Palladium Catalysis

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Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds

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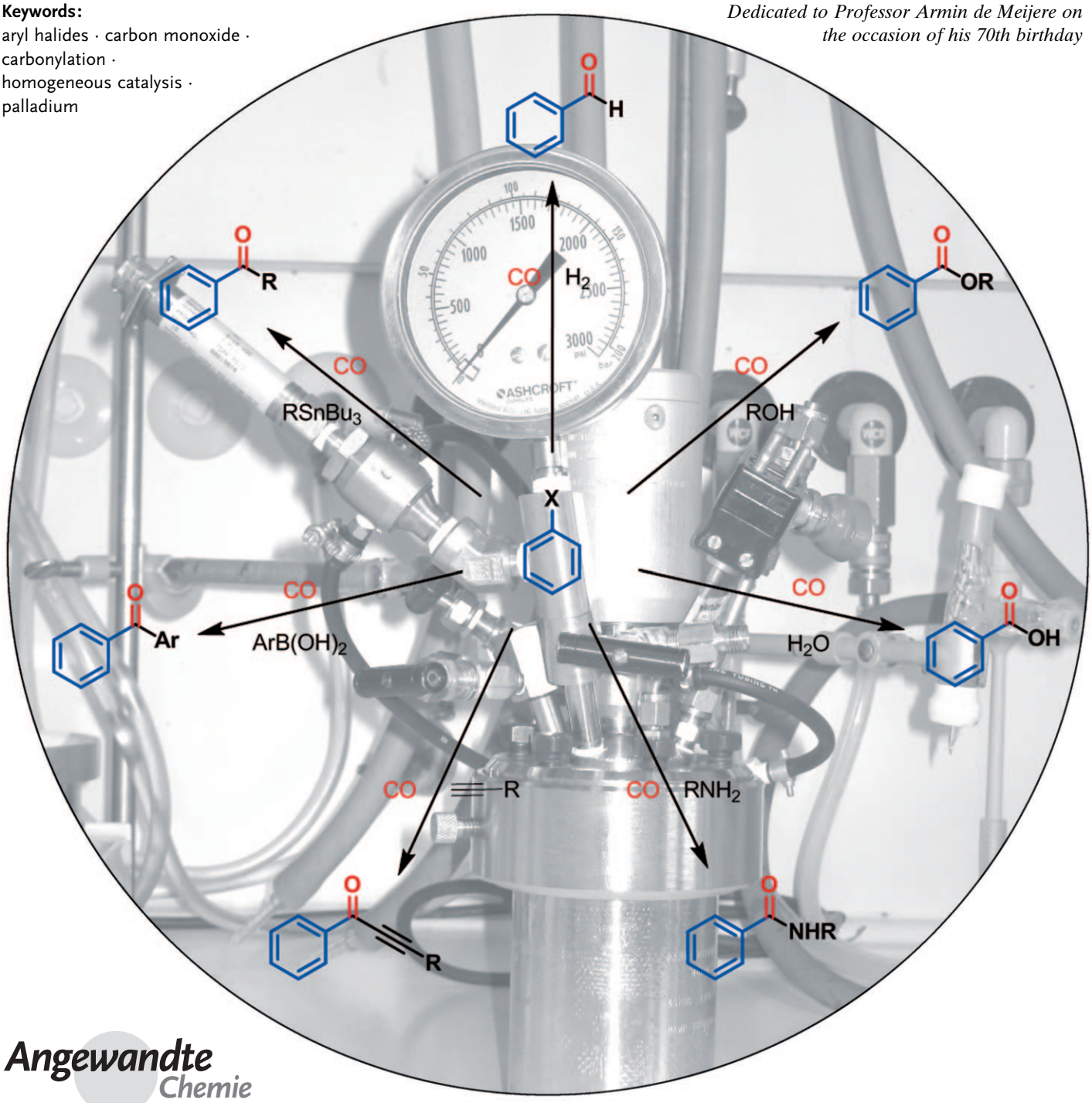
Keywords:
aryl halides · carbon monoxide · carbonylation · homogeneous catalysis · palladium

Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday



Palladium-catalyzed carbonylation reactions of aromatic halides in the presence of various nucleophiles have undergone rapid development since the pioneering work of Heck and co-workers in 1974, such that nowadays a plethora of palladium catalysts are available for different carbonylative transformations. The carboxylic acid derivatives, aldehydes, and ketones prepared in this way are important intermediates in the manufacture of dyes, pharmaceuticals, agrochemicals, and other industrial products. In this Review, the recent academic developments in this area and the first industrial processes are summarized.

From the Contents

1. Introduction

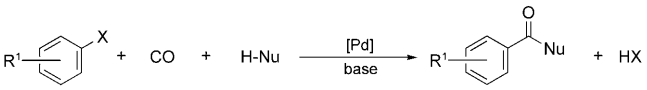
The development of environmentally benign and efficient synthetic methods continues to be a central goal of current research in chemistry. In this regard, catalysis and organometallic chemistry are key techniques for achieving these objectives and for contributing to a "greener" chemistry in the future. Among the different catalytic reactions, the refinement of readily available feedstocks to more-functionalized products is of particular importance. Prime examples for such transformations are carbonylation processes, which make use of carbon monoxide—currently the most important C_1 building block. Hence, carbonylations represent industrial core technologies for converting various bulk chemicals into a diverse set of useful products of our daily life. For example, the conversion of olefins—the basic raw materials for the chemical industry—by carbonylation gives access to more valuable products such as aldehydes, alcohols, and carboxylic acid derivatives. Despite large-scale applications in industry, reactions with carbon monoxide are comparatively seldom used in more complex organic syntheses. This might be because of the general reluctance to use gases as reagents and the necessity to use high-pressure equipment, although a number of catalytic carbonylations proceed at ambient to low pressures (<5 bar). However, little attention is paid to carbonylation chemistry in academic research.

