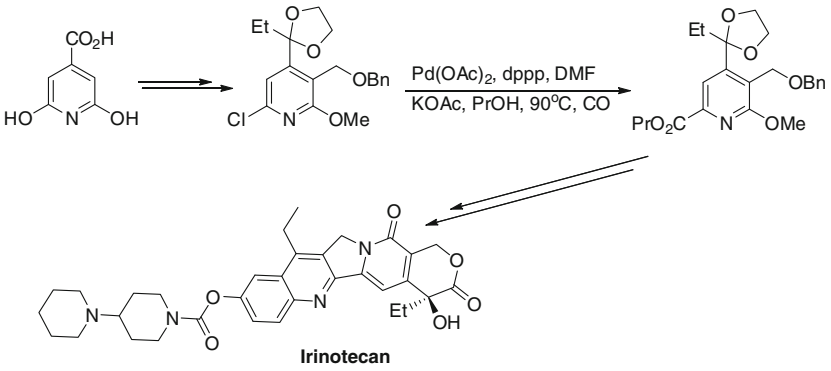
Additionally, carbonylation reactions were applied by various groups for the preparation of phosphatase inhibitors [53–56].

(+)-Camptothecin was isolated from *Chinese tree* by Wall and colleagues in 1966; its potent antitumor property has attracted interest from synthetic chemists. In 1997 Murata, Sakamoto and their team reported a methodology for the functionalization of heteroaromatics, and also applied it in the total synthesis of camptothecin [57]. Palladium-catalyzed carbonylation of benzylic substrates was

Scheme 10.7 Synthesis of furanones





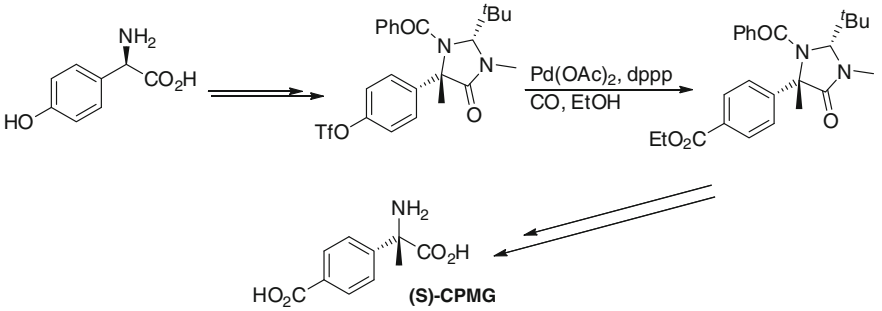


Scheme 10.8 Synthesis of camptothecin and irinotecan

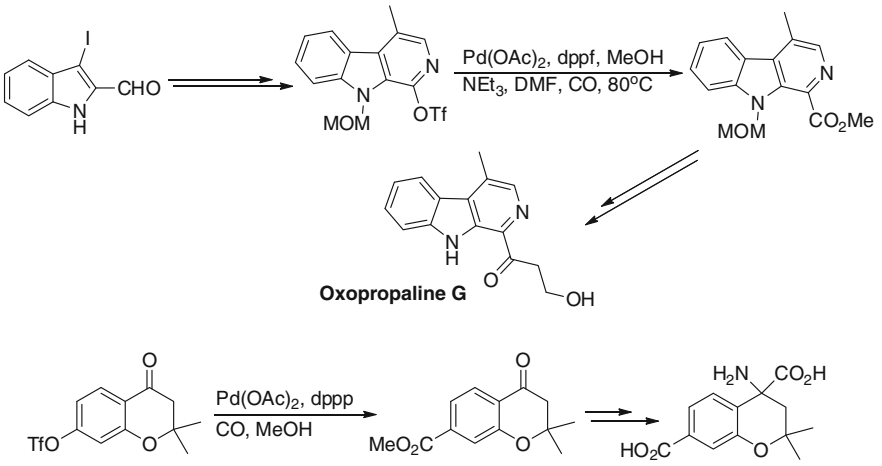
used to extend the carbon chain and introduce an ester group. That same year, Henegar's group reported the use of citrazinic acid as a starting material for the synthesis of camptothecin and irinotecan [58]. This procedure offers another pathway for the preparation of these derivatives (Scheme 10.8).

Ma and Tian reported the synthesis of (S)-(+)-αM4CPG from 4-hydroxyphenylglycine [59–61]. A palladium-catalyzed alkoxycarbonylation of aryl triflates was applied (Scheme 10.9).

Several methodologies based on the carbonylation of aryl triflates were developed and applied in the synthesis of bio-active molecules [62–70]. They all use a palladium-catalyzed carbonylative transformation of aryl triflates as the key step to preparing intermediates; oxopropaline, phenylglycines and phenylalanine were prepared (Scheme 10.10).



Scheme 10.9 Synthesis of (S)-(+)-αM4CPG



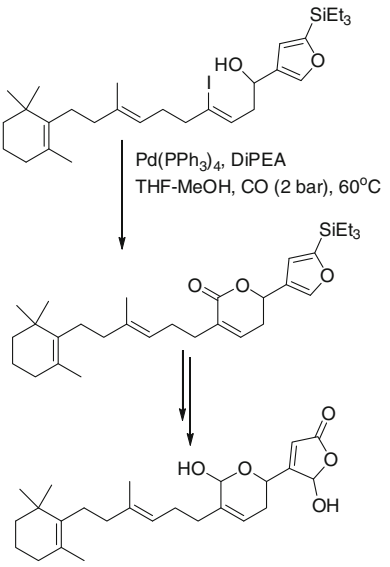
Scheme 10.10 Using aryl triflates as substrates

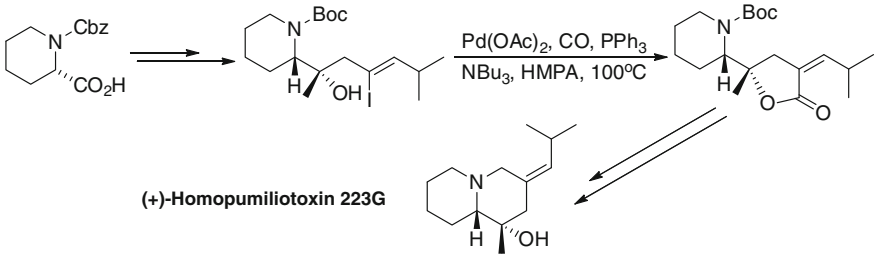
Vinyl halides, as an interesting family of substrates in addition to vinyl triflates, were applied and used in total syntheses as well. In 1997 manoalide as a marine anti-inflammatory sesterterpenoid was synthesized [71, 72]. Palladium-catalyzed alkoxycarbonylation of vinyl iodide was the key step in the synthetic procedure (Scheme 10.11).

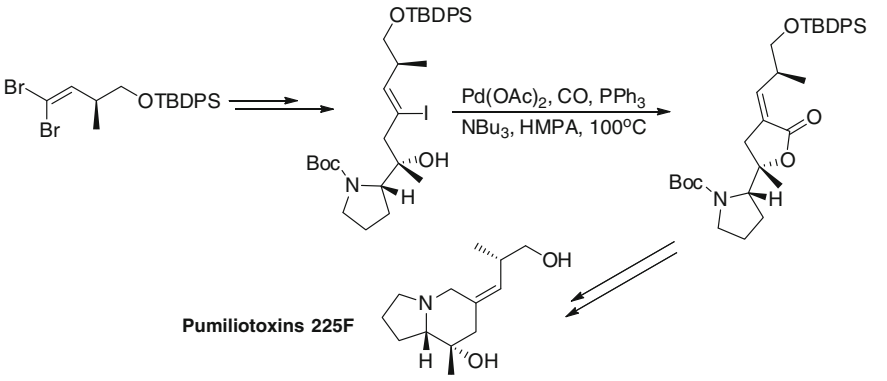
(+)-Homopumiliotoxin and Pumiliotoxin were totally synthesized in the late twentieth century by Kibayashi's goup [73–75]. Intramolecular alkoxycarbonylation for the formation of lactone frames were taken as a fundamental step (Scheme 10.12). Negishi and Liao reported a palladium-catalyzed carbonylative lactonization of (Z)-σ-iodoalkenols and applied that in the total synthesis of (+)-hamabiwalactone B [76].

Additionally, the carbonylation of alkene or alkyne with various nucleophiles offers alternative procedures for organic synthesis [77, 78]. Different kinds of

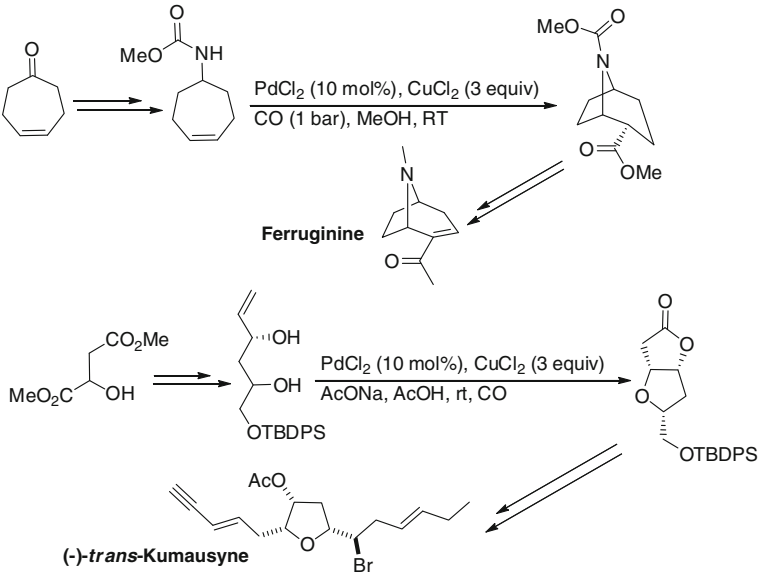
Scheme 10.11 Synthesis of Manoalide







Scheme 10.12 Synthesis of (+)-homopumiliotoxin and pumiliotoxins



Scheme 10.13 Synthesis of ferruginine, kumausyne and anatoxin

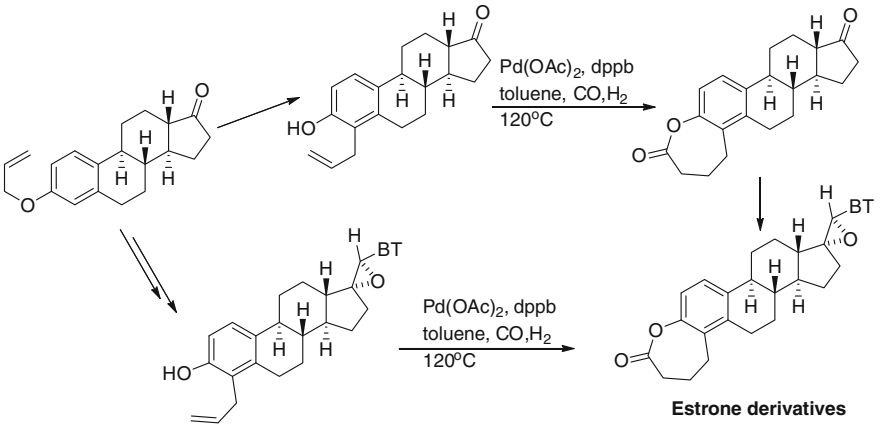
heterocycles can be prepared by these methodologies, and applied in the total synthesis of natural products by different groups [79–83]. Ferruginine, kumausyne and anatoxin were prepared by using carbonylation as the key step (Scheme 10.13).

The $Pd(OAc)_2$/dppb system was applied in the cyclocarbonylation of 4-allylsteroids for the formation of 7-membered lactone rings [84]. Based on this methodology, novel estrone derivatives were prepared in a different manner (Scheme 10.14).

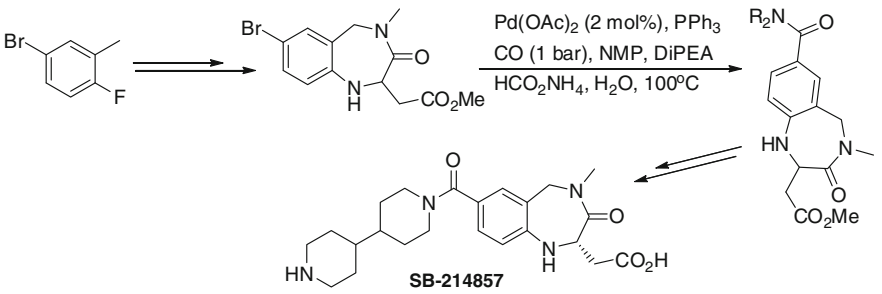
In 1999, Hayes and colleagues reported the synthesis of SB-214857, a potent GP IIb/IIIa antagonist, which had been proposed for clinical trials for the prevention of secondary thrombotic events such as heart attack and stroke [85]. 4-Bromo-1-fluoro-2-methylbenzene was used as a starting material, and palladium-catalyzed aminocarbonylation was applied for the preparation of one of the intermediates (Scheme 10.15). Carey's group did the synthesis from 2-nitrobenzyl alcohol, and palladium-catalyzed aminocarbonylation was applied [86, 87].

