

## Chapter 2

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

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

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

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

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

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

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

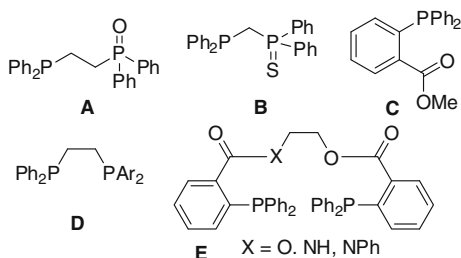
As we described above, the oxidative addition of methyl iodide to the  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  is the rate-determining step. Hence the activity of the Rh center can be improved by using strong electron donating ligands to increase its nucleophilicity, as the group of Cole-Hamilton reported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

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

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

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

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



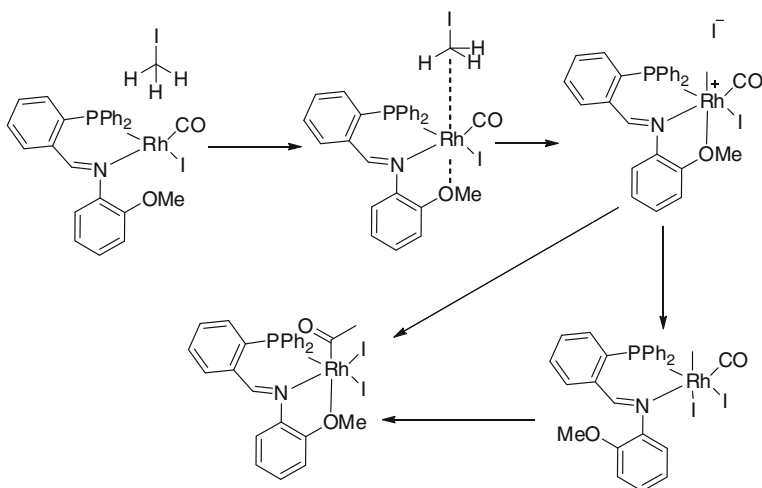
complexes were more active than the  $\text{PPh}_3$  analogue and the non-phosphine promoted  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  system.

Pringle and colleagues tested a series of asymmetrical fluorinated diphosphine ligands,  $\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PAr}$  (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  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  system produced better activity than all the catalysts tested here. In situ HPIR spectroscopy showed the absence of bands due to  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  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  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  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  $\text{SN}_2$  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  $1,2-(t\text{Bu}_2\text{PCH}_2)_2\text{C}_6\text{H}_4$  (DTBPMP) and  $[\text{RhCl}(\text{CO})_2]_2$  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  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$  (Monsanto catalyst), which is a less efficient catalyst, and the quaternary phosphonium cation,  $[(\text{Me}'\text{Bu}_2\text{PCH}_2)_2\text{C}_6\text{H}_4]^+$ . 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  $\text{C}_4$ -diphosphines, and the



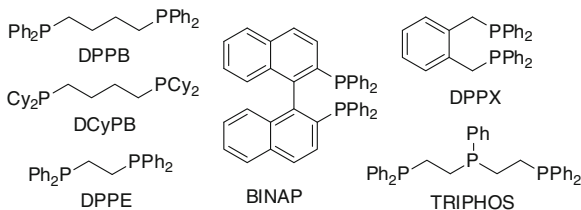
**Scheme 2.2** Rh-iminophosphine catalyzed carbonylation of MeI

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  $[\text{Rh}(\text{Xantphos})-(\text{COMe})\text{I}_2]$ , as the catalyst resting state, was isolated and shown to adopt a nearly octahedral geometry with the Xantphos ligand coordinated in a “pincer”  $\kappa^3\text{-P,O,P}$  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 ( $10^3\text{--}10^4$  times faster than  $[\text{Rh}(\text{CO})_2\text{I}_2]^-$ ), and more stable Rh(III) methyl complexes resulted from  $\alpha$ -diimine ligands with low steric bulk (e.g., bpy). In comparison, inhibited oxidative addition but promoted methyl migration, as observed with more bulky  $\alpha$ -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*<sup>TM</sup> 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.

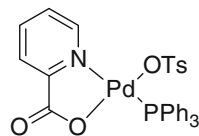
Cobalt in the same group with Rh and Ir was also explored in the carbonylation of methanol. The first report on this topic was in 1986, using  $\text{Co}_2(\text{CO})_8$  as the catalyst [47]. But the activity and selectivity of this system is low, and high temperatures and pressure (200 °C, 600 bar) were necessary. In 1999 Cole-Hamilton and colleagues found a high active cobalt catalyst based on the combination of  $\text{Cp}^*\text{Co}(\text{CO})_2$ ,  $\text{PEt}_3$  and MeI [48]. The  $[\text{CoI}(\text{CO})_2(\text{PEt}_3)_2]$  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-carboxylate 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<sub>2</sub> 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<sub>2</sub> 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  $\text{C}_{\text{sp}^3}\text{-X}$  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:  $\text{C-I} > \text{C-OTf} \geq \text{C-Br} \gg \text{C-Cl} \gg \text{C-F}$ . 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

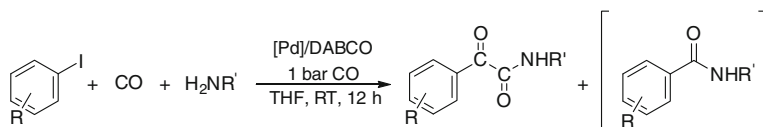


carboxylate salts or fluorides are used. One obvious advantage for carbonylation with respect to biologically active compound preparation is that a variety of carbonylation products can be easily prepared from the same aromatic substrate by simply changing the nucleophiles. Notably, such carbonylation 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,  $\alpha$ -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  $\alpha$ -keto amides were prepared under atmospheric pressure of CO at room temperature in the presence of a simple palladium-triphenylphosphine complex.

For intermolecular alkoxy carbonylation, [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 alkoxy carbonylation 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  $\text{PdX}_2(\text{PPh}_3)_2$  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%  $\text{Pd}(\text{PPh}_3)_4$  and three equivalents of  $\text{Et}_3\text{N}$  in *n*-butanol.



**Scheme 2.5** Palladium-catalyzed double carbonylation of aryl iodides

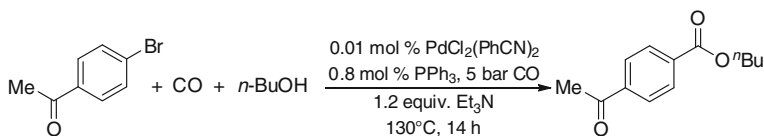
The optimization resulted in the highest turnover (TON up to 7,000) known until then for any alkoxy-carbonylation of aryl halides (Scheme 2.6).

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 alkoxy-carbonylations 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.