Arenes and heteroarenes are vital intermediates in the manufacture of agrochemicals, dyes, pharmaceuticals, and other industrial products, and thus there is continuing interest in easier and cost-efficient synthetic methods. In the past decades transition-metal-catalyzed coupling reactions of aryl halides with all types of nucleophiles have emerged as the most important tool for the production of substituted arenes.[1] This Review summarizes the recent work in the area of palladium-catalyzed carbonylation reactions of aryl halides and related compounds. In particular, coupling reactions of aryl-X compounds to give carboxylic acid derivatives, aldehydes, and ketones are described. The basics of this transformation were established in the mid-1970s by the pioneering work of Heck and co-workers, and the topic has notably developed since then. The present Review covers the main contributions to this area published between 2000 and 2008. While some previous studies have already been summarized,[2] there exists no recent compilation of palladium-catalyzed carbonylation reactions of aromatic halides.[3,121]

2. Carbonylation of Aromatic (Pseudo)Halides to Carboxylic Acid Derivatives

The palladium-catalyzed carbonylation of aryl–X compounds to give carboxylic acid derivatives is becoming a valuable tool in organic synthesis. While toluene derivatives are the feedstock for the industrial synthesis of simple benzoic acid derivatives, for example, monomers such as terephthalic acid for polyesters, organic halides are attractive precursors for higher-value fine chemicals and complex synthetic intermediates.

The term carbonylation covers a large number of closely related reactions that all have in common that carbon monoxide is incorporated into a substrate by the addition of CO to an aryl-, benzyl- or vinylpalladium complex in the presence of various nucleophiles (Scheme 1). In general, aromatic halides are treated with an appropriate nucleophile in a carbon monoxide atmosphere in the presence of a catalytic amount of a palladium complex, whereby, the leaving group X is formally replaced by the nucleophile with incorporation of one or two molecules of carbon monoxide. Typically, the reactions take place at 60–140 °C and 5–60 bar of carbon monoxide, and require a stoichiometric amount of base to regenerate the catalyst. In line with the C–X bond energy, the rate of the oxidative addition of the



1 X = Cl, Br, I, OSO_2R^2, N_2^+, ... Nu = OH, OR^3, NR^4R^5, ... 2

Scheme 1. General scheme for the carbonylation of aryl–X compounds.

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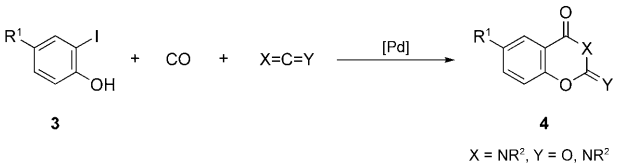
organic halide to an electronically unsaturated metal complex decreases in the order: C–I > C–OTf ≥ C–Br ≫ C–Cl ≫ C–F.[2b] In addition to (hetero)aryl halides, alkenyl–X compounds[4] as well as steroidal[5] derivatives have been successfully employed as reagents.

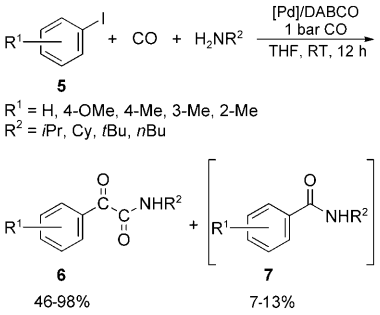
Not only carboxylic acids, esters, and amides are accessible by carbonylation, but anhydrides, acid fluorides, aldehydes, and ketones can also be easily synthesized. Which of these products is obtained depends on the nucleophile: water (hydroxycarbonylation), alcohols (alkoxycarbonylation), amines (aminocarbonylation), carboxylate salts, fluorides, hydrides, or organometallic reagents can be used. A variety of carbonylation products can be prepared from the same aromatic substrate simply by changing the nucleophile, an advantage with respect to biologically active compound libraries. Parallel pressure devices are nowadays commercially available to perform such reactions efficiently.

In addition to intermolecular carbonylations, intramolecular reactions are also possible, which allow for the synthesis of heterocycles. A prominent example is the intramolecular alkoxy- or aminocarbonylation (cyclocarbonylation) of hydroxy- or amino-substituted aryl/vinyl halides which enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, and other heterocycles.[6] The palladium-catalyzed cyclocarbonylation of *o*-iodoanilines/*o*-iodophenols with unsaturated halides/triflates or heterocumulenes (such as isocyanates, carbodiimides, and ketenimines) has been applied for the synthesis of different benzoxazinones (Scheme 2).[7]

A special carbonylation variant is the palladium-catalyzed double carbonylation, which usually requires high CO pressures and competes with monocarbonylation. The introduction of two molecules of carbon monoxide enables α-keto acids, esters, or amides to be attained from (hetero)aryl, alkenyl, and alkyl halides.[7a,8] A significant improvement of the existing protocols was reported in 2001 by Uozumi et al. They discovered that 1,4-diazabicyclo[2.2.2]octane (DABCO) is a superior base for the highly selective double carbonylation of aryl iodides with primary amines (Scheme 3).[9] Thus, the desired α-keto amides **6** were prepared under very mild conditions (1 bar CO, 25 °C) in the presence of a simple palladium–triphenylphosphane complex.



Scheme 2. Palladium-catalyzed cyclocarbonylation of *o*-iodophenols with heterocumulenes to give benzoxazinones.[7d]



Scheme 3. Palladium-catalyzed double carbonylation of aryl iodides with primary amines by Uozumi et al.[9]

2.1. Synthesis of Carboxylic Acid Derivatives from Aryl Bromides or Iodides

Until recently (hetero)aromatic bromides and iodides were most widely employed as starting materials in intermolecular alkoxycarbonylation,[10,11] aminocarbonylation,[11,12] and hydroxycarbonylation reactions.[13] The first palladium-catalyzed alkoxycarbonylation was described by Heck and coworkers in 1974.[14] Aryl and vinyl iodides and bromides were

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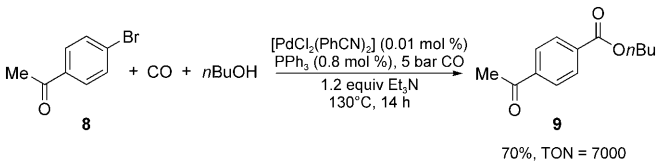
Matthias Beller studied chemistry at the University of Göttingen, Germany, and completed his PhD in 1989 in the group of Prof. L. Tietze. He then spent one year with Prof. K. B. Sharpless at MIT on a Liebig scholarship. From 1991 to 1995, he worked at Hoechst AG, where he ultimately directed the "Homogeneous Catalysis" project. In 1996 he moved to the TU München as C3 Professor and then in 1998 to the University of Rostock to head the IfOK. Since 2006 he has been director of the Leibniz-Institute for Catalysis. He has received the German Federal Cross of Merit and is head of the GDCH working group "Sustainable Chemistry".