(+)-Bicuculline as an effective antagonist of an inhibitory neurotransmitter, γ-aminobutyric acid (GABA), many procedures have been developed for its preparation. Orito and colleagues applied palladium-catalyzed alkoxycarbonylation as the key step in its total synthesis (Scheme 10.16) [88].

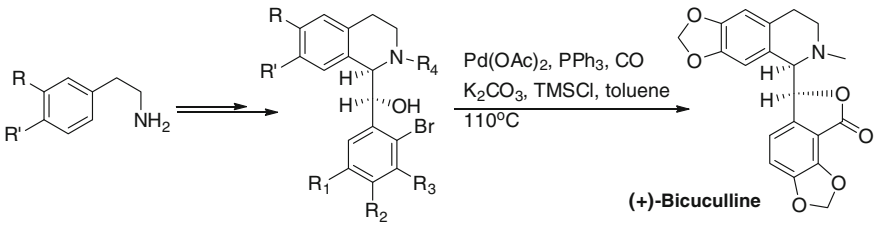
Boger and Boyce synthesized 1,2,9,9a-tetrahydrocyclopropa[c]pyrido[3,2-*e*]indol-4-one-7-carboxylate (CPyI), a parent molecular for antitumor molecular synthesis [89]. Starting from an aminophenol derivative and applied carbonylation as one of the steps, CPyI was prepared and further modified (Scheme 10.17).



Scheme 10.14 Synthesis of estrone derivatives

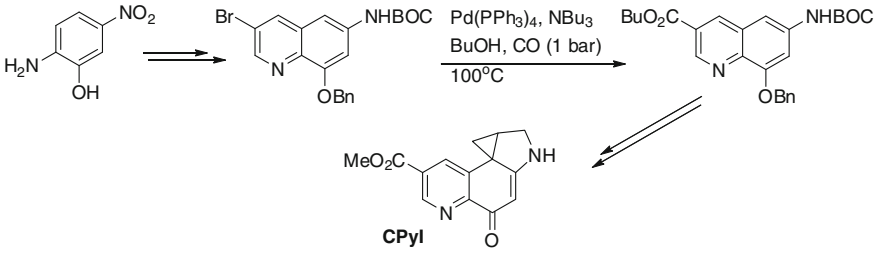


Scheme 10.15 Synthesis of SB-214857



Scheme 10.16 Synthesis of (+)-Bicuculline

Leighton and Bio reported the total synthesis of CP-263,114 in 1999 [90–92]. CP-263,114 is active against protein farnesyl transferase, and is now a medicinal target of great interest. This group totally synthesized Leucascandrolide A as well; a compound was isolated from the sponge *Leucascandra caveolata* shown activity



Scheme 10.17 Synthesis of CPyI

in antifungal, inhibiting the growth of *Candida albicans* [93]. Palladium-catalyzed carbonylation was applied in this total synthesis procedure and gave the key intermediate in moderate yield (Scheme 10.18).

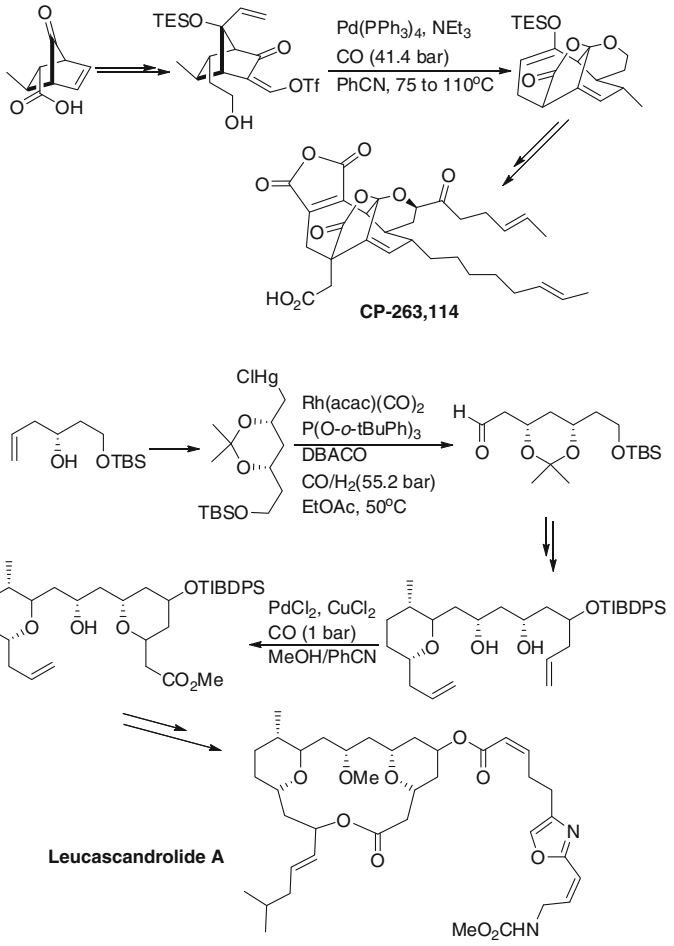
Yuehchukene is a novel class of bisindole alkaloids, first isolated as a racemate from *Murraya paniculata*, with a basic structure of hexahydroindeno[2,1-*b*]indole. It has been suggested that this compound exhibits mixed estrogen and anti-estrogen activities as well as potent anti-implantation. In 2000 Ishikura and his team reported a concise procedure for their preparation; a carbonylation reaction was applied for intermediate synthesis (Scheme 10.19) [94].

Cyclic pentapeptide is a potent inhibitor of $\alpha 4\beta 1$-mediated cell adhesion to CS-1 site and VCAM with IC_{50} ranging from 2 to 9 μM in cell adhesion assays. Under this background, Ho and Broka reported the synthesis of peptidomimetic tricyclic tetrahydrobenzo [*ij*] quinolone in 2000 [95]. Palladium-catalyzed alkoxycarbonylation of aryl triflate was applied and produced the needed intermediate in moderate yield (Scheme 10.20).

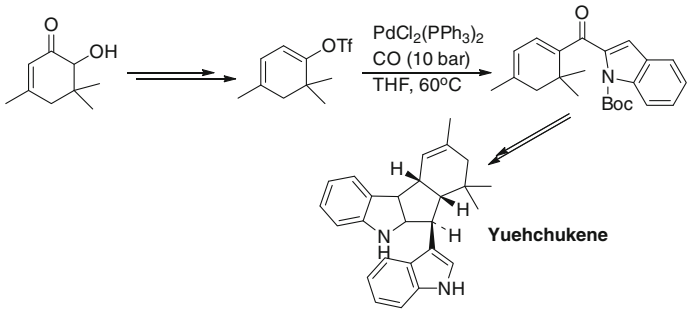
As 1-bromocodeine is readily prepared in multigram quantities, Davies and colleagues reported a procedure for its modification [96]. By palladium-catalyzed carbonylation reactions, codeines and morphines were elaborated. Wentland's team studied the carbonylative functionalization of 3-triflate substituted codeine derivatives and the biological activities of the products [97, 98].

(+)-Nodulisporic acid A, a novel indole terpene, which displays potent oral systemic activity against fleas in dogs, was isolated in 1997. In 2001 Smith III and colleagues reported the total synthesis of this compound [99, 100]. Palladium-catalyzed reductive carbonylation of vinyl triflate was applied, the formed intermediate was isolated in good yield and further transformed into the target product. That same year they also reported the total synthesis of (−)-cylindrocyclophanes A and F [101]. The compounds were isolated in 1990 and were found to be the major cytotoxic components in three different strains of the terrestrial blue-green algae *Cylindrospermun lichenforme*. Palladium-catalyzed reductive carbonylation of aryl iodides was applied in this total synthesis (Scheme 10.21).

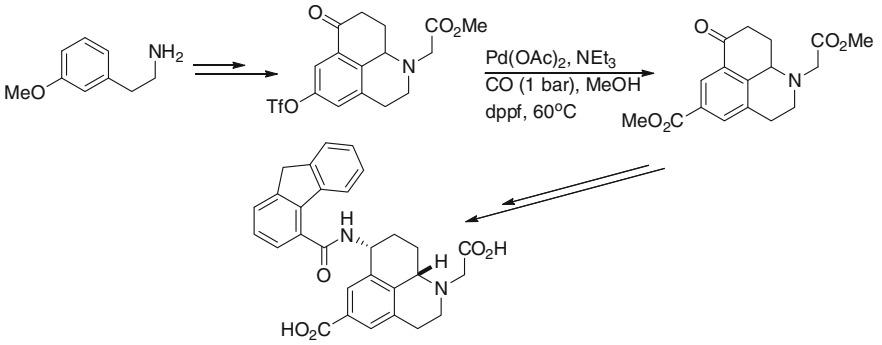
The 5-substituted-2-picolinic acids, such as fusaric acid and (*S*)-(+)-fusarinolic acid, are a class of alkaloid natural products with important biological activities. In particular, fusaric acid was shown to be a potent inhibitor of dopamine *β*-



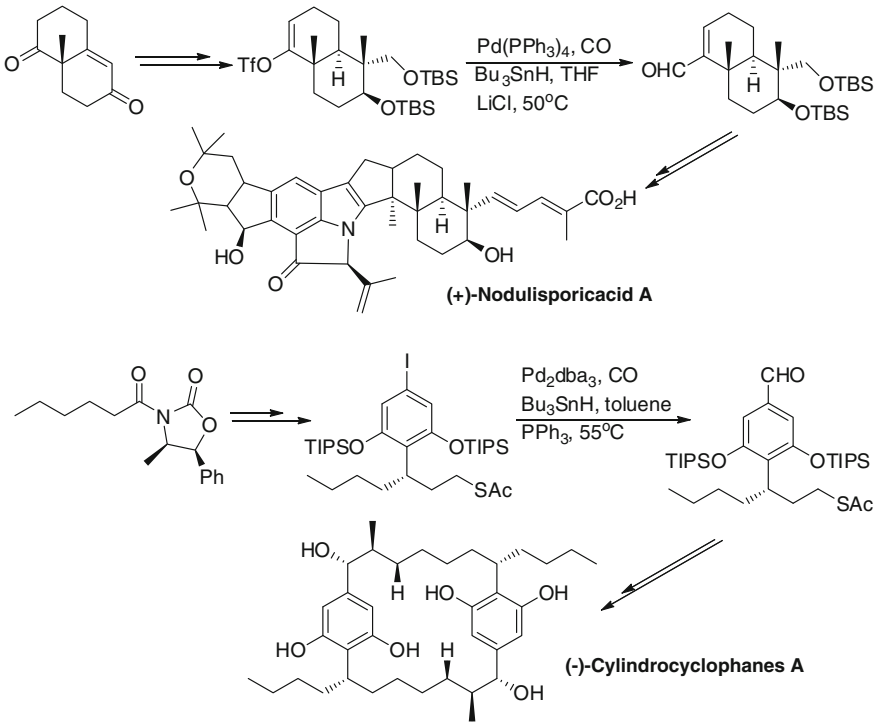
Scheme 10.18 Synthesis of CP-263, 114



Scheme 10.19 Synthesis of yuehchukene

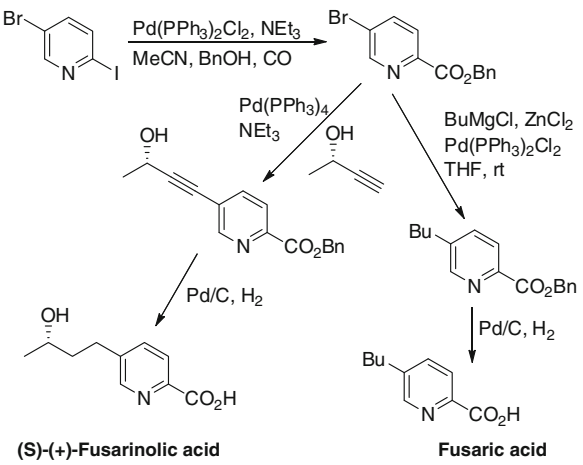


Scheme 10.20 Synthesis of peptidomimetic tricyclic tetrahydrobenzo [*ij*] quinolone