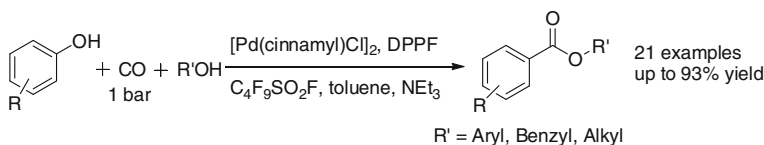
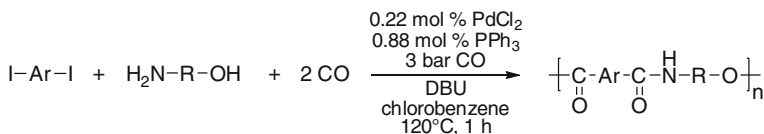
Bromoanisoles and unprotected bromoanilines, as examples of more challenging substrates, were recently overcome in methoxycarbonylation by Albaneze-Walker and colleagues [114]. Using 3 mol% of  $\text{PdCl}_2/\text{rac}$ -2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) at low pressure (4.5 bar CO, 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 alkoxy-carbonylation of phenols with alcohols and phenols via the in situ formation of  $\text{ArONf}$ . The reaction proceeds selectively to the desired benzoates in good yields (Scheme 2.7) [115, 116]. As phenols occur naturally and are readily available, applying phenols as electrophiles instead of aryl halides is an interesting topic. Additionally, in all the sulfonate compounds,  $\text{ArONf}$  is more stable than  $\text{ArOTf}$  and more active than  $\text{ArOTs}$  or  $\text{ArOMs}$ .

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 alkoxy-carbonylation of aryl bromides



**Scheme 2.7** Palladium-catalyzed carbonylation of phenols**Scheme 2.8** Palladium-catalyzed polycondensations

With the same reaction as that of alkoxy carbonylation, 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%  $\text{PdX}_2(\text{PPh}_3)_2$ . Stoichiometric amounts of a tertiary amine were required to neutralize the formed acid if weakly basic amines were used as nucleophiles.

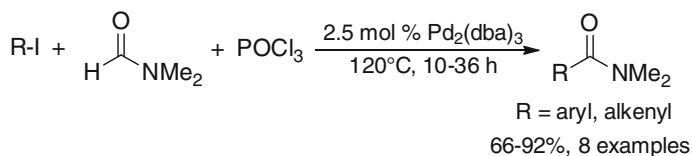
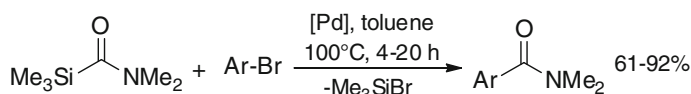
Aminocarbonylations of aryl iodides in the absence of carbon monoxide<sup>1</sup> and a base were realized in 2002 by a combination of phosphoryl chloride with *N,N*-dimethylformamide (DMF) [120]. With the assistance of 2.5 mol%  $\text{Pd}_2(\text{dba})_3$ , good to high yields of amides were obtained 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  $\text{Pd}(\text{PPh}_3)_4$  or  $\text{Pd}(\text{P}^t\text{Bu}_3)_2$  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.

Skyrstrup's group developed a two-reaction tubes technology for the CO free carbonylation reactions.<sup>2</sup> 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.

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

<sup>2</sup> For selected examples, see [122–124].

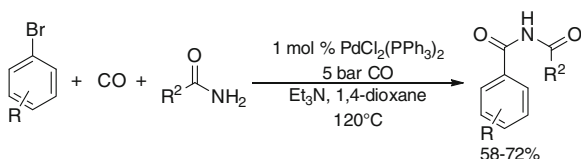
**Scheme 2.9** Palladium-catalyzed aminocarbonylation without CO**Scheme 2.10** Palladium-catalyzed aminocarbonylation of aryl bromides

More recently, a solid-phase palladium-catalyzed aminocarbonylation of aryl bromides or iodides utilizing molybdenumhexacarbonyl (Mo(CO)<sub>6</sub>) 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)<sub>2</sub>/PPh<sub>3</sub> [126–128]. Ferrocene amides and novel ferrocene  $\alpha$ -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<sub>3</sub>N 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

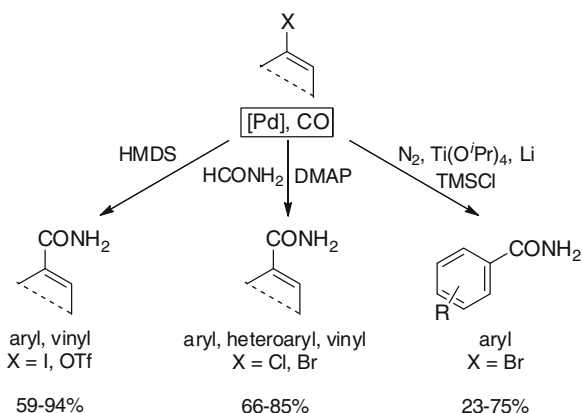
corresponding indole carboxylic amides via palladium-catalyzed carbonylation [130]. At 25 bar of CO and 130 °C, the use of  $\text{PdCl}_2(\text{PhCN})_2/1,1'$ -bis(diphenylphosphino)ferrocene (dppf) and  $\text{Et}_3\text{N}$  was found to be optimal for high yields (>90 %) for the reaction of indoles 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.

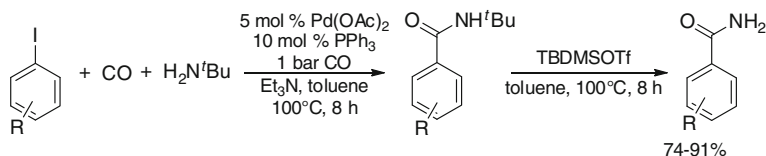
As the importance of primary amides, Morera and Ortar used hexamethyldisilazane (HMDS) as a source of ammonia in the carbonylation of aryl iodides and triflates to primary amides (Scheme 2.12) [131]. The desired products were isolated in high yields after hydrolysis. In addition, Indolese et al. reported 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  $\text{NaO}^t\text{Bu}$  [133].

Additionally, primary amides and ketoamides were synthesized in good yields via a more traditional carbonylation-deprotection sequence in the presence of  $\text{Pd}(\text{OAc})_2/2\text{PPh}_3$  (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  $\text{NH}_3$  and CO for primary amides synthesis (Scheme 2.14).

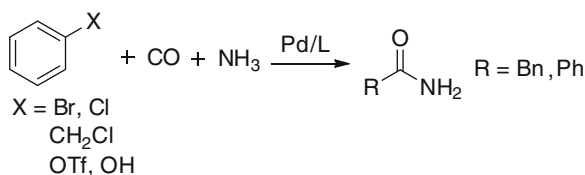
**Scheme 2.12** Palladium-catalyzed carbonylative synthesis of primary amides





**Scheme 2.13** Carbonylative synthesis of primary amides from aryl iodides

**Scheme 2.14** Procedures for carbonylative synthesis of primary amides

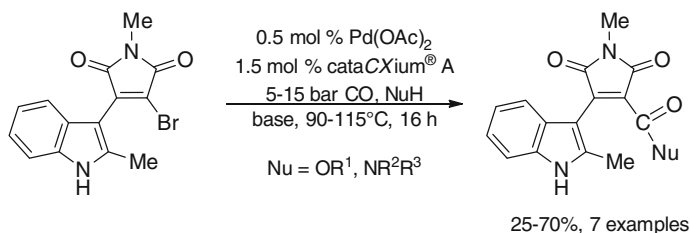
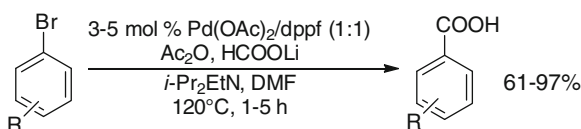


By using  $\text{Pd}(\text{OAc})_2$  and commercially available di-1-adamantyl-*n*-butylphosphine (cataCXium<sup>®</sup> A) as the catalyst system, various aromatic and heteroaromatic esters, amides, and acids were prepared from the corresponding bromoarenes in Beller's group [140]. Compared to most 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%  $\text{Pd}(\text{OAc})_2$  and dppf ( $\text{Pd}/\text{P} = 1$ ), 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.