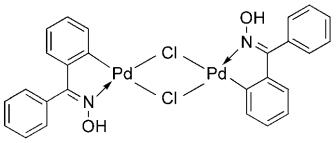
treated with carbon monoxide (1 bar) in *n*-butanol at 100 °C to synthesize carboxylic acid *n*-butyl esters. In general, good yields were obtained in the presence of 1.5 mol % of either $[PdX_2(PPh_3)_2]$ or the respective halo(aryl)bis(triphenylphosphane)palladium(II) complex in the presence of a slight excess of tri-*n*-butylamine as the base. Notably, the reaction without added phosphane ligands was limited to aryl iodides. Since that pioneering report, gradual improvements in terms of solvents, bases, and catalyst systems, particularly ligands, have been made, which have significantly broadened the scope of the method.

Notable progress has also been achieved with regard to catalyst productivity. In a detailed study on the palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone (**8**), reaction parameters such as temperature, carbon monoxide pressure, solvents, bases, different catalyst precursors, and the ligand/palladium ratio were investigated.[15] An almost quantitative yield of butyl ester **9** was achieved at low pressure (5 bar CO) and 100 °C in the presence of 0.3 mol % $[Pd(PPh_3)_4]$ and three equivalents of Et_3N by using *n*-butanol as the solvent. The optimization resulted in the highest turnover number (TON up to 7000) known until then for the alkoxycarbonylation of an aryl halide (Scheme 4).



Scheme 4. Optimized protocol for the palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone.[15]

Another way to improve the catalyst productivity in coupling reactions is the use of structurally more-stable catalyst precursors which slowly release a highly active species. For this purpose, a covalently bonded, cyclometalated dimeric palladium(II) catalyst was synthesized by Ramesh et al.[16] High selectivity and excellent yields for the reactions of various aryl iodides with aliphatic alcohols and phenols were maintained by utilizing a dimeric oxime-type palladacycle **10** (Figure 1). Apparently no by-products were detected and the complex was stable even at high temperature (120 °C) and 10 bar of carbon monoxide.



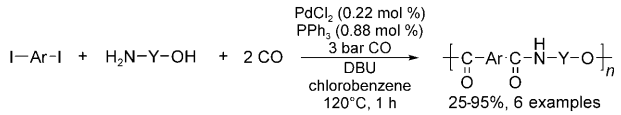
10

Figure 1. The dimeric oxime–palladium(II) catalyst **10**.[16]

Other attempts to develop more efficient and practicable catalysts for the alkoxycarbonylation of aromatic iodides include the use of a combined bimetallic ruthenium/palladium catalyst[17] and immobilized palladium complexes.[18] Advantageously, the immobilized catalysts could be removed effectively from the reaction mixture by a simple filtration process and could be reused several times with only a minor loss of activity.

More recently, the methoxycarbonylation of bromoanisoles and unprotected bromoanilines, which constitute more challenging substrates, was improved by Albaneze-Walker et al.[19] High yields (> 91 %) were achieved, except for *p*-bromoaniline (50 %), by employing 3 mol % $PdCl_2$/*rac*-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap) at low pressure (4.5 bar CO, 100 °C).

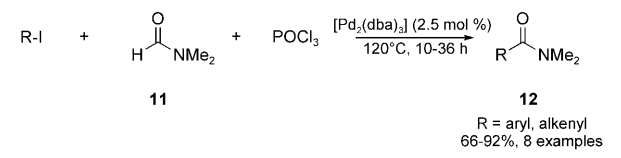
While most of the previous studies focused on monocarbonylation reactions, it has also been demonstrated that oligomerizations and polycondensations can be achieved. For example, a palladium-catalyzed carbonylation/polycondensation reaction of aromatic diiodides and aminohydroxy compounds was described by Chaudhari and co-workers (Scheme 5).[20] Thus, alternating polyesteramides were prepared in chlorobenzene with 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) as the base under 3 bar of carbon monoxide at 120 °C.



Scheme 5. Polyesteramide synthesis by catalytic carbonylation and polycondensation; Y = organic unit.[20]

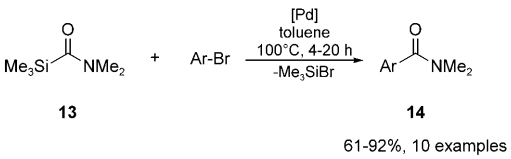
The first palladium-catalyzed amidation reaction of aryl–X compounds was again developed by Heck and co-workers. They demonstrated that secondary and tertiary amides are conveniently produced by carbonylation.[21] They treated (hetero)aryl bromides and vinyl iodides with primary or secondary amines under 1 bar CO pressure at 60–100 °C in the presence of 1.5 mol % $[PdX_2(PPh_3)_2]$, and found that stoichiometric amounts of a tertiary amine were required to neutralize the formed acid when weakly basic amines were employed as nucleophiles.

Aminocarbonylations in the absence of carbon monoxide[22] and base were realized in 2002 by adding phosphoryl chloride to the reaction of aryl iodides with *N*,*N*-dimethylformamide (**11**).[23] Good to high yields were obtained in toluene at 120 °C by utilizing 2.5 mol % $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone) as catalyst (Scheme 6). The generated Vilsmeier reagent was suggested to be essential for the reaction to take place. Another example of a palladium-catalyzed CO-free carbonylation was published by Cunico and Maity.[24] Depending on the substrate, 2 mol % of either



Scheme 6. Aminocarbonylation of aryl iodides without the addition of CO gas.[23]

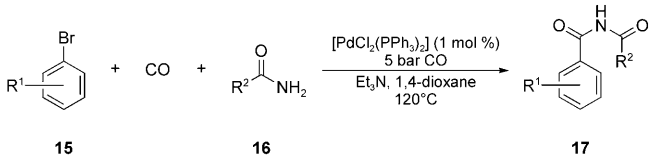
$[Pd(PPh_3)_4]$ or $[Pd(PtBu_3)_2]$ was used to catalyze the reaction of heteroaryl and aryl bromides with *N*,*N*-dimethylcarbamoyl(trimethyl)silane (**13**; Scheme 7). Thus, tertiary amides



Scheme 7. Direct carbamoylation of aryl bromides.[24]

can be prepared in good yields by direct carbamoylation. Notably, chlorobenzene, 1-chloro-4-methoxybenzene, and iodobenzene gave the desired products **14** in 74, 78, and 60% yield, respectively. A solid-phase palladium-catalyzed aminocarbonylation of aryl bromides or iodides was developed by utilizing $[Mo(CO)_6]$ as the carbon monoxide source.[25] In contrast to previous carbonylations with metal carbonyl compounds, these reactions proceeded under mild conditions in the absence of microwave irradiation.