Scheme 10.21 Synthesis of (+)-nodulisporic acid A and (−)-cylindrocyclophanes A

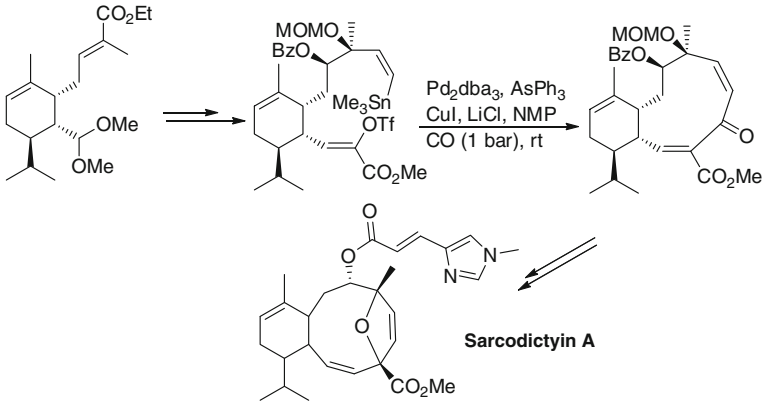
hydroxylase in vitro and in vivo and displayed notable antihypertensive activity. Fusaric acid also exhibited marked antitumor activity on human colon adenocarcinoma cell lines LoVo, SW48, SW480, and SW742, as well as the human mammary adenocarcinoma cell line MDA-MB-468. Other biological activities of



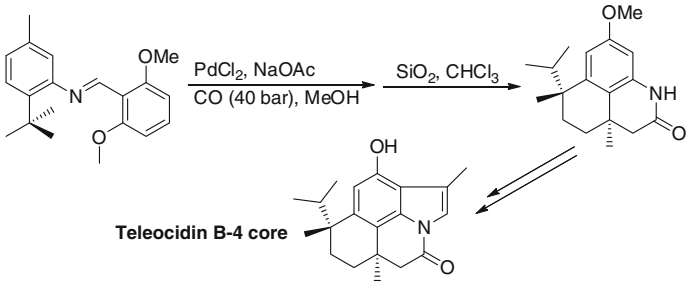
Scheme 10.22 Synthesis of fusaric acid and (*S*)-(+)-Fusarinolic acid

fusaric acid and its derivatives include neurogenic, wilting, and herbicidal activities, which were summarized in a recent review article [102]. In 2001 Song and Yee reported a concise procedure for the synthesis of fusaric acid and (*S*)-(+)-fusarinolic acid (Scheme 10.22) [103]. In this report, they systematically studied the monocarbonylation of 2,5-dibromopyridine under different conditions. And 5-bromo-2-iodopyridine was found to be the best starting material. This methodology was later applied in total to the synthesis of phosphodiesterase IV inhibitor [104].

A total synthesis of sarcodictyins was reported by Cennari and colleagues [105]. A palladium-catalyzed carbonylative Stille coupling of vinyl triflate was designed and used (Scheme 10.23).



Scheme 10.23 Synthesis of Sarcodictyins

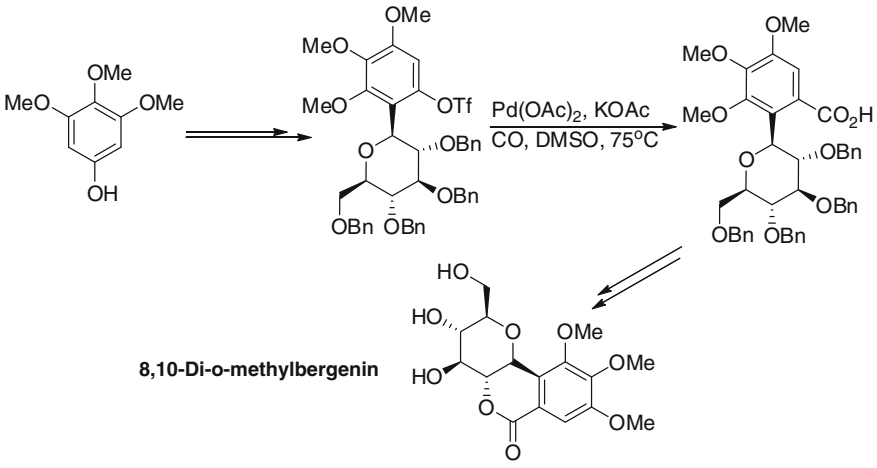


Scheme 10.24 Synthesis of teleocidin B4 core

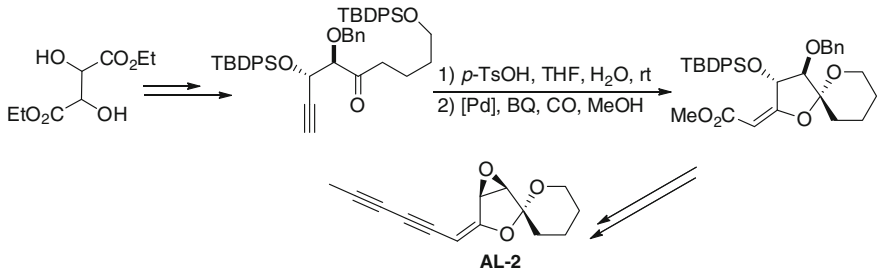
A process for the multigram preparation of 5-(2-methoxy-4-nitrophenyl)oxazole, a key intermediate for the preparation of the hepatitis C drug candidate VX-497 (merimepodib), was developed by Herr and colleagues [106]. Palladium-catalyzed reductive carbonylation of diazonium salt was applied and the formed aldehyde was subsequently used in the preparation of oxazole.

N-[4-[1-Ethyl-2-(2,4-diaminofuro[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid as an antifolate was synthesized by Gangjee and colleagues [107], and palladium-catalyzed alkoxycarbonylation of aryl triflate was applied. A palladium-mediated carbonylative C–H activation was developed by Sames and team and applied in the total synthesis of teleocidin B4 core (Scheme 10.24) [108].

C-Glycoside natural products exhibit medicinally interesting properties and have potential as antifungal and antitumorigenic treatments. Seeberger's group developed a short synthesis of *C*-glucoside 8,10-di-*O*-methylbergenin with a 33 % overall yield in only four steps from common glycosyl donors [109]. A palladium-catalyzed hydroxycarbonylation of aryl triflate was applied (Scheme 10.25).



Scheme 10.25 Synthesis of *C*-glycoside



Scheme 10.26 Synthesis of (−)-AL-2

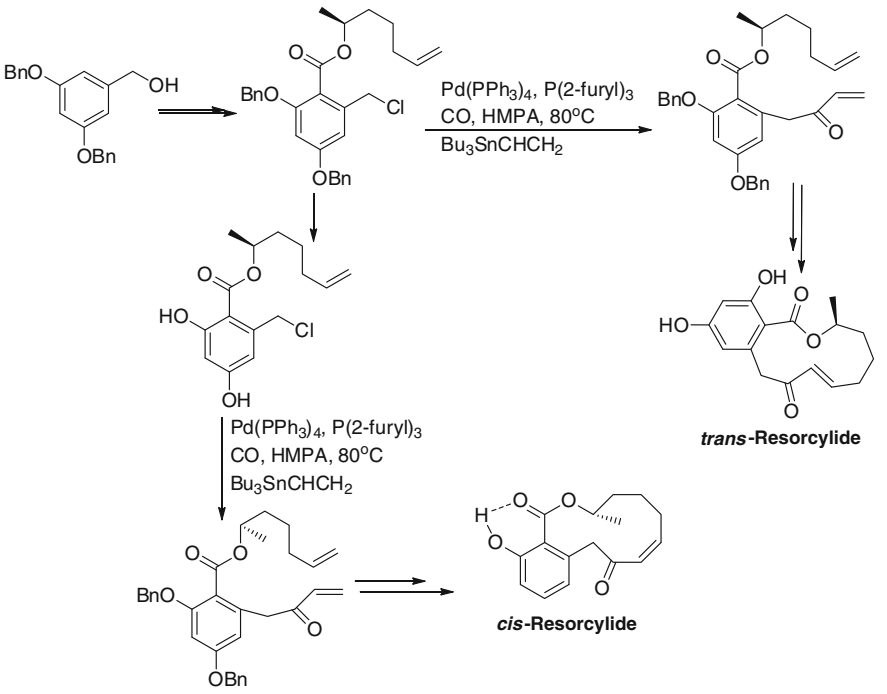
Mukai and Miyakoshi reported the total synthesis of (−)-AL-2, an example of a class of molecules with antitumor activities [110]. With 5 mol% of $Pd_2(dba)_3$ $CHCl_3$ and 20 equiv. of benzoquinone in methanol under a carbon monoxide atmosphere at room temperature, the intermediate was produced in a 41 % yield (Scheme 10.26).

Weinreb and colleagues reported the total synthesis of marine ascidian metabolite perphoramidine via a halogen-selective tandem Heck/carbonylation strategy [111].

In 2004, *trans*- and *cis*-resorcylide were totally synthesized, and palladium-catalyzed carbonylative Stille coupling was applied for the preparation of the intermediate (Scheme 10.27) [112]. *Trans*- and *cis*-resorcylides are both natural macrocyclic plant growth inhibitors, isolated independently from different *Penicillium* species. Together with zearalenone, lasiodiplodin, and the important antitumor agent radicicol, they constitute an important class of bioactive resorcylic macrolides.

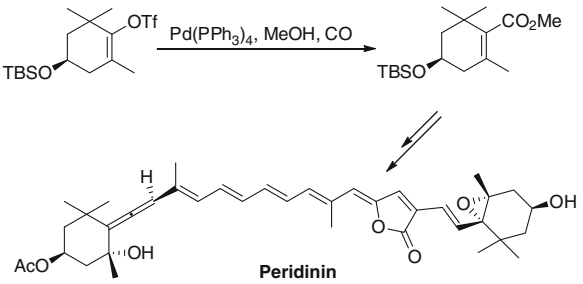
Peridinin, which was isolated from the planktonic algae dinoflagellates causing red tides, is a highly oxidized carotenoid containing an allene and a characteristic (*Z*)-γ-ylidenebutenolide function in the main conjugated polyene chain in addition to functionalized cyclohexane rings at both ends of the molecule. Peridinin was first isolated from the planktonic algae dinoflagellates causing red tides in 1890. In 2004 Katsumura and his colleagues reported the first example of controlling the stereochemistry of polyfunctional allenic carotenoids, and peridinin was totally synthesized [113]. The palladium-catalyzed alkoxycarbonylation of vinyl triflate was applied as the first step to increase the carbon chain (Scheme 10.28).

Coumestrol was first isolated from alfalfa, strawberry, Lucerne, and Ladino clover by Bickoff et al. in the 1950s, and has been reported to inhibit bone resorption and stimulate bone mineralization. In 2005 Larock and colleagues reported the synthesis of coumestrol and coumestans by the iodocyclization of acetoxy-containing 2-(1-alkynyl)anisoles and subsequent direct palladium-catalyzed carbonylation/lactonization [114]. The naturally occurring products were produced in good to excellent yields (Scheme 10.29).



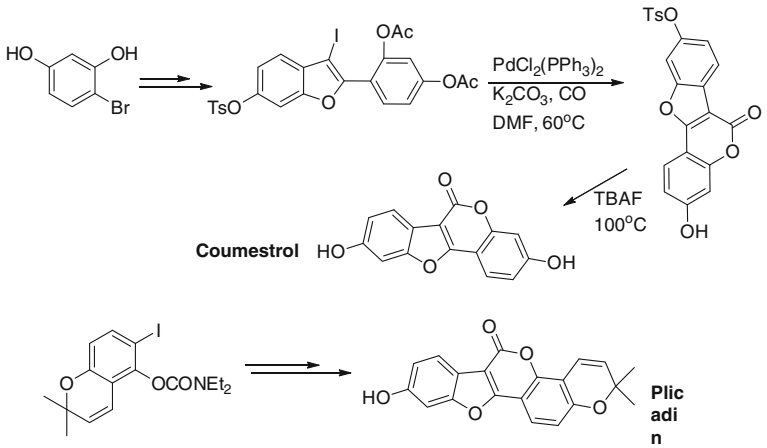
Scheme 10.27 Synthesis of *trans*- and *cis*-resorcylide

Scheme 10.28 Synthesis of peridinin

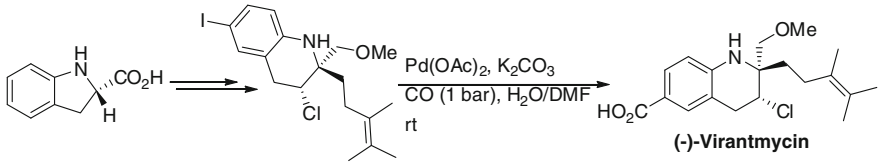


Hallberg's group applied aminocarbonylation in the functionalization of C_2-symmetric HIV-1 protease inhibitors [115]. $Mo(CO)_6$ was used as a CO source and microwave was used as a heating system.