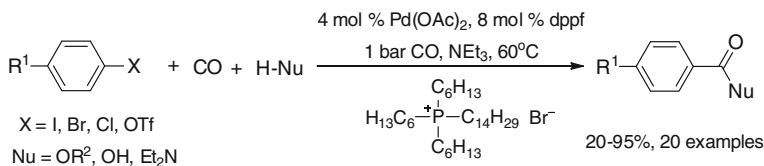
**Scheme 2.15** Carbonylative functionalize of 3-bromo-indolymaleimide**Scheme 2.16** Palladium-catalyzed hydroxycarbonylation of aryl bromides

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 alkoxy-carbonylation of bromobenzene, higher yields were obtained when 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF<sub>4</sub>] was used as the reaction medium compared with standard conditions. And the selectivity for the monocarbonylation of iodobenzene with *i*-PrOH or Et<sub>2</sub>NH was significantly enhanced by [bmim][BF<sub>4</sub>]. 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].

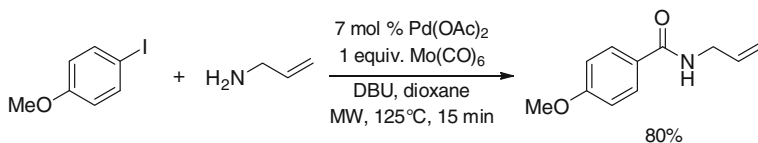
Larhed and colleagues developed the use of microwave irradiation in palladium-catalyzed carbonylations of aryl-X compounds [175–186]. Typically, these reactions were conducted in sealed vessels using microwave irradiation and either Mo(CO)<sub>6</sub> or formic acid derivatives as CO sources. Alternatively, 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)<sub>6</sub> 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-iodoanisol (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

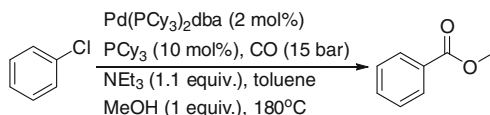
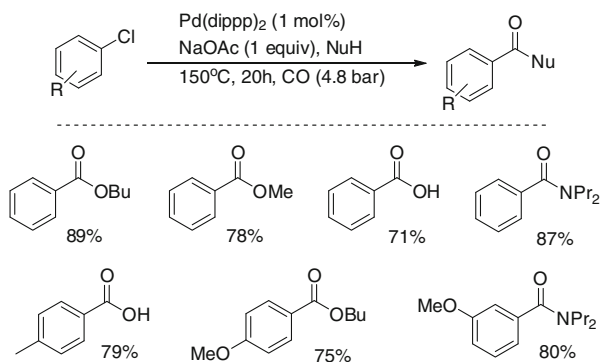


**Scheme 2.18** Mo(CO)<sub>6</sub>-mediated carbonylation of aryl iodides

Osborn and colleagues reported the catalytic carbonylation of chlorobenzene and dichloromethane [192]. By using [Pd(PCy<sub>3</sub>)<sub>2</sub>(dba)] as a catalyst in the presence of additional PCy<sub>3</sub>, chlorobenzene was catalytically carbonylated at 180 °C in toluene under 15 bar of CO using NEt<sub>3</sub> as a base (Scheme 2.19). In their report, instead of PCy<sub>3</sub>, P*i*Pr<sub>3</sub> can be used as an effective ligand for the activation of DCM at 25 °C to give ketene as well, but not P(CH<sub>2</sub>Ph)<sub>3</sub>, PPh<sub>2</sub>Cy and PPh<sub>3</sub>. In the case of chlorobenzene, Pd<sup>0</sup> complexes with P*t*Bu<sub>3</sub>, P*t*Bu<sub>2</sub>Ph, PPh<sub>2</sub>Cy and P(*m*-tol)<sub>3</sub> are non-active at all. Here it is also interesting to point out that chlorobenzene can react with [Pd(PCy<sub>3</sub>)<sub>2</sub>(dba)] to give a phenylpalladium 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 alkoxy carbonylation of chlorobenzene must be carried out at 180 °C.

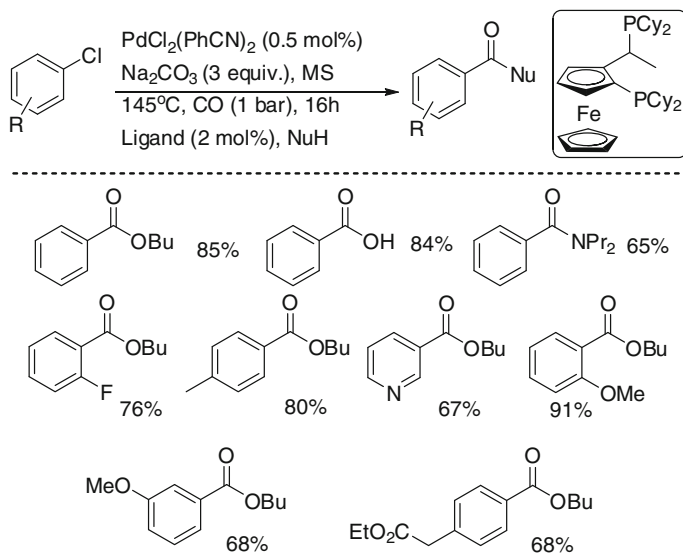
Meanwhile, Milstein's group succeeded with a breakthrough type of work on the carbonylation of aryl chlorides with his dippp (1,3-bis(di-isopropylphosphino)propane) ligand [193, 194]. In their studies, aryl chlorides were transformed into esters, amides, acids and aldehydes in good yields under relatively 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)<sub>2</sub> > Pd(P'*i*Pr<sub>2</sub>Bu)<sub>3</sub> ≫ Pd(dippe)<sub>2</sub> ≫ Pd(dppp)<sub>2</sub> 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**  $[\text{Pd}(\text{PCy}_3)_2(\text{dba})]$ -catalyzed carbonylation of chlorobenzene**Scheme 2.20**  $\text{Pd}(\text{dipp})_2$ -catalyzed carbonylation of aryl chlorides

1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicyclohexylphosphine 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(diphenylphosphino) 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-catalyzed carbonylation of aryl sulfonates [201]. The catalyst