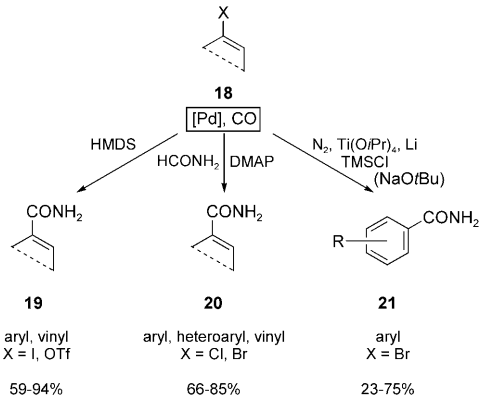
Several different research groups have investigated extending the scope of aminocarbonylations. As an example, carbonylation reactions of ferrocene derivatives in the presence of $Pd(OAc)_2/PPh_3$ were investigated by Skoda-Földes, Kollár, and co-workers.[26] They synthesized ferrocene amides and ferrocene α-ketoamides in good yields by palladium-catalyzed aminocarbonylation or double carbonylation of iodoferrocene at 40–50 bar CO. The selectivity of the reaction with less sterically hindered secondary amines is highly dependent on the reaction temperature. Thus, formation of double-carbonylated products was favored at 40–60 °C, whereas amides were produced almost exclusively at 100 °C.[26b,c] Analogous aminocarbonylation reactions of 1,1′-diiodoferrocene led to 1′-iodoferrocenecarboxamides and 1′-iodoferrocenylglyoxylic amide products.[26a] Schnyder and Indolese demonstrated that the scope of the aminocarbonylation could be expanded to the synthesis of unsymmetrical aroyl acyl imides **17** by treating aryl bromides with primary amides or sulfonamides under mild conditions (Scheme 8).[27] The best results were achieved with Et_3N as the base (58–72%).



Scheme 8. Synthesis of aroyl acyl imides by aminocarbonylation of aryl bromides.[27]

For the first time, nonprotected bromoindoles were converted directly into the corresponding indole carboxylic amides by palladium-catalyzed carbonylation.[28] At 25 bar CO and 130 °C, the use of $[PdCl_2(PhCN)_2]$, 1,1′-bis(diphenylphosphanyl)ferrocene (dppf), and Et_3N was found to give the highest yields (>90%) for the reaction of indoles with piperazine and morpholine derivatives, *n*-butylamine, and ethanol. Notably, the free carboxylic acid was also directly accessible in 67% yield. Furthermore, potentially bioactive amphetamine analogues were obtained in high yields by the optimized protocol.

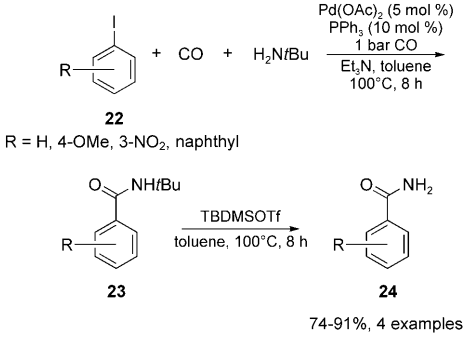
Only a few routes towards primary amides have been described to date (Scheme 9). Morera and Ortar used hexamethyldisilazane (HMDS) as an ammonia source in the



Scheme 9. Different carbonylation routes towards primary amides. TMS = trimethylsilyl.[29–31]

carbonylation of aryl iodides and triflates.[29] The desired products **19** were isolated in high yields after hydrolysis. In addition, Indolese and co-workers reported the efficient aminocarbonylation of aryl bromides with formamide at 5 bar carbon monoxide. Here, the use of 4-(dimethylamino)-pyridine (DMAP) as the base was the key factor for success.[30] Primary benzamides **21** were also prepared from aryl bromides by using CO and a titanium–nitrogen complex in conjunction with NaO*t*Bu in the absence of base.[31]

Primary amides **24** and ketoamides were synthesized in good yields by a more traditional carbonylation/deprotection sequence in the presence of $Pd(OAc)_2/2PPh_3$ (Scheme 10).[32] Initially, aryl iodides were treated with *tert*-butylamine under 1 bar CO. Ketoamides resulting from double carbonylation were mainly produced at a temperature of 60 °C, whereas



Scheme 10. Synthesis of primary amides by palladium-catalyzed aminocarbonylation followed by deprotection.[32]

formation of the amides **23** was favored at 100 °C. After isolation, the products were heated with one equivalent of *tert*-butyldimethylsilyl triflate (TBDMSOTf) in toluene at 100 °C to obtain the corresponding primary derivatives **24**.

We prepared various aromatic and heteroaromatic esters, amides, and acids from the corresponding bromoarenes by making use of a novel catalyst system consisting of $Pd(OAc)_2$ and commercially available di-1-adamantyl-*n*-butylphosphane[33] (cata*CX*ium A, **25**; Figure 2).[34] Compared to most known carbonylation protocols, the reactions proceeded at comparably low catalyst loadings (< 0.5 mol % Pd) in the presence of carbon monoxide (5 bar) to give the desired compounds in excellent yields. Most recently, this catalyst system was applied to synthesize potentially bioactive 3-alkoxycarbonyl- and 3-aminocarbonyl-4-indolylmaleimides from 3-bromoindolylmaleimide **26** (Scheme 11).[35]

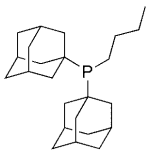


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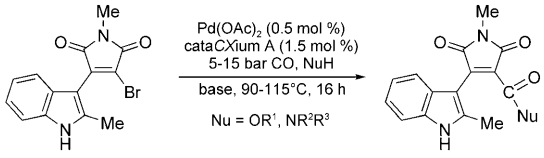
Figure 2. Cata*CX*ium A (**25**).