The benzastatin family and virantmycin are a novel class of indoline and tetrahydroquinoline alkaloids isolated from *Streptomyces nitrosporeous*. Benzastatins show inhibitory activity against glutamate toxicity and lipid peroxidation in rat liver microsomes that can be used to prevent brain ischemia injury, and consists of indoline alkaloids such as benzastatin E, and tetrahydroquinoline alkaloids such as benzastatin C that are structurally related to virantmycin. (−)-Virantmycin, a



Scheme 10.29 Synthesis of coumestrol and plicadin



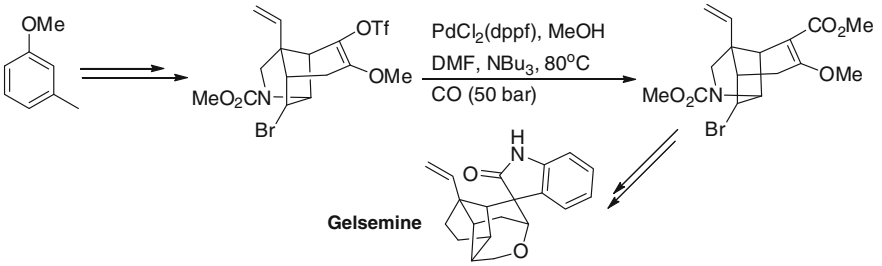
Scheme 10.30 Synthesis of (−)-virantmycin

potent inhibitor of RNA and DNA viruses, is a unique 2,2-disubstituted tetrahydroquinoline alkaloid with contiguous quaternary and tertiary stereocenters. In 2005 Kogen and colleagues reported the stereospecific synthesis of 2,2,3-trisubstituted tetrahydroquinolines and applied in the total syntheses of benzastatin E and natural virantmycin [116]. Palladium-catalyzed hydroxycarbonylation was used at the last stage for carboxylic acid formation (Scheme 10.30).

Overman and colleagues reported the total synthesis of (±)-Gelsemine in 2005 [117]. 1.1 % of the overall yield from 3-methylanisole was succeeded via 26 isolated intermediates. Palladium-catalyzed alkoxycarbonylation of vinyl triflate was applied (Scheme 10.31).

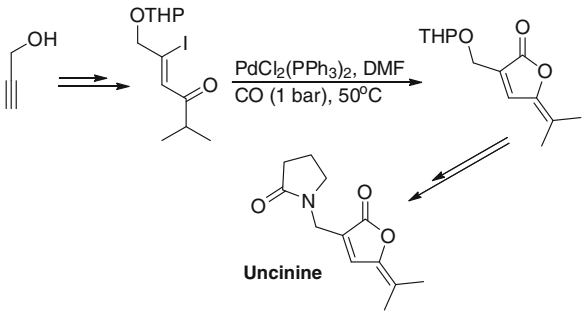
Uncinine is a novel butenolide alkaloid, isolated from *Artabotrys uncinatus*, a plant used as a traditional folk medicine in China for the treatment of nasopharyngeal carcinoma. Pour and colleagues did the total synthesis, and palladium-catalyzed carbonylation of vinyl iodide was applied (Scheme 10.32) [118].

The pyrrolo[2,3-*d*]pyrimidine skeleton is often encountered in important pharmacologically active substances, and more recently it has been observed in a class of marine natural products known as rigidins. These alkaloids have been obtained from tunicates obtained near Okinawa and New Guinea and they have been shown to exhibit very significant calmodulin antagonist activities. Gupton's



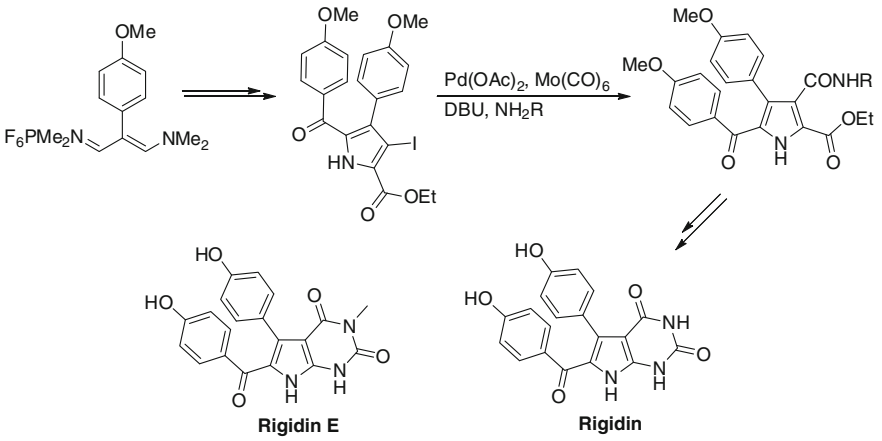
Scheme 10.31 Synthesis of (±)-gelsemine

Scheme 10.32 Synthesis of uncinine

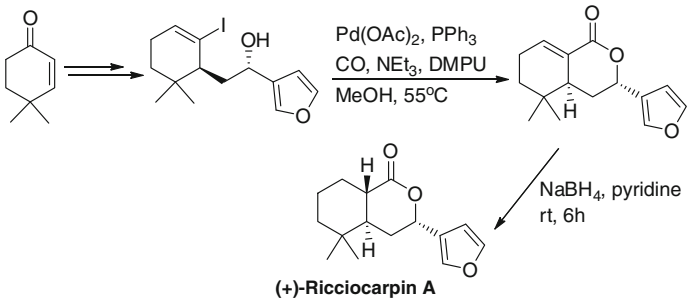


group reported the total synthesis of rigidin and rigidin E [119]. Palladium-catalyzed aminocarbonylation was applied as the key step (Scheme 10.33).

(+)-Ricciocarpin A, a furanosesquiterpene lactone, was first isolated from an axenic culture of the European liverwort *Ricciocarpos natans* in 1990. It bears a δ-



Scheme 10.33 Synthesis of rigidin and rigidin E



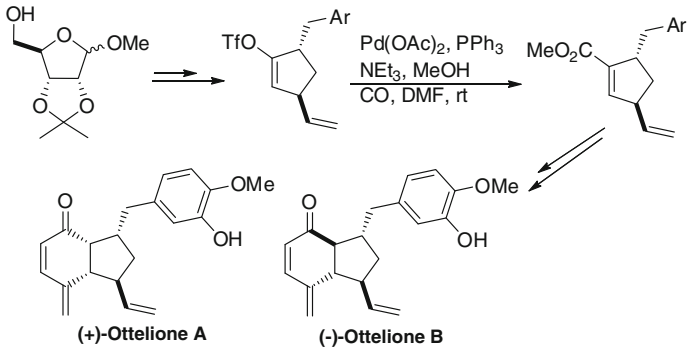
Scheme 10.34 Synthesis of (+)-ricciocarpin A

lactone functionality appended with a 3-furyl group and displays high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis. Liu and Jan used palladium-catalyzed carbonylation of vinyl iodide in the total synthesis of (+)-ricciocarpin A in 2006, with 4,4-domethyl-2-cyclohexenone used as the starting material (Scheme 10.34) [120].

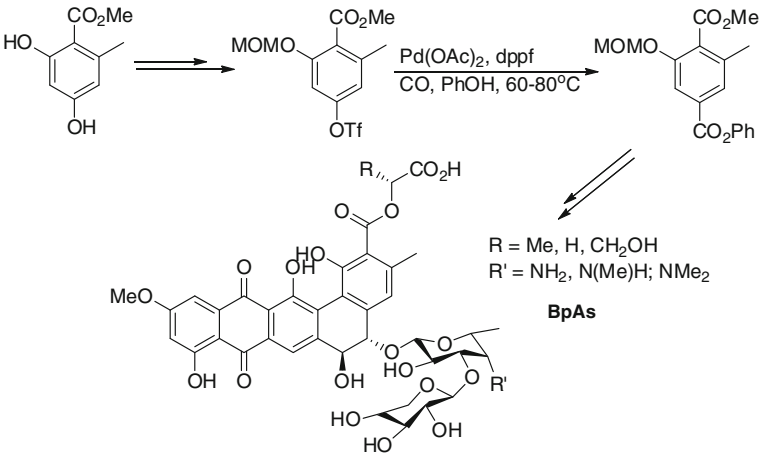
The otteliones are exceedingly powerful anticancer agents, as judged by in vitro tests against a large panel of tumor cell lines. Both compounds were isolated from a freshwater plant, *Ottelia alismoides*, collected in Egypt. Clive and Liu reported the total synthesis of these compounds in 2008 [121]. They started from optical pure cyclopropane formed from a chiral pool, and a carbonylation reaction was applied (Scheme 10.35).

The benanomicin-pradimicin antibiotics (BpAs) were isolated from the culture of the Actinomyces species in 1988, with potent antifungal and anti-HIV activities. Many procedures have been reported for their synthesis. Suzuki and colleagues reported a general route to BpAs [122]. A palladium-catalyzed alkoxycarbonylation of aryl triflates with phenol was used in this procedure (Scheme 10.36).

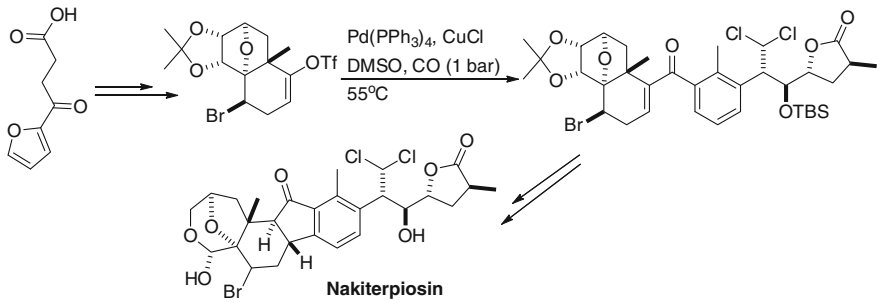
Nakiterpiosin is a marine sponge metabolite that exhibits potent cytotoxicity against the P388 murine leukemia cell line (GI_{50} 10 ng/mL). It was the first C-nor-



Scheme 10.35 Synthesis of otteliones



Scheme 10.36 Synthesis of BpAs

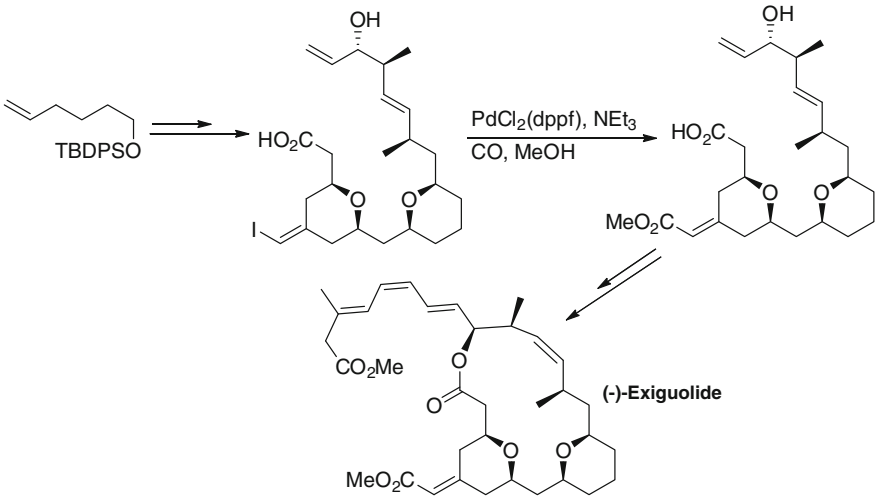


Scheme 10.37 Synthesis of nakiterpiosin

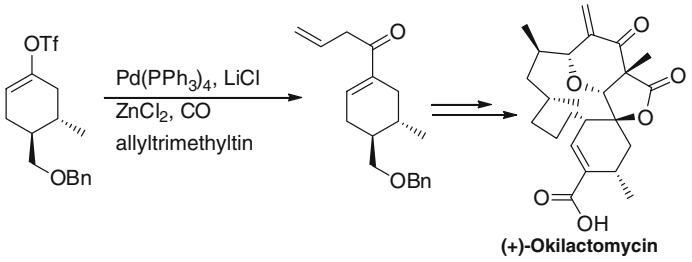
D-homosteroid isolated from a marine source. In 2008 Chen's group reported the total synthesis of this compound by using a palladium-catalyzed carbonylative Stille-coupling of vinyl triflate as the key step (Scheme 10.37) [123, 124].

(−)-Exiguolide was isolated by Ikegami's group in 2006 from the marine sponge *Geodia exigua.* (−)-Exiguolide inhibits the fertilization of sea urchin gametes, which indicates that this compound could inhibit the fusion of viruses with cell membranes. In 2010 Roulland and colleagues reported the total synthesis of (−)-exiguolide with carbonylation as one of the steps (Scheme 10.38) [125, 126].