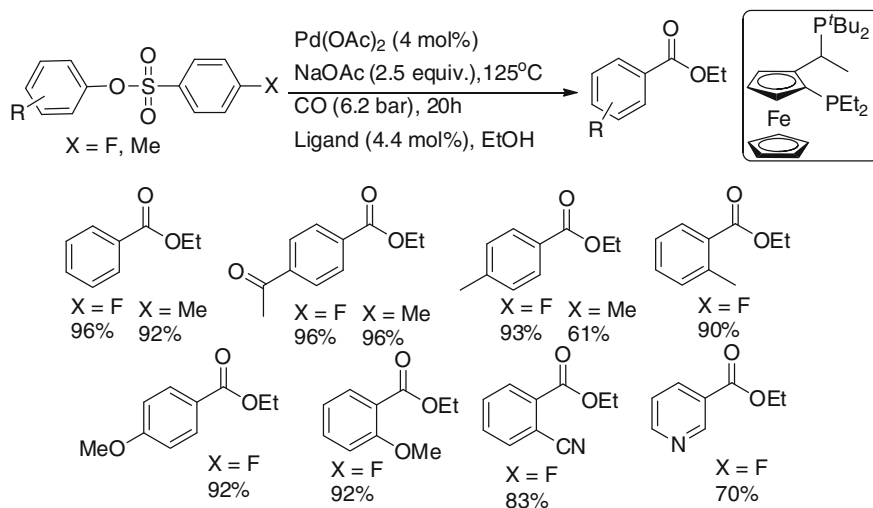
**Scheme 2.21** Pd-*Josiphos*-catalyzed carbonylation of aryl chlorides

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



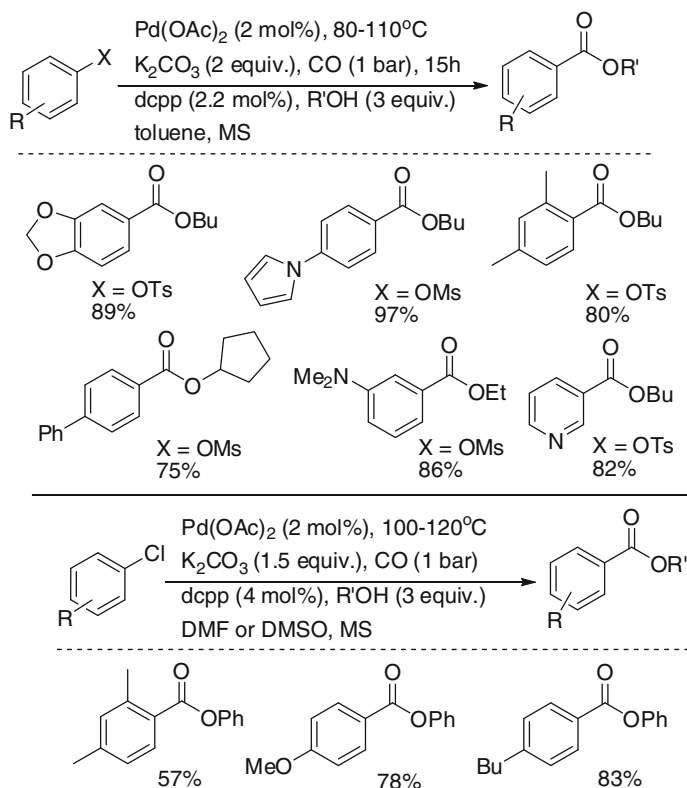


**Scheme 2.22** Pd-Josiphos-catalyzed carbonylation of aryl arenesulfonates

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 nanoparticle, biphasic system and Lewis acids as well.

$\text{Pd/C}$  was found to act as an effective catalyst for the carbonylation of aryl chlorides as  $200^\circ\text{C}$  [206]. It was found that both activated and non-activated aryl chlorides were transformed into the corresponding methyl esters [ $\text{CO}$  (3 bar),  $\text{AcONa}$ ,  $\text{MeOH}$ ], and the addition of  $\text{K}_2\text{Cr}_2\text{O}_7$  can enhance the catalytic activity. The role of  $\text{K}_2\text{Cr}_2\text{O}_7$  is very likely to reoxidize large particles of metallic palladium into a highly dispersed palladium(II) species that can be reduced again under  $\text{CO}$  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  $\text{KOH}$  under 1 bar of  $\text{CO}$  at  $100^\circ\text{C}$ ; both activated and non-activated aryl chlorides were carbonylated in good yields. In 1997 the combination of  $\text{PdCl}_2(\text{PCy}_3)_2\text{-K}_2\text{CO}_3$  aqueous solution-triethylamine [ $\text{CO}$  (5 bar),  $180^\circ\text{C}$ ] was a highly selective procedure for the hydrocarbonylation of chlorobenzene [208]. 4-Chlorobenzophenone and/or benzoyl chloride can be synthesized by  $\text{PdCl}_2$  in the presence of Lewis acids ( $\text{AlCl}_3$  or  $\text{GaCl}_3$ ) from chlorobenzene under 10 bar of  $\text{CO}$  at  $120^\circ\text{C}$  [209]. In the absence of  $\text{PdCl}_2$ , 4-chlorobenzaldehyde was produced as the product of the Gattermann-

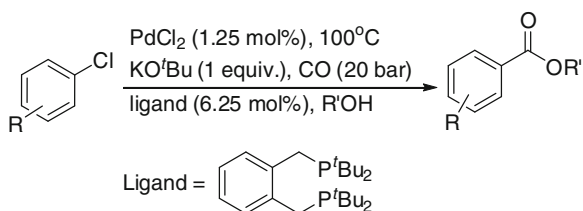


**Scheme 2.23**  $\text{Pd}(\text{OAc})_2$ -DCPP-catalyzed carbonylation of ArCl and ArOTs

Koch reaction, which is promoted by  $\text{AlCl}_3$  [210]. Activated aryl chlorides can also give the corresponding carbonylated products in low to moderate yields in ionic liquids using Pd-benzothiazole carbene 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**  $\text{PdCl}_2$ -BDTBPMB-catalyzed carbonylation of activated ArCl



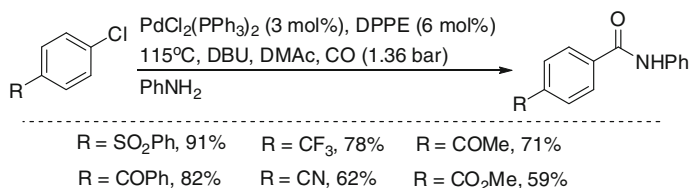
chlorides; electron-rich aryl chlorides were not effectively amidated, even after adding iodide (Scheme 2.25).

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.