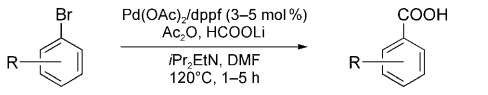


26 **27**

25-70%, 7 examples

Scheme 11. Carbonylation of 3-bromoindolylmaleimide **26**.[35]

Cacchi and et al. developed a protocol for the hydroxycarbonylation of aryl and vinyl halides or triflates in which a combination of acetic anhydride and lithium formate was used as a condensed source of carbon monoxide.[36] The transformations tolerated a wide range of functional groups, including ether, ketone, ester, and nitro groups. In 2006, the same carbonyl source was adapted for the palladium-catalyzed hydroxycarbonylation of aryl bromides (Scheme 12).[37]



28 **29**

R = 4-Me, 4-Ph, 4-COOEt, 4-Br, 4-Cl, 4-F, 4-CF_3, ... 61-97%, 12 examples

Scheme 12. Hydroxycarbonylation of aryl bromides with acetic anhydride/lithium formate as the carbonyl source.[37]

The reaction of bromoarenes with acetic anhydride and lithium formate proceeded smoothly in DMF at 120 °C in the presence of 3–5 mol % $Pd(OAc)_2$ and dppf (Pd/ligand 1:1) to provide carboxylic acids **29** in good yields. The protocol was also applied to the synthesis of terephthalic acid from 1,4-dibromobenzene (75 %).

Cacchi et al. subsequently presented an efficient hydroxycarbonylation of aryl iodides in which recoverable carbon aerogels doped with palladium nanoparticles were used as the catalyst.[38] High to excellent yields were maintained in DMF at 100 °C with acetic anhydride/lithium formate together with lithium chloride and *N*,*N*-diisopropylethylamine as the base. The catalyst could be reused up to 12 times in the reaction of *p*-iodotoluene without any appreciable loss of activity.

Intermolecular carbonylation reactions of aryl iodides, bromides, and triflates have been applied in numerous syntheses of biologically active compounds and natural products.[39] A compilation of some selected examples is shown in Figure 3. For better understanding the bond formed in the carbonylation step is marked.

Palladium-catalyzed carbonylations of arene diazonium salts[40] and diaryl iodonium salts are less common.[41] While aryl triflates are used regularly as substrates,[42] interestingly, only three palladium-catalyzed carbonylation reactions of aryl *p*-toluenesulfonates (tosylates) are known to date.[43–45] The first successful alkoxycarbonylation of 4-substituted aryl tosylates was described by Kubota et al. in 1998.[43] The reactions were performed either in methanol or in ethanol in the presence of $PdCl_2$ and 1,3-bis(diphenylphosphanyl)propane (dppp) under 10 bar CO at 150 °C. Unfortunately, only 4-acetylphenyl tosylate gave the desired ethyl ester in satisfying yield (81 %). Low conversions were observed for electron-rich or electronically neutral substrates. In 2006, Cai et al. utilized a catalyst system derived from $Pd(OAc)_2$ (4 mol %) and a Josiphos ligand (4.4 mol %) to synthesize ethyl benzoates from aryl arenesulfonates under 6 bar of carbon monoxide.[44] Yields of isolated products greater than 90 % were obtained for most aryl *p*-fluorobenzenesulfonates. The less-reactive aryl tosylates yielded ethyl benzoate, ethyl 4-methylbenzoate, ethyl 4-acetobenzoate, and ethyl 4-cyanomethylbenzoate in 92, 61, 96, and 93 %, respectively.

An active and efficient catalyst for the alkoxycarbonylation of aryl tosylates was disclosed recently by the research group of Buchwald.[45] Under mild conditions (80–110 °C, 1 bar CO), electron-rich, electron-poor, and heterocyclic tosylates **40** were treated with several primary alcohols in the presence of $Pd(OAc)_2$ and electron-rich, chelating 1,3-bis(dicyclohexylphosphanyl)propane (dcpp; Scheme 13). Clean conversion and no competing formation of ether by-products were observed when molecular sieves were added. Notably, different functional groups, for example, aldehyde, ketone, ester, or cyano were tolerated. Furthermore, the alkoxycarbonylation of aryl methylsulfonates (mesylates) was demonstrated for the first time (75–97 % yield).

The use of nonvolatile ionic liquids (ILs) as solvents in palladium-catalyzed carbonylations was demonstrated first by Tanaka and co-workers.[46] Compared to those obtained under standard conditions, higher yields for the alkoxycarbonylation of bromobenzene were obtained when 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) was employed as the reaction medium. Furthermore, the selectivity of 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 could be recycled seven times. Since this report, the replacement of traditional solvents by quaternary ammonium halides, imidazolium- or pyridinium-derived ILs has gained increasing importance.[47]

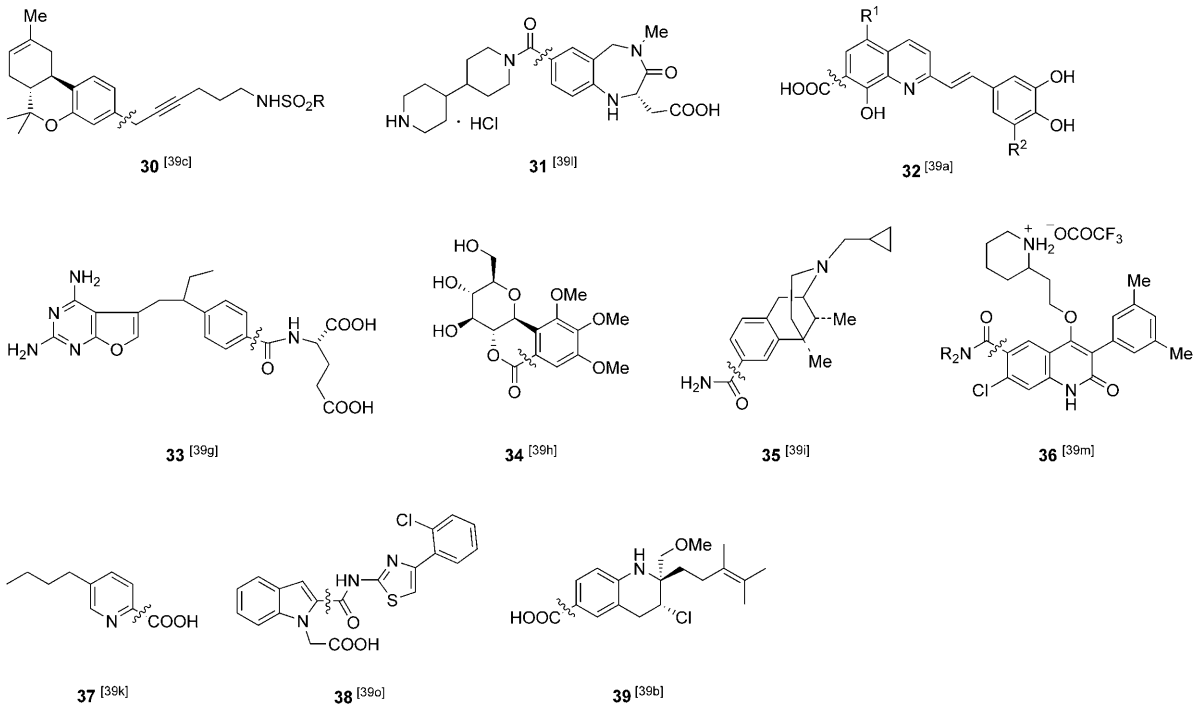
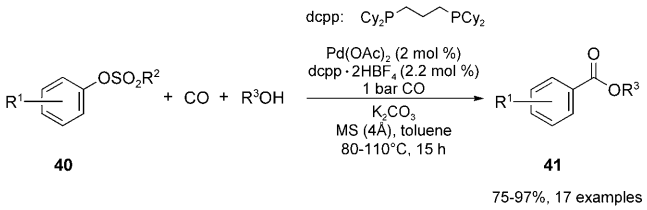
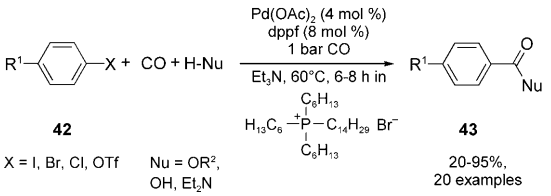