(+)-Okilactomycin was isolated by Imai and associates in 1987; it is an architecturally complex polyketide antitumor antibiotic derived from a bioactive filtrate produced by the actinomycetes, *Streptomyces griseoflavus*, obtained from a soil sample on the island of Zamami, Okinawa, Japan. (+)-Okilactomycin exhibits significant in vitro cytotoxicity when assayed against a number of human cancer cell lines, including lymphoid leukemia L1210 and leukemia P388



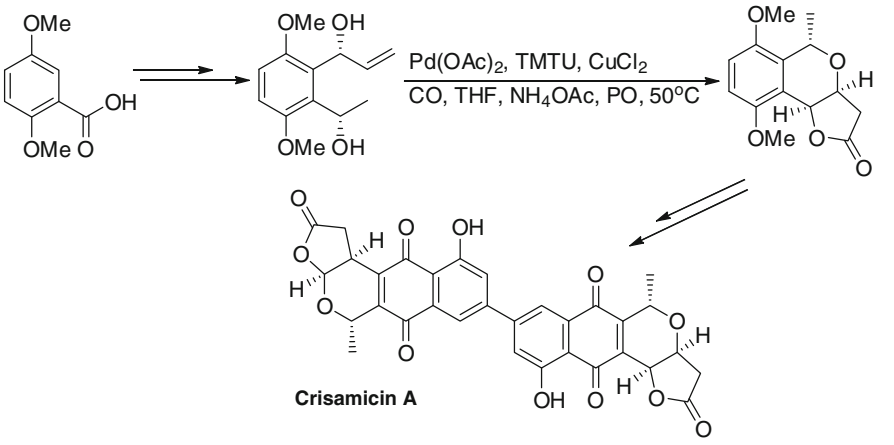
Scheme 10.38 Synthesis of (−)-exiguolide



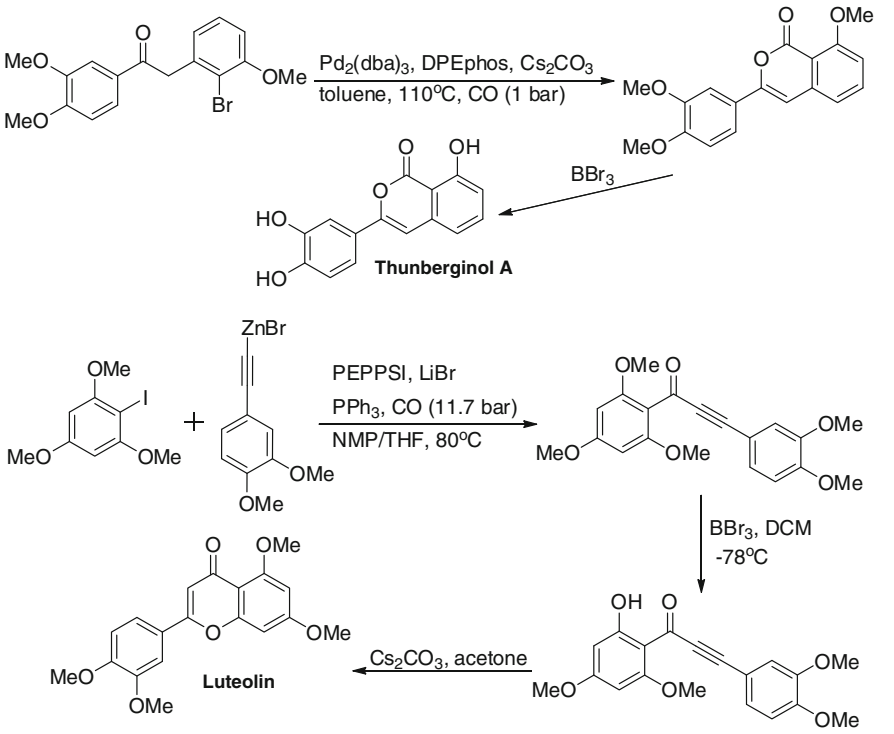
Scheme 10.39 Synthesis of (+)-okilactomycin

($IC_{50} = 0.09$ and 0.037 μg/mL, respectively), as well as in vivo activity against Ehrlich ascites carcinoma. Smith and colleagues reported the total synthesis in 2009 which involve palladium-catalyzed carbonylative Stille coupling as one of the steps (Scheme 10.39) [127].

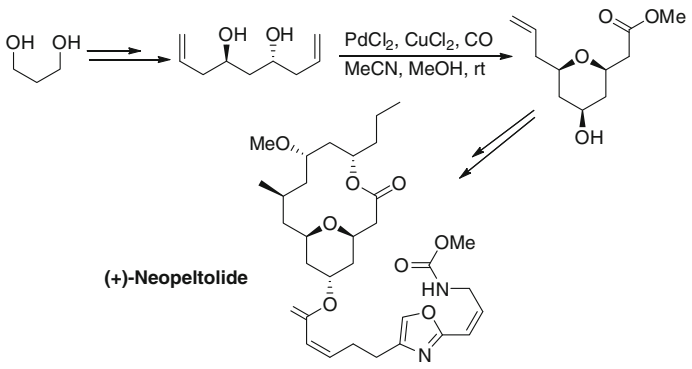
Crisamicin A, a natural product that contains two pyran-fused lactones that are C_2-symmetric to each other, represents a prominent member of the dimeric pyranonaphthoquinone family of antibiotics and was first isolated in 1986 from the micro-organism *Micromonospora purpureochromogenes* that was obtained from a mud sample in the Philippines. Crisamicin A exhibited activity against B16 murine melanoma cells, the herpes simplex, and vesicular stomatitis viruses. Yang, Wang and their colleagues for the first time did the total synthesis and Pd/TMTU-catalyzed alkoxycarbonylative annulation to generate a unique *cis*-pyran-fused lactone (Scheme 10.40) [128].



Scheme 10.40 Synthesis of crisamicin A



Scheme 10.41 Synthesis of luteolin and thunberginol A



Scheme 10.42 Synthesis of neopeltolide

Flavanoids and isocoumarin are common substructures found in many natural products. Palladium-catalyzed carbonylation reactions were applied in the synthesis of luteolin [129] and thunberginol A [130] as well (Scheme 10.41).

Neopeltolide was isolated from a deep-water sponge of the neopeltidae family by Wright and colleagues in 2007. Neopeltolide exhibits significantly potent in vitro cytotoxicity toward several different cancer cell lines, including A-549 human lung adenocarcinoma, NCI-ADR-RES human ovarian sarcoma, and P388 murine leukemia cell lines, with IC50s of 1.2, 5.1, and 0.56 nM, respectively. Neopeltolide also inhibited the growth of the fungal pathogen *Candida albicans* with a minimum inhibitory concentration of 0.62 μg/ml. A concise total synthesis was reported in 2011 [131]. Palladium-catalyzed alkoxycarbonylation as one of the key steps was included in the route (Scheme 10.42).

In this chapter we have summarized and discussed the applications of transition metal catalyzed carbonylation reactions in total synthesis. A number of biologically active molecules have been synthesized by using carbonylation as one of the key steps. These examples of total synthesis greatly increased the values of carbonylation reactions and encouraged the basic methodology development in this area.

In next chapter we will try to give a short discussion from the aspects of reaction mechanism.

References

1. Nicolaou, K.C., Sorensen, E.J.: Classics in total synthesis: targets, strategies methods. Wiley, New York (1996)
2. Nicolaou, K.C., Snyder, S.A.: Classics in total synthesis II: more targets, strategies methods. Wiley, New York (2003)
3. Nicolaou, K.C.: Tetrahedron **59**, 6683 (2003)
4. Seebach, D.: Angew. Chem. Int. Ed. **29**, 1320 (1990)

5. Yamaguchi, J., Yamaguchi, A.D., Itami, K.: Angew. Chem. Int. Ed. **51**, 8960 (2012)
6. Nicolaou, K.C., Vourloumis, D., Winssinger, N., Baran, P.S.: Angew. Chem. Int. Ed. **39**, 44 (2000)
7. Nicolaou, K.C., Edmonds, D.J., Bulger, P.G.: Angew. Chem. Int. Ed. **45**, 7134 (2006)
8. Nicolaou, K.C., Bulger, P.G., Sarlah, D.: Angew. Chem. Int. Ed. **44**, 4442 (2005)
9. Nicolaou, K.C., Snyder, S.A., Montagnon, T., Vassilikogiannakis, G.: Angew. Chem. Int. Ed. **41**, 1668 (2002)
10. Yu, S., Ma, S.: Angew. Chem. Int. Ed. **51**, 3074 (2012)
11. Nicolaou, K.C., Bulger, P.G., Sarlah, D.: Angew. Chem. Int. Ed. **44**, 4490 (2005)
12. Seeman, J.I.: Angew. Chem. Int. Ed. **46**, 1378 (2007)
13. Nicolaou, K.C., Chen, J.S., Edmonds, D.J., Estrada, A.A.: Angew. Chem. Int. Ed. **48**, 660 (2009)
14. Izquierdo, J., Hutson, G.E., Cohen, D.T., Scheidt, K.A.: Angew. Chem. Int. Ed. **51**, 11686 (2012)
15. Schetter, B., Mahrwald, R.: Angew. Chem. Int. Ed. **45**, 7506 (2006)
16. Kaufman, T.S., Rúveda, E.A.: Angew. Chem. Int. Ed. **44**, 854 (2005)
17. Nicolaou, K.C., Ellery, S.P., Chen, J.S.: Angew. Chem. Int. Ed. **48**, 7140 (2009)
18. Scott, A.I.: Angew. Chem. Int. Ed. **32**, 1223 (1993)
19. Graening, T., Schmalz, H.-G.: Angew. Chem. Int. Ed. **43**, 3230 (2004)
20. Hoffmann, R.W.: Angew. Chem. Int. Ed. **52**, 123 (2013)
21. Eggersdorfer, M., Laudert, D., Létinois, U., McClymont, T., Medlock, J., Netscher, T., Bonrath, W.: Angew. Chem. Int. Ed. **51**, 12960 (2012)
22. Takahashi, T., Nagashima, T., Tsuji, J.: Chem. Lett., 369 (1980)
23. Takahashi, T., Ikeda, H., Tsuji, J.: Tetrahedron Lett. **21**, 3885 (1980)
24. Ishikura, M., Mori, M., Terashima, M. Ban, Y.J. Chem. Soc. Chem. Commun., 741 (1982)
25. Mori, M., Uozumi, Y., Kimura, M., Ban, Y.: Tetrahedron **42**, 3793 (1986)
26. Crisp, G.T., Scott, W.J., Stille, J.K.J.: Am. Chem. Soc. **106**, 7500 (1984)
27. Skoda-Földes, R., Kollár, L., Heil, B., Gálik, G., Tuba, Z., Arcadi, A.: Tetrahedron: Asymmetry **2**, 633 (1991)
28. Ciattini, P.G., Morera, E., Ortar, G.: Tetrahedron Lett. **32**, 6449 (1991)
29. McGuire, M.A., Sorenson, E., Owings, F.W., Resnick, T.M., Fox, M., Baine, N.H.J.: Org. Chem. **59**, 6683 (1994)
30. Skoda-Földes, R., Csákai, Z., Kollár, L., Szalontai, G., Horváth, J., Tuba, Z.: Steroids **60**, 786 (1995)
31. Mourino, A., Torneiro, M., Vitale, C., Fermandez, S., Pérez-Sestelo, J., Anné, S., Gregorio, C.: Tetrahedron Lett. **38**, 4713 (1997)
32. Xiang, A.X., Watson, D.A., Ling, T., Theodorakis, E.A.J.: Org. Chem. **63**, 6774 (1998)
33. Almstead, J.K., Demuth Jr, T.P., Ledoussal, B.: Tetrahedron: Asymmetry **9**, 3179 (1998)
34. McGuire, M.A., Sorenson, E., Klein, D.N., Baine, N.H.: Synth. Commun. **28**, 1611 (1998)
35. Arcadi, A., Asti, C., Brandolini, L., Caselli, G., Marinelli, F., Ruggieri, V.: Bioorg. Med. Chem. Lett. **9**, 1291 (1999)
36. Skoda-Földes, R., Szarka, Z., Kollár, L., Dinya, Z., Horváth, J., Tuba, Z.J.: Org. Chem. **64**, 2134 (1999)
37. Yu, M.S., Baine, N.H.: Tetrahedron Lett. **40**, 3123 (1999)
38. Jakubec, P., Hawkins, A., Felzmann, W., Dixon, D.J.J.: Am. Chem. Soc. **134**, 17482 (2012)
39. Phoenix, S., Reddy, M.S., Deslongchamps, P.J.: Am. Chem. Soc. **130**, 13989 (2008)
40. Murai, A., Tanimoto, N., Sakamoto, N., Masamune, T.J.: Am. Chem. Soc. **1988**, 110 (1985)
41. Chu, L., Mrozik, H., Fisher, M.H., Brown, J.E., Cheng, K., Chan, W.W.-S., Schoen, W.R., Wyvratt, M.J., Butler, B.S., Smith, R.G.: Bioorg. Med. Chem. Lett. **5**, 2245 (1995)
42. Holt, D.A., Levy, M.A., Ladd, D.L., Oh, H.-J., Erb, J.M., Heaslip, J.I., Brandt, M., Metcalf, B.W.J.: Med. Chem. **33**, 937 (1990)
43. Holt, D.A., Levy, M.A., Oh, H.-J., Erb, J.M., Heaslip, J.I., Brandt, M., Lan-Hargest, H.-Y., Metcalf, B.W.J.: Med. Chem. **33**, 943 (1990)