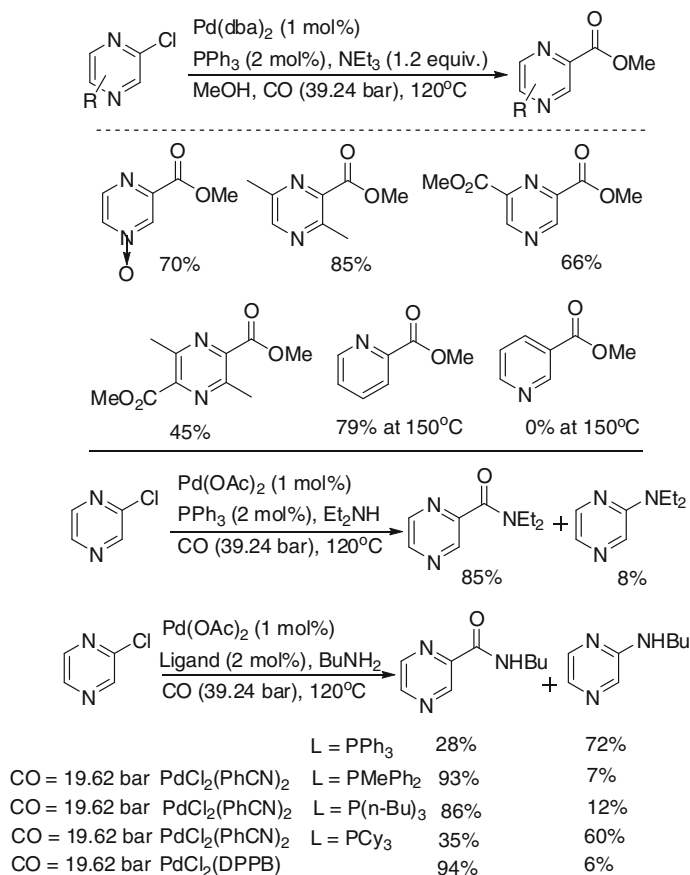
In 1984 Head and colleagues reported a palladium-catalyzed carbonylative synthesis of heterocyclic esters from the corresponding halides [213]. The main substrates are heterocyclic bromides; one example of heterocyclic chloride was also described. Using  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst under 7.9 bar of CO at 100 °C in ethanol with  $\text{NEt}_3$  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  $\text{Pd}(\text{OAc})_2$  (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  $\text{PdCl}_2(\text{PPh}_3)_2$ , 10 mol% of  $\text{PPh}_3$ , in methanol with  $\text{NEt}_3$  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  $\text{PdCl}_2(\text{PPh}_3)_2$  (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 methoxycarbonylation of 2-chloropyrazine,  $\text{PPh}_3$  and DPPE gave excellent yields of ester while tri-*n*-butylphosphine or tricyclohexylphosphine was not effective. With 1 mol% of  $\text{Pd}(\text{dba})_2$ , 2 mol% of  $\text{PPh}_3$ , at 120 °C under 39.24 bar of CO, chloropyrazines were easily carbonylated, including *N*-



**Scheme 2.25**  $\text{PdCl}_2(\text{PPh}_3)_2$ -DPPE-catalyzed carbonylation of activated ArCl

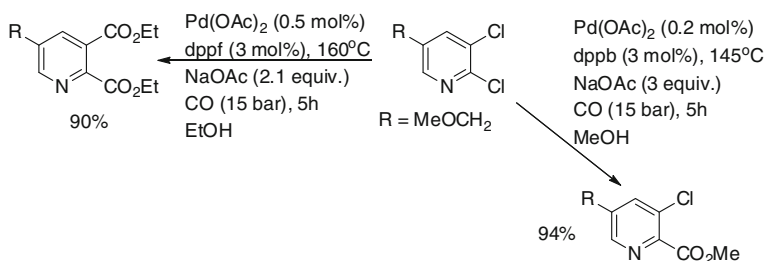


**Scheme 2.26** Palladium-catalyzed carbonylation of 2-chloropyridines

oxide. The reactivity of substrates increases in the order as: 2-chloropyridine > 2-chloropyridine  $\gg$  3-chloropyridine. In the aminocarbonylation of 2-chloropyridine, 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 dicarbonylation of 2,3-dichloropyridines (Scheme 2.27) [219, 220]. The choice of base and ligand plays a crucial role in the carbonylation. When  $\text{Na}_2\text{CO}_3$  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 alkoxy carbonylation 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].  $\text{PdCl}_2(\text{PCy}_3)_2$  was found to be the only efficient catalyst.  $\text{Ru}_3(\text{CO})_{12}$  and ammonium formate improved the yield and selectivity.

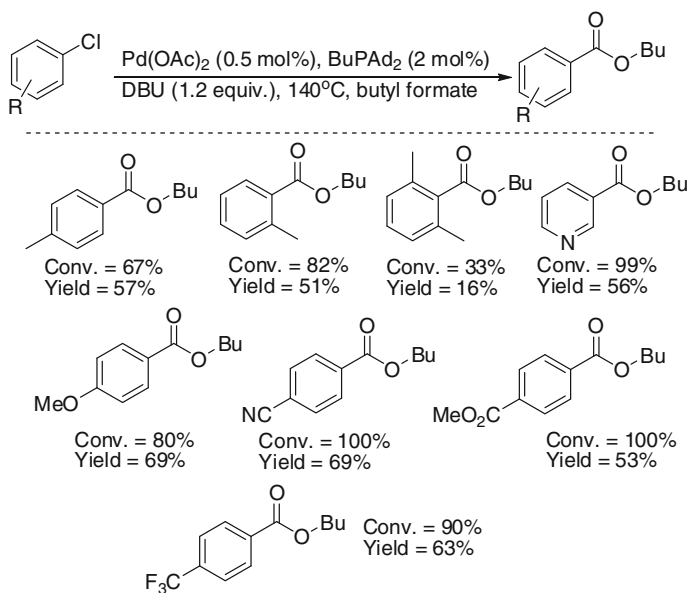
More recently, an improved protocol for palladium-catalyzed alkoxy-carbonylation of aryl chlorides with alkyl formates was developed by Beller and colleagues [225]. In the presence of palladium(II) acetate/*n*-butylbis(1-adamantyl)phosphine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, for 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  $\text{Mo(CO)}_6$  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  $[(t\text{-Bu})_3\text{P}]\text{HBF}_4$  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  $\text{Mo(CO)}_6$  as a solid carbon monoxide source.

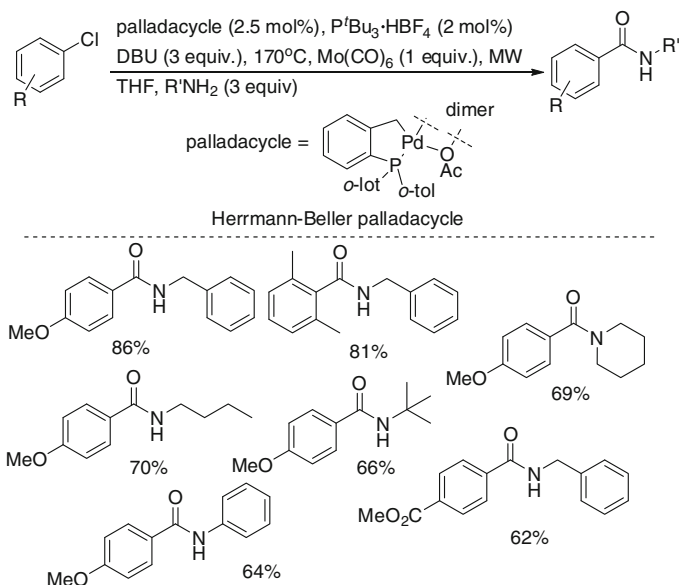
In addition to intermolecular carbonylations, there are intramolecular reactions that allow for the synthesis of various heterocycles. As a prime example, the intramolecular alkoxy- or aminocarbonylation (cyclocarbonylation) of hydroxyl- or amino-substituted aryl/vinyl halides enables the synthesis of 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  $\text{PdCl}_2(\text{PPh}_3)_2$  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].