Figure 3. Examples of biologically active compounds synthesized by palladium-catalyzed alkoxy- and aminocarbonylations. (The bonds formed by carbonylation are indicated in each case.)



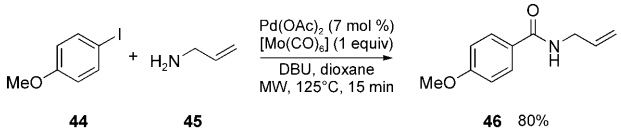
Scheme 13. Palladium-catalyzed alkoxycarbonylation of aryl tosylates and mesylates by Buchwald and co-workers.[45]

Recently, the phosphonium IL trihexyl(tetradecyl)phosphonium bromide has proven to be an effective reaction medium for different carbonylation reactions of aryl and vinyl bromides or iodides under mild conditions (Scheme 14).[48]



Scheme 14. Palladium-catalyzed carbonylation reactions in a liquid phosphonium salt as the solvent.[48]

Microwave-assisted palladium-catalyzed carbonylations of aryl–X compounds have been reported mainly by Larhed and co-workers.[49] These reactions were typically conducted in sealed vessels under microwave irradiation with either $[Mo(CO)_6]$ or formic acid derivatives as CO-releasing reagents. Alternatively, alkoxy- and hydroxycarbonylations of aryl iodides with gaseous carbon monoxide have been performed by employing pre-pressurized reaction vessels in conjunction with microwave heating.[50] Very recently, a microwave-promoted palladium-catalyzed aminocarbonylation of (hetero)aryl halides (X = I, Br, Cl) using $[Mo(CO)_6]$ and allylamine (**45**) as the nucleophile was also described.[51] Surprisingly, no side products resulting from the competing Heck reaction were detected. Aminocarbonylation was achieved for the first time on a larger laboratory scale (25 mmol) starting from 4-iodoanisole (**44**; Scheme 15). Microwave-assisted protocols have also found several applications in the synthesis of biologically active compounds.[52]



Scheme 15. Microwave-assisted aminocarbonylation on a 25 mmol scale. MW = microwaves.[51]

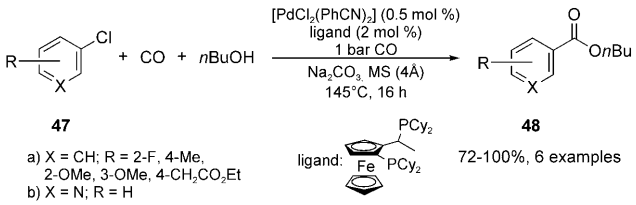
2.2. Synthesis of Carboxylic Acid Derivatives from Aryl Chlorides

Since aryl chlorides are often cheap, relatively inert, and widely available in bulk quantities, there still exists a considerable interest in replacing aryl bromides/iodides by the corresponding chlorides. However, it is well-known that chloroarenes show much lower reactivity because of the high stability of the carbon–chlorine bond. Hence, more efficient

catalyst systems and more severe conditions are required to activate these substrates towards oxidative addition[53] and carbonylation reactions. In the past, chloroarene(tricarbonyl)chromium complexes with reduced π-electron density were employed to effect the carbonylation of aryl chlorides with alcohols or amines at high pressure.[54] Milstein and co-workers utilized palladium complexes of the bulky and electron-rich bidentate ligand 1,3-bis(diisopropylphosphanyl)propane (dippp) to synthesize carboxylic acids, esters, and amides in high yields (5 bar CO).[55] However, the reactions still required comparably high temperatures (150 °C) and precautious handling of the pyrophoric ligand.

In another approach, PCy_3 and related ligands were applied to overcome the problem of the clustering and agglomeration of Pd atoms.[56] The combination of palladium on charcoal and $K_2Cr_2O_7$ afforded only low yields (20 %) for the carbonylation of a series of chloroarenes in methanol at 200 °C after 50 h.[57] A palladium-catalyzed aminocarbonylation of electron-deficient chloroarenes in the presence of 1,2-bis(diphenylphosphanyl)ethane (dppe) and a slight excess of sodium iodide under milder conditions was also described.[58]

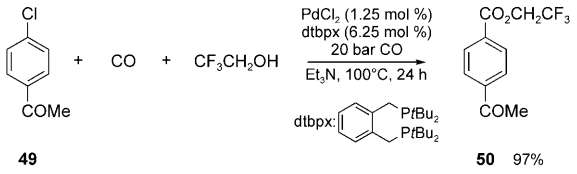
It was shown in our research group that the carbonylation of electron-deficient, electronically neutral, and electron-rich aryl chlorides **47** may take place at lower carbon monoxide pressure (Scheme 16).[59] A study of the reaction parameters



Scheme 16. Butoxycarbonylation of aryl chlorides.[59]

and different catalytic systems revealed the advantages of cyclohexyl-substituted, bidentate ferrocenylphosphane ligands. Thus, air-stable and commercially available 1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane gave quantitative conversion and good to excellent yields when *n*-butanol, water, or di-*n*-propylamine was used together with Na_2CO_3 as the base.[59b] Unfortunately, an excess of the ligand relative to the metal (P:Pd 8:1) and relatively high temperatures (145 °C) were required. However, a turnover number of almost 1600 was observed for the conversion of chlorobenzene into *n*-butyl benzoate with only 0.05 mol % $[PdCl_2(PhCN)_2]$, thus underlining the high productivity of this catalyst system.