44. Blaszczak, L.C., Brown, R.F., Cook, G.K., Hornback, W.J., Hoying, R.C., Indelicato, J.M., Jordan, C.L., Katner, A.S., Kinnick, M.D., McDonald III, J.H., Morin, J.M., Munroe, J.E., Pasini, C.E.J.: Med. Chem. **33**, 1656 (1990)
45. Hiyama, T., Wakasa, N., Ueda, T., Kusumoto, T.: Bull. Chem. Soc. Jpn. **63**, 640 (1990)
46. Scrivanti, A., Matteoli, U.: Tetrahedron Lett. **36**, 9015 (1995)
47. Takahata, H., Banba, Y., Momose, T.: Tetrahedron: Asymmetry **2**, 445 (1991)
48. Hümmer, W., Dubois, E., Gracza, T., Jäger, V.: Synthesis, 634 (1997)
49. Szolcsányi, P., Gracza, T., Koman, M., Prónayová, N., Liptaj, T.: Tetrahedron: Asymmetry **11**, 2579 (2000)
50. Nesbitt, C.L., McErlean, C.S.P.: Org. Biomol. Chem. **9**, 2198 (2011)
51. Knight, S.D., Overman, L.E., Pairaudeau, G.J.: Am. Chem. Soc. **115**, 9293 (1993)
52. Adam, W., Klug, P.: Synthesis, 567 (1994)
53. Tilley, J.W., Danho, W., Lovey, K., Wagner, R., Swistok, J., Makofske, R., Michalewsky, J., Triscari, J., Nelson, D., Weatherford, S.J.: Med. Chem. **34**, 1125 (1991)
54. Wrobel, J., Dietrich, A.: Tetrahedron Lett. **34**, 3543 (1993)
55. Ye, B., Burke Jr, T.R.: Tetrahedron **52**, 9963 (1996)
56. Nelson, P.H., Carr, S.F., Devens, B.H., Eugui, E.M., Franco, F., Gonzalez, C., Hawley, R.C., Loughhead, D.G., Milan, D.J., Papp, E., Patterson, J.W., Rouhafza, S., Sjogren, E.B., Smith, D.B., Stephenson, R.A., Talamas, F.X., Waltos, A.-M., Weikert, R.J., Wu, J.C.J.: Med. Chem. **39**, 4181 (1996)
57. Murata, N., Sugihara, T., Kondo, Y., Sakamoto, T.: Synlett, 298 (1997)
58. Henegar, K.E., Ashford, S.W., Baughman, T.A., Sih, J.C., Gu, R.-L.J.: Org. Chem. **62**, 6588 (1997)
59. Ma, D., Tian, H.: Tetrahedron: Asymmetry **7**, 1567 (1996)
60. Ma, D., Tian, H.J.: Chem. Soc. Perkin Trans. **1**, 3493 (1997)
61. Ma, D., Tian, H., Zou, G.J.: Org. Chem. **64**, 120 (1999)
62. Choshi, T., Matsuya, Y., Okita, M., Inada, K., Sugino, E., Hibino, S.: Tetrahedron Lett. **39**, 2341 (1998)
63. Ma, D., Tian, H., Sun, H., Kozikowski, A.P., Pshenichkin, S., Wroblewski, J.T.: Bioorg. Med. Chem. Lett. **7**, 1195 (1997)
64. Morera, E., Ortar, G., Varani, A.: Synth. Commun. **28**, 4279 (1998)
65. Henley, P.D., Kilburn, J.D.: Chem. Commun., 1335 (1999)
66. Hersperger, R., Bray-French, K., Mazzoni, L., Müller, T.J.: Med. Chem. **43**, 675 (2000)
67. Linnanen, T., Brisander, M., Unelius, L., Sundholm, G., Hacksell, U., Johansson, A.M.J.: Med. Chem. **43**, 1339 (2000)
68. Hammarberg, E., Nordvall, G., Leideborg, R., Nylöf, M., Hanson, S., Johansson, L., Thorberg, S., Tolf, B., Jerning, E., Svantesson, G.T., Mohell, N., Ahlgren, C., Westlind-Danielsson, A., Gsöregh, I., Johansson, R.J.: Med. Chem. **43**, 2837 (2000)
69. Sun, H., Mahadevan, A., Razdan, R.K.: Tetrahedron Lett. **45**, 615 (2004)
70. Gosselin, F., Britton, R.A., Davies, I.W., Dolman, S.J., Gauvreau, D., Hoerrner, R.S., Hughes, G., Janey, J., Lau, S., Molinaro, C., Nadeau, C., O'Shea, P.D., Palucki, M., Sidler, R.J.: Org. Chem. **75**, 4154 (2010)
71. Pommier, A., Kocienski, P.J.: Chem. Commun., 1139 (1997)
72. Pommier, A., Stepanenko, V., Jarowicki, K., Kocienski, P.J.J.: Org. Chem. **68**, 4008 (2003)
73. Aoyagi, S., Hasegawa, Y., Hirashima, S., Kibayashi, C.: Tetrahedron Lett. **39**, 2149 (1998)
74. Hirashima, S., Aoyagi, S., Kibayashi, C.J.: Am. Chem. Soc. **121**, 9873 (1999)
75. Aoyagi, S., Hirashima, S., Saito, K., Kibayashi, C.J.: Org. Chem. **67**, 5517 (2002)
76. Liao, B., Negishi, E.-I.: Heterocycles **52**, 1241 (2000)
77. Wu, X.-F., Neumann, H., Beller, M.: ChemSusChem **6**, 229 (2013)
78. Brennführer, A., Neumann, H., Beller, M.: ChemCatChem **1**, 28 (2009)
79. Lütjens, H., Scammells, P.J.: Tetrahedron Lett. **39**, 6581 (1998)
80. da Rocha, L.L., de O., Dias, A., dos Santos, E.N., Augusti, R., Gusevskaya, E. J. Mol. Catal. A: Chem. **132**, 213 (1998)
81. Ham, W.-H., Jung, Y.H., Lee, K., Oh, C.-Y., Lee, K.-Y.: Tetrahedron Lett. **38**, 3247 (1997)

82. Boukouvalas, J., Fortier, G., Radu, I.-I.J.: Org. Chem. **63**, 916 (1998)
83. Oh, C.-Y., Kim, K.-S., Ham, W.-H.: Tetrahedron Lett. **39**, 2133 (1998)
84. Troisi, L., Vasapollo, G., El Ali, B., Mele, G., Florio, S., Capriati, V.: Tetrahedron Lett. **40**, 1771 (1999)
85. Etridge, S.K., Hayes, J.F., Walsgrove, T.C., Wells, A.S.: Org. Process Res. Dev. **3**, 60 (1999)
86. Andrews, I.P., Atkins, R.J., Badham, N.F., Bellingham, R.K., Breen, G.F., Carey, J.S., Etridge, S.E., Hayes, J.F., Hussain, N., Morgan, D.O., Share, A.C., Smith, S.A.C., Walsgrove, T.C., Wells, A.S.: Tetrahedron Lett. **42**, 4915 (2001)
87. Atkins, R.J., Banks, A., Bellingham, R.K., Breen, G.F., Carey, J.S., Etridge, S.K., Hayes, J.F., Hussain, N., Morgan, D.O., Oxley, P., Passey, S.C., Walsgrove, T.C., Wells, A.S.: Org. Process Res. Dev. **7**, 663 (2003)
88. Orito, K., Miyazawa, M., Kanbayashi, R., Tokuda, M., Suginome, H.J.: Org. Chem. **64**, 6583 (1999)
89. Boger, D.L., Boyce, C.W.J.: Org. Chem. **65**, 4088 (2000)
90. Bio, M.W., Leighton, J.L.J.: Am. Chem. Soc. **121**, 890 (1999)
91. Bio, M.M., Leighton, J.L.: Org. Lett. **2**, 2905 (2000)
92. Bio, M.M., Leighton, J.L.J.: Org. Chem. **68**, 1693 (2003)
93. Hornberger, K.R., Hamblett, C.L., Leighton, J.L.J.: Am. Chem. Soc. **122**, 12894 (2000)
94. Ishikura, M., Imaizumi, K., Katagiri, N.: Heterocycles **53**, 2201 (2000)
95. Ho, W.-B., Broka, C.J.: Org. Chem. **65**, 6743 (2000)
96. Davies, S.G., Goodwin, C.J., Pyatt, D., Smith, A.D.J.: Chem. Soc. Perkin Trans. **1**, 1413 (2001)
97. Wentland, M.P., Lou, R., Dehnhardt, C.M., Duan, W., Cohen, D.J., Bidlack, J.M.: Bioorg. Med. Chem. Lett. **11**, 1717 (2001)
98. Wentland, M.P., Lou, R., Ye, Y., Cohen, D.J., Richardson, G.P., Bidlack, J.M.: Bioorg. Med. Chem. Lett. **11**, 623 (2001)
99. Smith III, A.B., Cho, Y.S., Ishiyama, H.: Org. Lett. **3**, 3971 (2001)
100. Smith III, A.B., Kürti, L., Davulcu, A.H., Cho, Y.S.: Org. Process Res. Dev. **11**, 19 (2007)
101. Smith III, A.B., Adams, C.M., Kozmin, S.A., Paone, D.V.J.: Am. Chem. Soc. **123**, 5925 (2001)
102. Wang, H., Ng, T.B.: Life Sci. **65**, 849 (1999)
103. Song, J.J., Yee, N.K.J.: Org. Chem. **66**, 605 (2001)
104. Albaneze-Walker, J., Murry, J.A., Soheili, A., Ceglia, S., Springfield, S.A., Bazaral, C., Dormer, P.G., Hughes, D.L.: Tetrahedron **61**, 6330 (2005)
105. Ceccarelli, S.M., Piarulli, U., Telser, J., Gennari, C.: Tetrahedron Lett. **42**, 7421 (2001)
106. Herr, R.J., Fairfax, D.J., Meckler, H., Wilson, J.D.: Org. Process Res. Dev. **6**, 677 (2002)
107. Gangjee, A., Zeng, Y., McGuire, J.J., Kisliuk, R.L.J.: Med. Chem. **2002**, 45 (1942)
108. Dangel, B.D., Godula, K., Youn, S.W., Sezen, B., Sames, D.J.: Am. Chem. Soc. **124**, 11856 (2002)
109. Herzner, H., Palmacci, E.R., Seeberger, P.H.: Org. Lett. **4**, 2965 (2002)
110. Miyakoshi, N., Mukai, C.: Org. Lett. **5**, 2335 (2003)
111. Artman III, G.D., Weinreb, S.M.: Org. Lett. **5**, 1523 (2003)
112. Couladouros, E.A., Mihou, A.P., Bouzas, E.A.: Org. Lett. **6**, 977 (2004)
113. Furuichi, N., Hara, H., Osaki, T., Nakano, M., Mori, H., Katsumura, S.J.: Org. Chem. **69**, 7949 (2004)
114. Yao, T., Yue, D., Larock, R.C.J.: Org. Chem. **70**, 9985 (2005)
115. Wannberg, J., Kaiser, N.K., Vrang, L., Samuelsson, B., Larhed, M., Hallberg, A.J.: Comb. Chem. **7**, 611 (2005)
116. Ori, M., Toda, N., Takami, K., Tago, K., Kogen, H.: Tetrahedron **61**, 2075 (2005)
117. Madin, A., O'Donnell, C.J., Oh, T., Old, D.W., Overman, L.E., Sharp, M.J.J.: Am. Chem. Soc. **127**, 18054 (2005)
118. Fáková, H., Pour, M., Kunes, J., Senel, P.: Tetrahedron Lett. **46**, 8137 (2005)

119. Gupton, J.T., Banner, E.J., Scharf, A.B., Norwood, B.K., Kanters, R.P.F., Dominey, R.N., Hempel, J.E., Kharlamova, A., Bluhn-Chertudi, I., Hickenboth, C.R., Little, B.A., Sartin, M.D., Coppock, M.B., Krumpe, K.E., Burnham, B.S., Holt, H., Du, K.X., Keertikar, K.M., Diebes, A., Ghassemi, S., Sikorski, J.A.: Tetrahedron **62**, 8243 (2006)
120. Jan, N.-W., Liu, H.-J.: Org. Lett. **8**, 151 (2006)
121. Clive, D.L.J., Liu, D.J.: Org. Chem. **73**, 3078 (2008)
122. Tamiya, M., Ohmori, K., Kitamura, M., Kato, H., Arai, T., Oorui, M., Suzuki, K.: Chem. Eur. J. **13**, 9791 (2007)
123. Gao, S., Wang, Q., Chen, C.J.: Am. Chem. Soc. **131**, 1410 (2009)
124. Gao, S., Wang, Q., Huang, L.J., Lum, L., Chen, C.J.: Am. Chem. Soc. **132**, 371 (2010)
125. Cook, C., Guinchard, X., Liron, F., Roulland, E.: Org. Lett. **12**, 744 (2010)
126. Cook, C., Guinchard, X., Liron, F., Roulland, E.J.: Org. Chem. **77**, 6728 (2012)
127. Smith III, A.B., Bosanac, T., Basu, K.J.: Am. Chem. Soc. **131**, 2348 (2009)
128. Li, Z., Gao, Y., Tang, Y., Dai, M., Wang, G., Wang, Z., Yang, Z.: Org. Lett. **10**, 3017 (2008)
129. O'Keefe, B.M., Simmons, N., Martin, S.F.: Tetrahedron **67**, 4344 (2011)
130. Tadd, A.C., Fielding, M.R., Willis, M.C. Chem. Commun., 6744 (2009)
131. Yang, Z., Zhang, B., Zhao, G., Yang, J., Xie, X., She, X.: Org. Lett. **13**, 5916 (2011)

Chapter 11
A Discussion Between Carbonylation, Noncarbonylation and Decarbonylation

We have discussed various types of carbonylation reactions and their applications in total synthesis in the last ten chapters. In order to evaluate our knowledge of this area, we will discuss the relationship among carbonylation, noncarbonylation and decarbonylation.