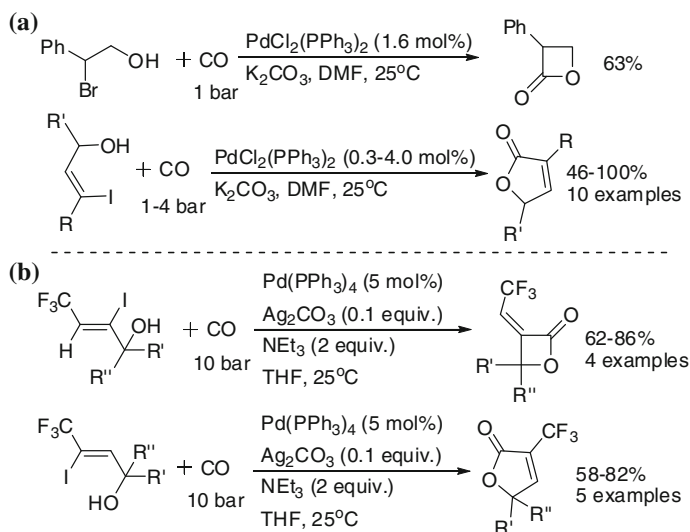
Shibasaki and colleagues reported the asymmetric synthesis of  $\alpha$ -methylene lactones starting from prochiral alkenyl halides in 1991 [232]. In the presence of



**Scheme 2.28**  $\text{Pd}(\text{OAc})_2/\text{BuPAd}_2$ -catalyzed carbonylation of aryl chlorides



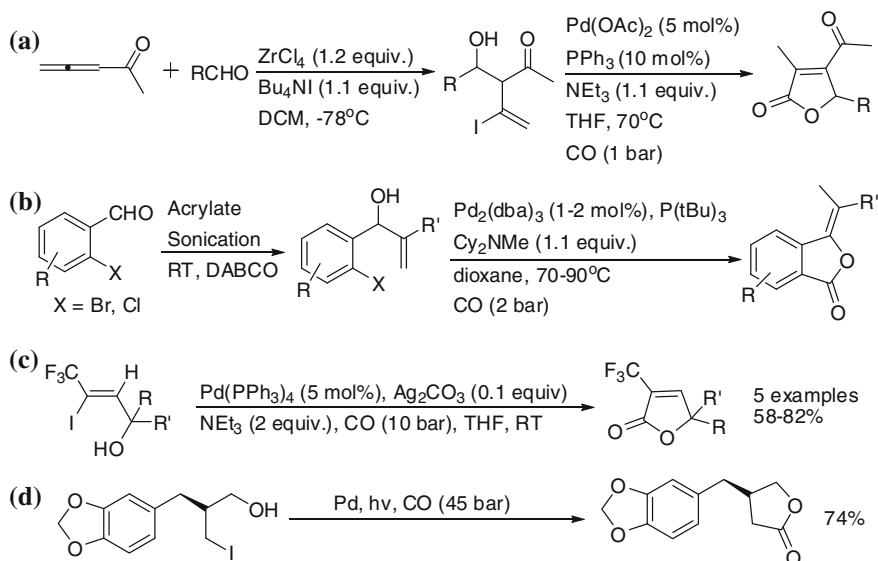
**Scheme 2.29** Palladacycle-catalyzed carbonylation of aryl chlorides



**Scheme 2.30** Palladium-catalyzed carbonylative syntheses of lactones

5 mol% of  $\text{Pd}(\text{OAc})_2$  and chiral ligands [(*S,S*)-chiraphos], under 1 bar of CO, the reaction was completed in one hour at 80 °C in DMSO with  $\text{K}_2\text{CO}_3$  as the base. In 1994, Negishi's group reported on the palladium-catalyzed cyclic carbometallation-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  $\text{ZrCl}_4$  as a catalyst in good yields. These 3-iodohomoallylic alcohols can be further transformed into  $\alpha,\beta$ -unsaturated  $\gamma$ -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(*5H*)-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,  $\alpha$ -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.

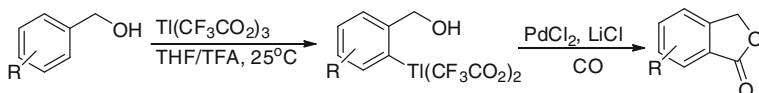
Larock and Fellows reported on the thallation-carbonylation of benzyl alcohols in 1982 [241]. Thallium (III) trifluoroacetate was used for the ortho-thallation of



**Scheme 2.31** Palladium-catalyzed cyclocarbonylations

arenes, which are subsequently carbonylated with 10 mol% of  $\text{PdCl}_2$ , 2 equivalents of  $\text{LiCl}$ , and  $\text{MgO}$  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  $\text{Pd}(\text{OAc})_2$  and  $\text{PPh}_3$  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



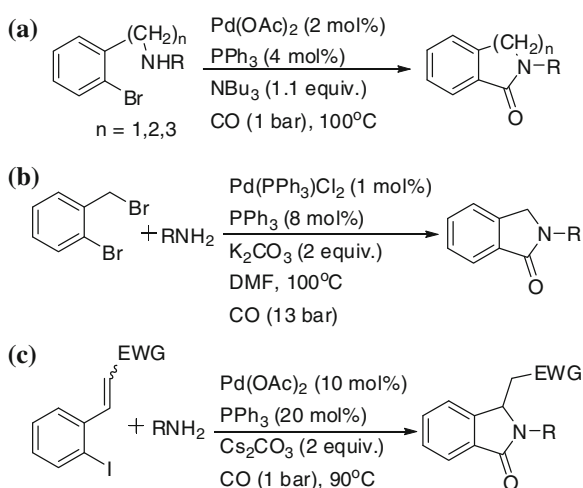
**Scheme 2.32** Thallation-carbonylation of arenes



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  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{PPh}_3$  as the catalyst system and  $\text{NEt}_3$  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

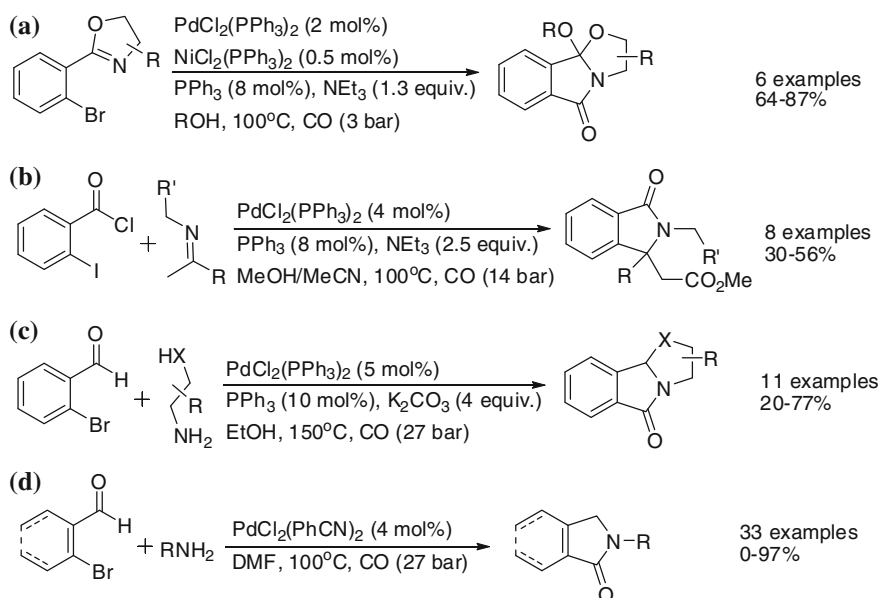
**Scheme 2.33** Palladium-catalyzed carbonylative synthesis of isoindolin-1-ones