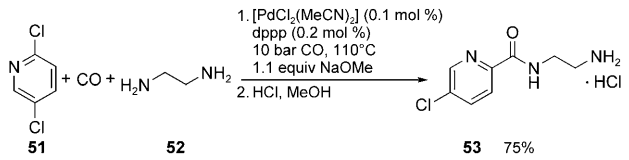
More recently, the alkoxycarbonylation of aromatic chlorides in the presence of a catalyst system based on a palladium complex of 1,2-bis(di-*tert*-butylphosphanyl)-*o*-xylene (dtbpx) was investigated in detail by Cole-Hamilton and co-workers.[60] Only moderate yields were observed for strongly activated methyl 4-chlorobenzoate and 4-chlorocyanobenzene when methanol was employed as the nucleophile. Unfortunately, some by-products resulting from nucleophilic aromatic substitution, reduction, dehalogenation, and transesterification were detected, in all cases. However, the selectivity for the transformation of 4-chloroacetophenone (**49**) was improved dramatically by using 2,2,2-trifluoroethanol as the nucleophile (Scheme 17).



Scheme 17. Alkoxycarbonylation of 4-chloroacetophenone according to Cole-Hamilton and co-workers.[60]

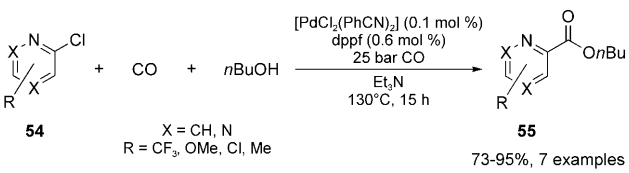
Activated and deactivated chloroarenes were transformed into a variety of benzamides by using $[Mo(CO)_6]$ as a solid source of carbon monoxide and microwave irradiation (170 °C).[61] The combination of Herrmann's palladacycle[62] and commercially available $[(t\mathrm{Bu})_3\mathrm{PH}]BF_4$ gave useful product yields (51–91 %) under non-inert conditions after only 15–25 minutes of heating.

From an industrial point of view, the carbonylation of heteroaryl chlorides,[63] particularly pyridine derivatives, is of special interest, since the resulting products are valuable intermediates for the synthesis of biologically active compounds such as herbicides and pharmaceuticals.[64,65] For example, the aminocarbonylation of 2,5-dichloropyridine (**51**) with ethylendiamine (**52**) is applied at Hoffmann–La Roche for the short industrial production of Lazabemide hydrochloride (**53**), a monoamine oxidase B inhibitor (Scheme 18).[66]



Scheme 18. Synthesis of Lazabemide hydrochloride by aminocarbonylation of 2,5-dichloropyridine.[66]

In 2001, we discovered that heteroaryl chlorides can be activated towards alkoxycarbonylation in the presence of 1,4-bis(diphenylphosphanyl)butane (dppb) or dppf as the ligand and Et_3N.[59c,65] Thus, the conversion of 2- and 4-chloropyridines, chloropyrazines, and chloroquinolines at low catalyst loadings (0.1 mol % $[PdCl_2(PhCN)_2]$, 0.6 mol % dppf), 25 bar CO, 130 °C led to good to excellent yields of the corresponding butyl esters **55** (73–95 %, Scheme 19). In contrast, less-



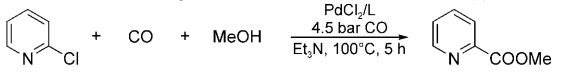
Scheme 19. Butoxycarbonylation of heteroaryl chlorides.[59c,65]

activated 3-chloropyridines were carbonylated under the same conditions by employing 1,4-bis(dicyclohexylphosphanyl)butane and NaOAc as the base. A catalyst turnover number of 13000 was obtained for the reaction of 2-chloropyridine with *n*-butanol by using only 0.005 mol% $[PdCl_2(PhCN)_2]$ and dppb (P/Pd 240:1).

Bessard and co-workers presented an ethoxycarbonylation process for the preparation of pyridine mono- and dicarboxylates from 2,3-dichloro-5-(trifluoromethyl)-pyridine.[67] Interestingly, the synthesis of ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate was conducted on a 0.5 mol scale. The reaction was carried out with 0.5 mol% $Pd(OAc)_2$ and 3 mol% dppf at 15 bar CO. After 5 h at 80°C, the monoester was isolated in 94% yield. The corresponding diester was produced selectively on a 10 mmol scale by increasing the temperature to 150°C. 2-Chloropyridine was used as a model substrate by Blaser et al. for the development of a simple parallel procedure for the carbonylation of aryl halides with alcohols and CO in standard autoclave equipment.[68]

The methoxycarbonylation of heterocyclic chlorides was accomplished with $PdCl_2$/(*rac*-binap) at 4.5 bar CO and 100°C.[19] The excellent stability of the catalyst ensured that no side reactions occurred, and the methyl esters were isolated in good to excellent yields (60–99%). However, attempts to carbonylate chlorobenzene and 3-chloropyridine failed. The screening of diverse bidentate ligands for the reaction of 2-chloropyridine (**56**) revealed an effect of the bite angle of the ligand on the rate of conversion (Table 1). Except

Table 1: Effect of bite angle on the conversion of 2-chloropyridine.[19]



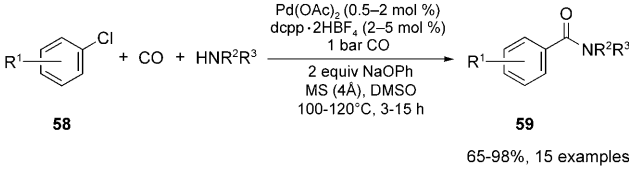
56 **57**

Entry	Ligand L[a]	Natural bite angle	Conversion [%][b]
1	dppm	72	3
2	dppe	78	6
3	dppp	91	86
4	tol-binap	91	98
5	*rac*-binap	92	94
6	dppb	99	35
7	DPEphos	102	13
8	phanephos	104	13
9	xantphos	110	99
10	norphos	123	1