Mechanistically, transition metal-catalyzed carbonylation (taking palladium, for example) includes elemental steps such as oxidative addition, coordination and the insertion of carbon monoxide (transmetalation), reductive elimination (Scheme 11.1). In carbonylative coupling reactions, the oxidative additional step needs an electron-rich metal center, but the CO coordination and insertion requires an electron-deficient metal center; the reductive elimination can be promoted by bulky ligands, while the CO coordination and insertion step demand that the ligand not be too bulky. Evaluated temperature can favor an oxidative addition, while it also favors the decarbonylation of an acylpalladium complex (the reverse reaction of CO insertion). The key to developing a successful carbonylative coupling reaction is finding the proper combination of reaction temperature, ligand and the other parameters.

At the stage it is interesting to note the relationship between palladium-catalyzed coupling reactions and their carbonylative coupling reactions. In principle, the reactions work under carbonylative coupling conditions and can also give their noncarbonylation product under CO-free conditions [1, 2]. But it is not restricted that noncarbonylative coupling must be developed before the carbonylative coupling. Such an aminocarbonylation was reported by Heck and colleagues in the 1970s, but the Buchwald-Hartwig amination was established between 1994 and the late 2000s [3–6]. On the other hand, some substrates have been extensively applied in noncarbonylative coupling reactions, but their carbonylative versions are rarely reported, such as aryl chloride, aryl tosylates and aryl mesylates.

Aryl chlorides are important starting materials in palladium-catalyzed coupling reactions [7]. Compared with the corresponding aryl iodides or aryl bromides, the advantages of aryl chlorides are obviously that they are inexpensive, easy to prepare, stable, etc. The same is true if we compare aryl tosylates or aryl mesylates with their aryl triflates analogs. Even though aryl chlorides, aryl mesylates and aryl acetates have been studied and have succeeded in cross-coupling reactions, their

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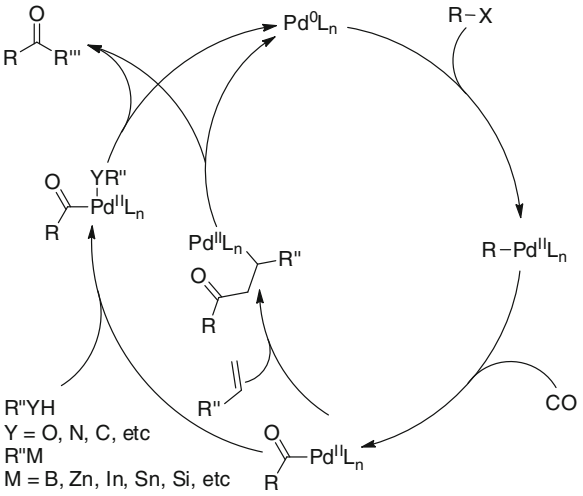
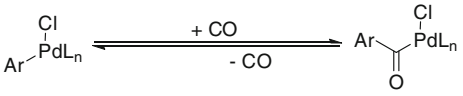
Scheme 11.1 Reaction mechanism for Pd-catalyzed carbonylation reactions



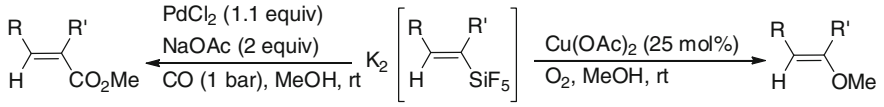
Scheme 11.2 Carbonylation and decarbonylation equilibrium



carbonylative coupling transformations are still rarely reported. Until the present, no general methodology has been developed for the carbonylative coupling of aryl chlorides. All the known procedures need either a high temperature (>140 °C) or a strong base. The possible explanations for this situation are: (1) CO coordinated to metal center decreased the electron density that inhibited the oxidative addition step in some distant; (2) the high temperature required by the oxidative addition or the strong base needed by transmetalation destroyed the formed arylpalladium or acylpalladium species; and (3) in order to avoid the high temperature caused decarbonylation, high pressures of CO are normally applied to drive the reaction, but this may result in the formation of a palladium carbon monoxide complex that is inactive for a cross-coupling reaction (Scheme 11.2).

With this in the background, it will be interesting to discuss the relationship between carbonylation, noncarbonylation and decarbonylation.

Organopentafluorosilicates are recognized as a class of versatile intermediates in various organic syntheses. Kumada and colleagues developed methodologies for the transformation of organopentafluorosilicates into various chemicals [8, 9]. In the case of palladium-mediated carbonylation of silicates, the reaction works at room temperature under atmospheric pressure of carbon monoxide in MeOH. The reaction works with $PdBr_2$ as a promoter as well, but $Pd(OAc)_2$ did not give any carbonylation product. While the direct etherification took place under 25 mol % of $Cu(OAc)_2$ in MeOH at room temperature, the presence of air or O_2 can drive the reaction in a catalytic manner. $CuBr_2$, $CuCl_2$, $Cu(SCN)_2$ only gave the ligand



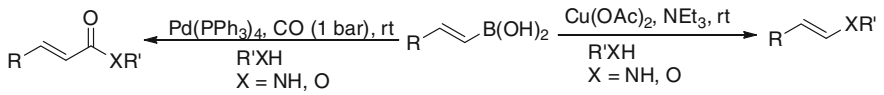
Scheme 11.3 Transformation of alkenylsilicates

transfer products, and no ether was formed. In an inert gas atmosphere, a Cu(I) species was confirmed by titration [10] (Scheme 11.3).

Organoboron reagents are important reagents in organic chemistry that enable many chemical transformations. The reaction of organo boronic acid, vinyl boronate esters and organoborate salts with amines and alcohols give another way for the C–N, C–O bonds to form besides the Buchwald-Hartwig amination. This type of reaction typically uses $Cu(OAc)_2$ as the catalyst, with stoichiometric amounts of $Cu(OAc)_2$ or catalytic amounts of $Cu(OAc)_2$ together with additional oxidants such as air, O_2, TEMPO, in the presence of NEt_3 or pyridine as base; at either room temperature or evaluated temperature, the desired products can be produced in good yields.[1] The carbonylation version of these types of reactions were developed as well [16–20]. In the presence of a palladium catalyst, oxidant and base, esters were produced (Scheme 11.4). Until the present, amines were not used as nucleophiles in the oxidative carbonylation of organoborons; one of the reasons might be the formation of urea.

The oxidative coupling of arylboronic acids with olefins and their carbonylation version are interesting to compare [21–24]. In the report from Wu,[2] they developed the coupling of arylboronic acids with styrenes in the presence of a palladium catalyst in DMF at 50 °C with 1 bar of O_2. In 2012 Beller's team reported on the carbonylation version [24]. In this publication, the use of DMSO as a solvent and DPPP as a ligand are crucial for the success of this transformation (Scheme 11.5).

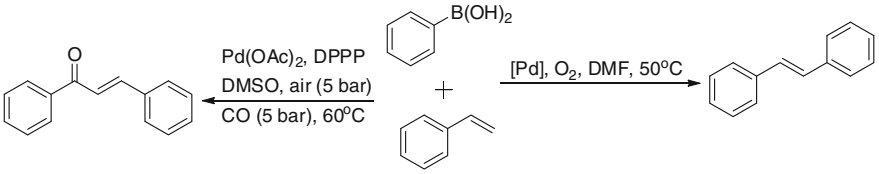
In 2012 Lei and his colleagues reported the transformation of diaryl ethers to xanthones in the presence of palladium and CO [25]. The noncarbonylation version was reported as well [26, 27]. As shown in Scheme 11.6, the reaction conditions are not very different. All need the presence of TFA to assistant C–H bond activation. One more example is the reaction of aniline with terminal alkynes via an in situ formation of diazonium salts [1, 2]. The carbonylation and



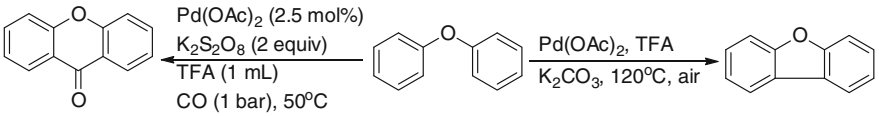
Scheme 11.4 Transformation of organoboron reagents

[1] For selected examples, see [11–15].

[2] For selected examples, see [21–23].



Scheme 11.5 Transformation of arylboronic acids



Scheme 11.6 Transformation of diaryl ethers

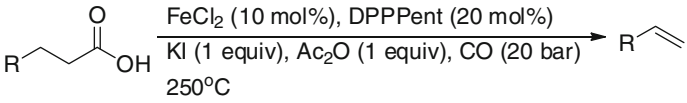
noncarbonylation versions were reported by Beller's group. The difference in the reaction conditions is only at solvent and the presence of CO (10 bar). For the typical cross coupling reactions, the difference between carbonylation and noncarbonylation is even smaller. This is so for Suzuki coupling and carbonylative Suzuki coupling, etc., [28].

Additionally, the carbonylative Heck reaction was developed by Beller's group [29–31]. The reaction condition requires the higher loading of alkenes (6 equiv) and the presence of CO compared with Heck coupling.

The opposite of carbonylation is decarbonylation. In order to understand carbonylation reactions, decarbonylation reactions will be discussed below.

In 2012 Ryu and his colleagues reported the iron-catalyzed decarbonylation of aliphatic carboxylic acids to α-olefins (Scheme 11.7) [32]. In their mechanism study, they found the formation of CO but not CO_2. If the reaction was carried out under low or no pressure (0–5 bar) of carbon monoxide, internal an olefin was observed [33]. In the proposed reaction mechanism, the reaction starts from acid anhydride, which was produced from the reaction of substrate and Ac_2O. Then it reacts with the in situ-formed iron-carbonyl complex, which was generated by $FeCl_2$, phosphine ligand, KI, and CO, and decarbonylation occurred under high temperatures. Notably, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, $[Fe(CO)_2Cp]_2$ did not give the decarbonylation product.

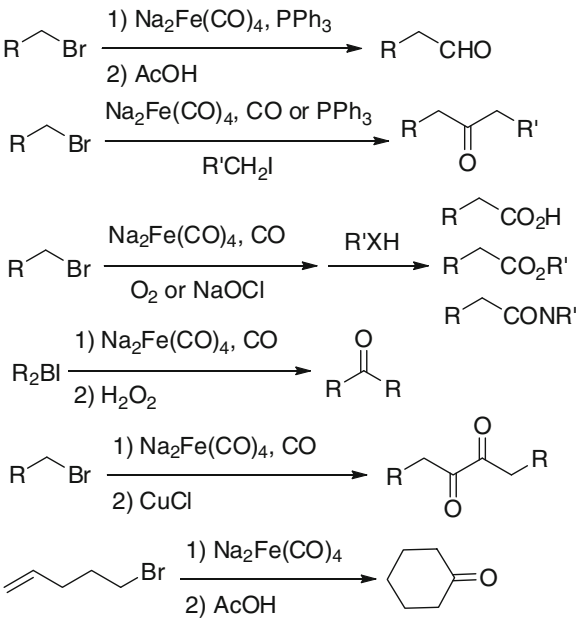
From the other side, the carbonylation of alkyl halides needs stoichiometric amounts of iron salt, such as the Collman reagent $[Na_2Fe(CO)_4]$. The first



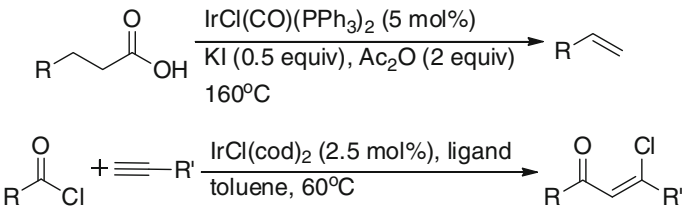
Scheme 11.7 Iron-catalyzed decarbonylation of carboxylic acid

successful application of sodium tetracarbonylferrate (II) in carbonylation was developed by Cooke in 1970 [34]. He synthesized various aldehydes from corresponding alkyl bromides in the presence of a 1.4 equivalent of $Na_2Fe(CO)_4$ and PPh_3. Later on, carboxylic acid derivatives, such as amides, esters and ketones, etc., were prepared by various research groups from corresponding alkyl halides or aryl lithium (Scheme 11.8) [34–44]. The reactions need additional CO or PPh_3 to assist the insertion of CO into the C–Fe bond. The main problem of these methodologies is the necessity for an excess of iron salts, and a catalytic version is still urgently needed.