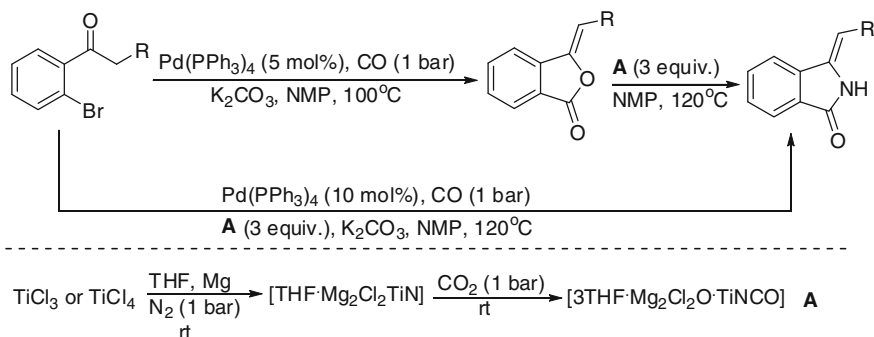
intramolecular acylpalladation to the imine gives the alkylpalladium(II) intermediate. Subsequent hydrogenolysis with molecular hydrogen leads to the isoindolin-1-one. It is assumed that hydrogen is produced by the reaction of CO with H<sub>2</sub>O generated in the initial condensation stage.

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<sub>2</sub> 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



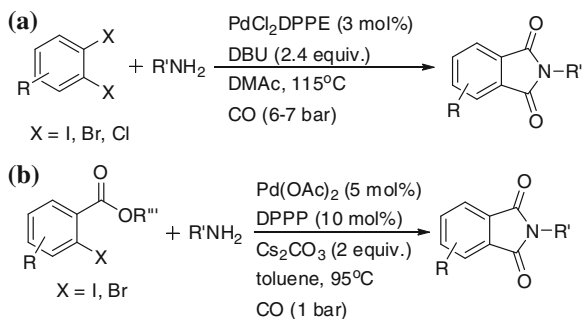
**Scheme 2.35** Palladium-catalyzed carbonylative synthesis of isoindolin-1-ones

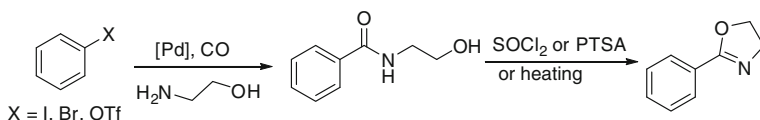
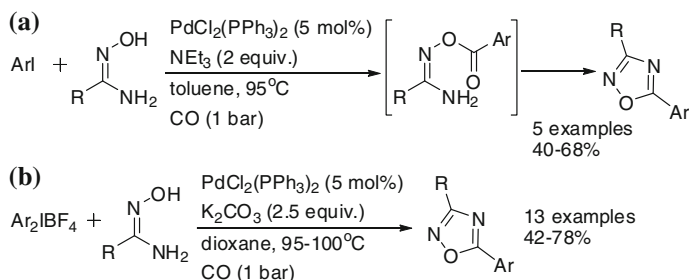
functional groups and excellent yields of products were obtained. The recyclability of the catalytic system was also investigated. Larock's group developed the straightforward carbonylation of *o*-halobenzoates and primary amines to phthalimides [266]. This method gave the corresponding products in good 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  $\text{Mo(CO)}_6$  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  $\alpha,\beta$ -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



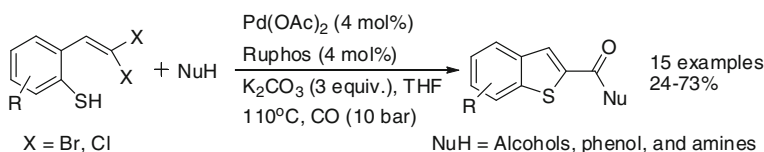
**Scheme 2.37** Palladium-catalyzed carbonylative syntheses of oxazolines**Scheme 2.38** Palladium-catalyzed carbonylative syntheses of oxadiazoles

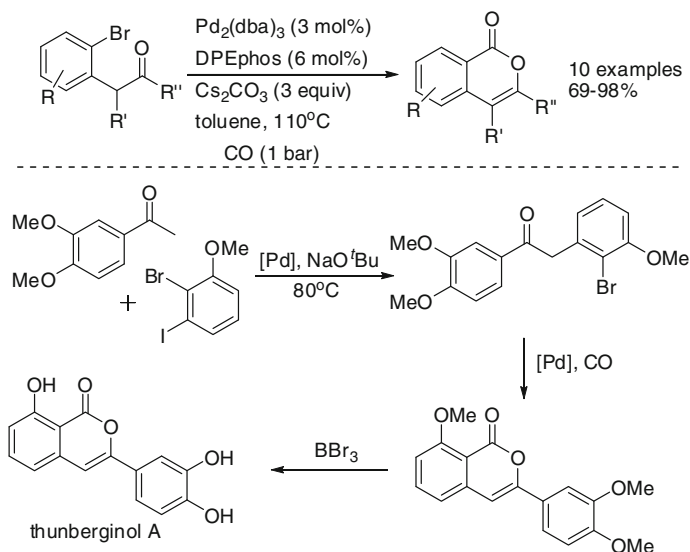
Afterwards, Chen and Zhou described a similar reaction with diaryliodonium salts as starting materials (Scheme 2.38b) [272].