The above-mentioned decarbonylation of aliphatic acid was also described by the same group, with iridium as the catalyst [45]. Using $IrCl(CO)(PPh_3)_2$ as a catalyst, when combined with KI as an additive, it served as an excellent catalyst for the decarbonylation of long-chain aliphatic carboxylic acids to give internal alkenes with high selectivity. In combination with KI and Ac_2O as additives under controlled temperatures, decarbonylation proceeded to give terminal alkenes with high selectivity. In comparison, Tsuji and colleagues reported an iridium-catalyzed addition of aroyl chlorides and aliphatic acid chlorides to terminal alkynes, and (*Z*)-*β*-chloro-α,*β*-unsaturated ketones were selectively produced (Scheme 11.9) [46]. The additional reactions proceed regio- and stereoselectively with the suppression of decarbonylation and *β*-hydrogen elimination, which might be due to the ligands that were applied. From the point of view of the reaction mechanism, the oxidative addition of aroyl chlorides to [Ir]L (L = IPr) occurs in the presence of alkynes. The insertion of Ir–Cl to alkyne is much faster than decarbonylation.



Scheme 11.8 $Na_2Fe(CO)_4$-mediated carbonylation reactions



Scheme 11.9 Ir-catalyzed reactions of acid and acid chloride

On the other hand, the oxidative addition of aliphatic acid chlorides occurs in the absence of alkyne, but the oxidative addition complex could not be isolated due to fast decarbonylation followed by facile β-hydrogen elimination. The decarbonylation of carboxylic acid was reported with palladium catalysts as well [47–56]. In general, the reactions to acid anhydride as the intermediate need relatively high temperatures.

A brief description of the relationship between carbonylation, noncarbonylation and decarbonylation has been given in this chapter. There are still no general rules for guiding the methodology that is developing on this topic.

References

1. Wu, X-F., Neumann, H., Beller, M.: Chem. Commun. **47**, 7959 (2011)
2. Wu, X.-F., Neumann, H., Beller, M.: Angew. Chem. Int. Ed. **50**, 11142 (2011)
3. Paul, F., Patt, J., Hartwig, J.F.J.: Am. Chem. Soc. **116**, 5969 (1994)
4. Guram, A.S., Buchwald, S.L.J.: Am. Chem. Soc. **116**, 7901 (1994)
5. Louie, J., Hartwig, J.F.: Tetrahedron Lett. **36**, 3609 (1995)
6. Guram, A.S., Rennels, R.A., Buchwald, S.L.: Angew. Chem. Int. Ed. **34**, 1348 (1995)
7. Littke, A.F., Fu, G.C.: Angew. Chem. Int. Ed. **41**, 4176 (2002)
8. Tamao, K., Kakui, T., Kumada, M.: Tetrahedron Lett. **20**, 619 (1979)
9. Tamao, K., Kakui, T., Kumada, M.: Tetrahedron Lett. **21**, 4105 (1980)
10. Jenkins, C.L., Kochi, J.K.J.: Am. Chem. Soc. **94**, 843 (1972)
11. Lam, P.Y.S., Vincent, G., Bonne, D., Clark, C.G.: Tetrahedron Lett. **44**, 4927 (2003)
12. Quach, T.D., Batey, R.A.: Org. Lett. **5**, 1381 (2003)
13. Winternheimer, D.J., Merlic, C.A.: Org. Lett. **12**, 2508 (2010)
14. Chan, D.G., Winternheimer, D.J., Merlic, C.A.: Org. Lett. **13**, 2778 (2011)
15. Shade, R.E., Hyde, A.M., Olsen, J.-C., Merlic, C.A.J.: Am. Chem. Soc. **132**, 1202 (2010)
16. Ohe, T., Ohe, K., Uemura, S., Sugita, N.J.: Organometal. Chem. **344**, C5 (1988)
17. Yamashina, N., Hyuga, S., Hara, S., Suzuki, A.: Tetrahedron Lett. **30**, 6555 (1989)
18. Cho, C.S., Ohe, T., Uemura, S.J.: Organometal. Chem. **496**, 221 (1995)
19. Yamamoto, Y.: Adv. Synth. Catal. **352**, 478 (2010)
20. Liu, Q., Li, G., He, J., Liu, J., Li, P., Lei, A.: Angew. Chem. Int. Ed. **49**, 3371 (2010)
21. Jung, Y.C., Mishra, R.K., Yoon, C.H., Jung, K.W.: Org. Lett. **5**, 2231 (2003)
22. Leng, Y., Yang, F., Wei, K., Wu, Y.: Tetrahedron **66**, 1244 (2010)
23. Andappan, M.M.S., Nilsson, P., Larhed, M.: Chem. Commun. 218 (2004)
24. Wu, X.-F., Neumann, H., Beller, M.: Chem. Asian J. **7**, 282 (2012)

25. Zhang, H., Shi, R., Gan, P., Liu, C., Ding, A., Wang, Q., Lei, A.: Angew. Chem. Int. Ed. **51**, 5204 (2012)
26. Liegault, B., Lee, D., Huestis, M.P., Stuart, D.R., Fagnou, K.J.: Org. Chem. **73**, 5022 (2008)
27. Hagelin, H., Oslob, J.D., Akermark, B.: Chem. Eur. J. **5**, 2413 (1999)
28. Wu, X.-F., Neumann, H., Beller, M.: Chem. Soc. Rev. **40**, 4986 (2011)
29. Wu, X.-F., Neumann, H., Spannenberg, A., Schulz, T., Jiao, H., Beller, M.J.: Am. Chem. Soc. **132**, 14596 (2010)
30. Wu, X.-F., Neumann, H., Beller, M.: Angew. Chem. Int. Ed. **49**, 5284 (2010)
31. Wu, X.-F., Jiao, H., Neumann, H., Beller, M.: ChemCatChem **3**, 726 (2011)
32. Maetani, S., Fukuyama, T., Suzuki, N., Ishihara, D., Ryu, I.: Chem. Commun. **48**, 2552 (2012)
33. Jennerjahn, R., Jackstell, R., Piras, I., Franke, R., Jiao, H., Bauer, M., Beller, M.: ChemSusChem **5**, 734 (2012)
34. Cooke, M.P.J.: Am. Chem. Soc. **92**, 6080 (1970)
35. Collman, J.P., Winter, S.R., Clark, D.R.J.: Am. Chem. Soc. **94**, 1788 (1972)
36. Siegl, W.O., Collman, J.P.J.: Am. Chem. Soc. **94**, 2516 (1972)
37. Collman, J.P., Winter, S.R., Komoto, R.G.J.: Am. Chem. Soc. **95**, 249 (1973)
38. Collman, J.P., Hoffman, N.W.J.: Am. Chem. Soc. **95**, 2689 (1973)
39. Mérour, J.Y., Roustan, J.L., Charrier, C., Collin, J.J.: Organomet. Chem. **51**, C24 (1973)
40. Ungurenasu, C., Cotzur, C.: Poly. Bull. **6**, 299 (1982)
41. Sundararajan, G.: Organometallics **10**, 1377 (1991)
42. Devasagayaraj, A., Tao, M.L.N., Periasamy, M.J.: Organomet. Chem. **421**, 147 (1991)
43. Devasagayaraj, A., Periasamy, M.: Tetrahedron Lett. **33**, 1227 (1992)
44. Periasamy, M., Devasagayaraj, A., Radhakrishnan, U.: Organometallics **12**, 1424 (1993)
45. Maetani, S., Fukuyama, T., Suzuki, N., Ishihara, D., Ryu, I.: Organometallics **30**, 1389 (2011)
46. Iwai, T., Fujihara, T., Terao, J., Tsuji, Y.J.: Am. Chem. Soc. **134**, 1268 (2012)
47. Blaser, H.-U., Spencer, A.J.: Organometal. Chem. **233**, 267 (1982)
48. Sugihara, T., Satoh, T., Miura, M.: Tetrahedron Lett. **46**, 8269 (2005)
49. Gooßen, L.J., Khan, B.A., Fett, T., Treu, M.: Adv. Synth. Catal. **352**, 2166 (2010)
50. Gooßen, L.J., Paetzold, J.: Angew. Chem. Int. Ed. **41**, 1237 (2002)
51. Gooßen, L.J., Paetzold, J.: Angew. Chem. Int. Ed. **2004**, 43 (1095)
52. Gooßen, L.J., Rodríguez, N.: Chem. Commun. 724 (2004)
53. Gooßen, L.J., Ghosh, K.: Euro. J. Org. Chem. 3254 (2002)
54. Le Notre, J., Scott, E.L., Franssen, M.C.R., Sanders, J.P.M.: Tetrahedron Lett. **51**, 3721 (2010)
55. Gooßen, L.J., Riley, S.: Synthesis **44**, 3003 (2012)
56. Gooßen, L.J., Paetzold, J., Winkel, L.: Synlett 1721 (2002)

Chapter 12
Summary and Outlook

We have discussed developments in the area of transition metal catalyzed carbonylative coupling reactions of C–X bonds. Starting from the original work of Heck and his group's use of oxygen and nitrogen nucleophiles, various novel carbonylation reactions have been developed over the past decades. Due to the advancements in "classical" coupling methodology, these days a plethora of transition metal catalysts is also available for the carbonylative activation of C–X bonds and related substrates. Although cross-coupling reactions have become reliable transformations for all kinds of sophisticated natural product syntheses, this is only partly true for catalytic carbonylation reactions. The necessity to use carbon monoxide still hinders more applications of carbonylation reactions, because most synthetic organic chemists are reluctant to use high pressure equipment, even though most carbonylative coupling reactions can be run at ambient or low pressure (1–5 bar).

Notably, often a high pressure of CO retards the oxidative addition of the metal center to the C–X compound due to the δ-acidic nature of CO as a ligand. Hence, catalytic performance is in general superior under milder conditions. It should also be noted that nowadays commercially available apparatuses exist that conveniently allow for parallel carbonylations, typically 6–16 fold.

What are the goals for the coming years in carbonylation reactions?

In the case of carbonylative coupling reactions, for example, catalyst efficiency (activity and productivity) in such reactions is still low compared to the more famous Suzuki or Heck reactions. In addition, substrates—especially (nitrogen) heteroarenes and more functionalized coupling partners—still represent significant challenges. Here, the development of better catalysts (ligands) will be a key issue. Clearly, such new catalyst systems should be tested initially in simpler benchmark reactions; however, this should be only the start and not the end of a catalyst development as it has often been in the past. With regard to sustainability, a major challenge will be the development of catalytic carbonylation reactions by directly employing arenes via C–H activation processes. The advantages of such methods are obvious: cheaper substrates and less waste. Obviously, these reactions would also be of principal interest to bulk chemicals.

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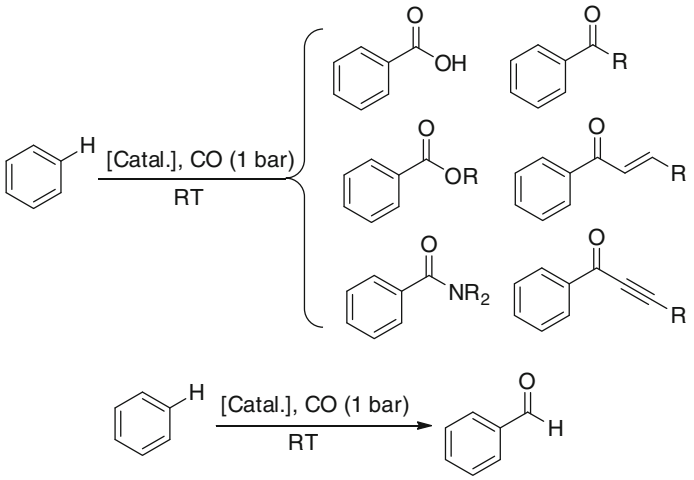

Scheme 12.1 Dream reactions

In the case of oxidative carbonylation reactions, air or other green oxidants should be applied more often in these reactions, especially in the industrially relevant direct carbonylation of arenes. For the more functionalized substrates which are interesting in organic synthesis, more selective catalyst systems are needed and directing groups might be omitted in the future.

Regarding the CO source, alternative CO sources should be discovered and applied in organic synthesis. Besides $M(CO)_x$, formic acid and aldehyde, can we use CO_2 in carbonylation by in situ reduction?

Regarding the catalysts, the performance of palladium in carbonylative coupling is outstanding. But the other cheap potential catalysts like Fe and Cu have not yet been explored.

More specifically, we have several dream reactions. Can they be realized in the near future (Scheme 12.1)?

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