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 alkoxy-carbonylation or aminocarbonylation as the key step (Scheme 2.41) [275–279]. Starting from the

**Scheme 2.39** Palladium-catalyzed carbonylative synthesis of benzothiophenes

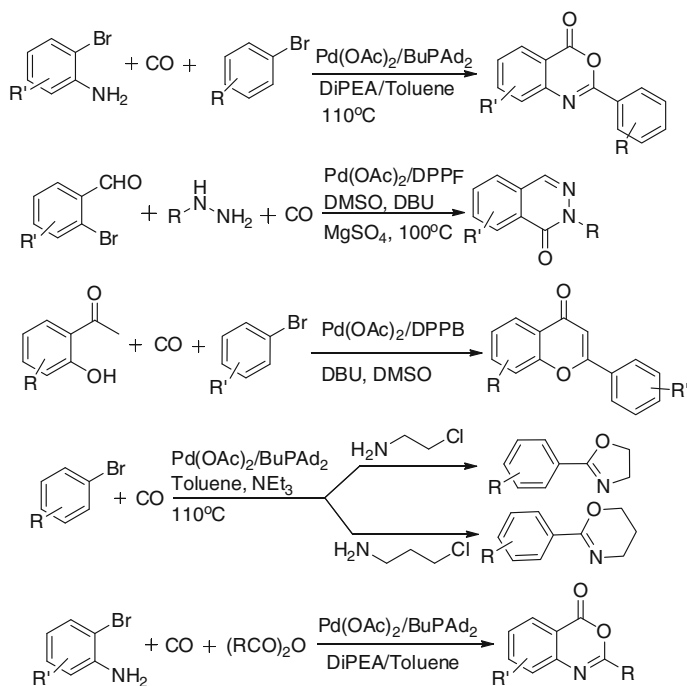


**Scheme 2.40** Palladium-catalyzed carbonylative synthesis of isocumarins

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

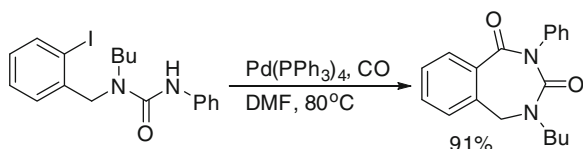
While most of the carbonylative cyclizations focused on the formation of five- and six-membered rings, there are also a few examples known for the preparation of larger rings. For example, in 1999 the palladium-catalyzed synthesis of a 2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepine-1,3-dione derivative was reported by Bocelli et al. [280]. Using 1-butyl-1(*o*-iodobenzyl)-3-phenylurea as a starting material at  $80^\circ\text{C}$  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  $\text{PdI}_2$  and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-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].



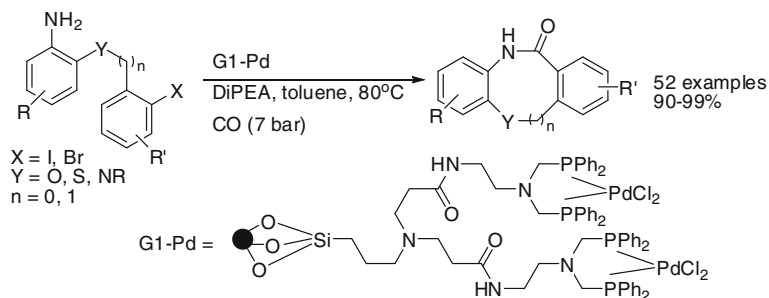
**Scheme 2.41** Carbonylative syntheses of heterocycles

**Scheme 2.42** Palladium-catalyzed carbonylative synthesis of benzodiazepinedione

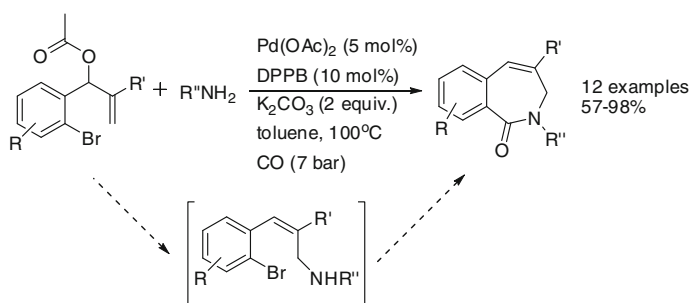


More recently, Alper and colleagues described a convenient protocol for the synthesis of substituted benzazepine derivatives (Scheme 2.44) [286]. This protocol is based on the sequential palladium-catalyzed allylic amination and a subsequent intramolecular carbonylation reaction. The substrates were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

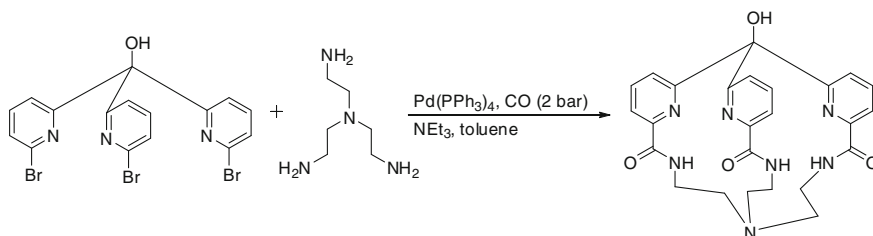
Larock and Cho developed a palladium-catalyzed intramolecular cyclocarbonylation of hydroxyl-substituted 3-iodofurans leading to the corresponding lactone-containing furans [287]. The 3-iodofurans are readily prepared by iodocyclization of 2-(1-alkenyl)-2-alken-1-ones in the presence of various diols. 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 macrospheptide 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

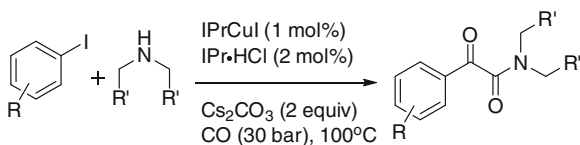


**Scheme 2.45** Palladium-catalyzed carbonylative synthesis of H<sub>3</sub>L

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



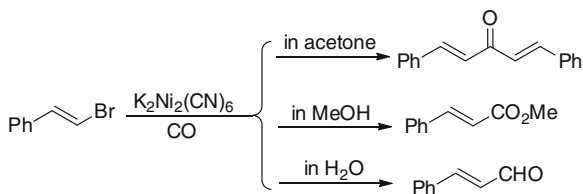
with  $\text{FeCl}_2$  as promoters, were needed. Later on they found that  $\text{Co}_2(\text{CO})_8$  can effectively transform benzyl chlorides and bromides to the corresponding acid products in an aqueous system.  $\eta^1$ -Benzyl-,  $\eta^3$ -Benzyl-, and ( $\eta^1$ -phenylacetyl)cobalt carbonyls were investigated as intermediates of this process.

In 1970 Hashimoto published a report on the reaction of potassium hexacyanodinitrile 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*- $\beta$ -bromostyrene was transformed into methyl *trans*-cinnamat. Surprisingly, cinnamaldehyde was also formed in a 10 % yield (Scheme 2.47). The reaction of nickel carbonyl  $[\text{Ni}(\text{CO})_4]$  with organic halides was studied by Bauld in 1963 [296]. Aryl iodides were reacted with  $\text{Ni}(\text{CO})_4$  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  $\text{Ni}(\text{CO})_4$  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  $[\text{Ni}(\text{CO})_3\text{CN}^-]$  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  $\text{Mo}(\text{CO})_6$ . 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



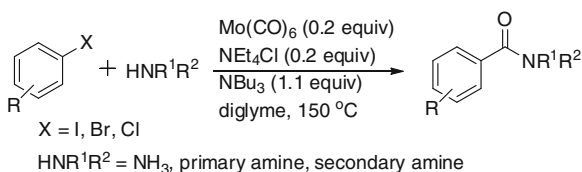


**Table 2.1** Nickel-catalyzed carbonylation of organo halides $R \times \longrightarrow [5N \text{ NaOH, solvent PTC}]Ni(CN)_2 \cdot 4H_2O (10 \text{ mol } \%) RCO_2H$ 

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

[a] in toluene,  $C_{16}H_{33}N(CH_3)_3^+Br^-$ 

[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.

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