[a] DPEphos = bis(2-(2-diphenylphosphanyl)phenyl)ether; dppm = 1,1-bis(diphenylphosphanyl)methane; norphos = 2,3-bis(diphenylphosphanyl)bicyclo[2.2.1]hept-5-ene; phanephos = 4,12-bis(diphenylphosphanyl)-[2.2]-paracyclophane; tol-binap = (*R*)-2,2'-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl. [b] Reaction conditions: 0.1 mol% $PdCl_2$/L, 4.5 bar CO, 1.3 equiv Et_3N, MeOH, 100°C, 5 h.

for 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene (Xantphos, Table 1, entry 9), conversions higher than 85% were obtained for phosphanes with a natural bite angle near 90°. Recently, polychlorinated pyridines have also been carbonylated in 2-ethyl-1-hexanol under atmospheric CO pressure and in standard laboratory glassware.[69]

A general protocol for the aminocarbonylation of (hetero)aryl chlorides was presented in 2007 by Buchwald and co-workers.[70] In an extension of their work on alkoxycarbonylations, they showed that several substituted aryl and heteroaryl chlorides react well with primary, α-branched primary, cyclic and acyclic secondary, as well as aryl amines in the presence of $Pd(OAc)_2$ and dcpp (Scheme 20). The

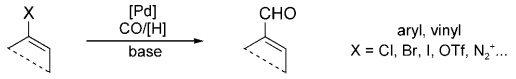


Scheme 20. Palladium-catalyzed aminocarbonylation of aryl chlorides by Buchwald and co-workers.[70]

corresponding amides **59** were obtained in good to excellent yields (65–98%) when anhydrous sodium phenoxide was used as the base. An advantage of the reaction is that it proceeds at an atmospheric pressure of carbon monoxide. The authors ascribed the mild reaction conditions to the fact that the basic additive NaOPh acted as a nucleophilic catalyst. Phenyl 3-methoxybenzoate has been identified as the key intermediate, which is then converted into the desired amide product.

3. Reductive Carbonylation

One of the most synthetically useful carbonylation reactions is the reductive carbonylation (formylation) of aryl–X or vinyl–X derivatives to aromatic or α,β-unsaturated aldehydes (Scheme 21). These aldehydes are important



60 **61**

Scheme 21. General palladium-catalyzed reductive carbonylation reaction.

building blocks for the preparation of biologically active molecules or their intermediates both in academic syntheses as well as on an industrial scale. It is well known that the formyl group readily undergoes a wide range of transformations, for example, C–C and C–N coupling reactions, or reductions. As an example from industry, a few products prepared from 4-fluorobenzaldehyde are presented in Figure 4.

Although a variety of catalysts are available today for the alkoxy- and aminocarbonylation of aryl and vinyl halides (see Section 2), there are comparatively few general protocols concerning the synthetically more interesting formylation of these substrates. The palladium-catalyzed reductive carbonylation reaction was discovered by Schoenberg and Heck in

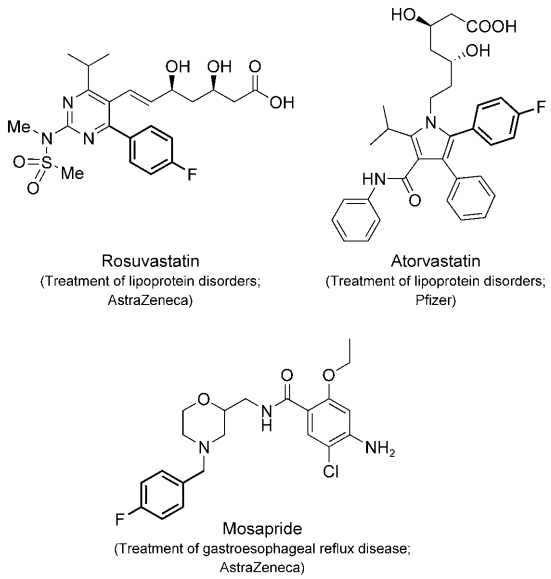


Figure 4. 4-Fluorobenzaldehyde as a building block for pharmaceuticals.

1974.[71] However, high pressure (80–100 bar) and temperatures of 80–150 °C were essential to convert aryl and vinyl bromides or iodides in the presence of synthesis gas into the corresponding aldehydes. Furthermore, a comparably large amount of $[PdX_2(PPh_3)_2]$ was required to achieve good yields. One decade later, this formylation method was improved upon by Baillargeon and Stille,[72] who employed metal hydrides as the reducing agents. Aryl iodides, benzylic halides, vinyl iodides and triflates, and allylic halides were successfully carbonylated in 2.5–3.5 h under mild conditions (50 °C, 1–3 bar CO) by using tributyltin hydride (Bu_3SnH). Tin hydrides have since been used for reductive carbonylations in several natural product syntheses (Figure 5).[73]

Despite their general application in the past, tin hydrides should not be used today because of their toxicity and waste generation. An alternative approach is based on the use of

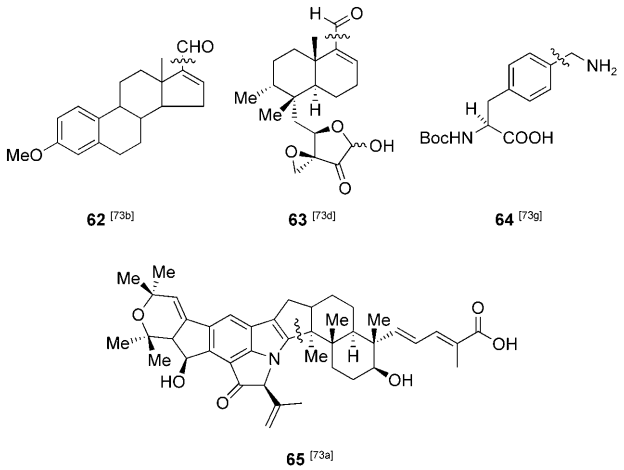
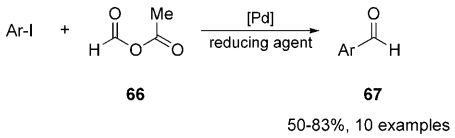


Figure 5. Examples of reductive carbonylations in natural product syntheses. (The bonds formed by carbonylation are indicated in each case.) Boc = *tert*-butoxycarbonyl.

organosilanes[74,75] in conjunction with carbon monoxide. Ashfield and Barnard[56a,76] tested the practicability of different R_3SiH systems for various known palladium catalysts. They demonstrated that many optimization experiments are inevitable to find the appropriate parameters (catalyst, base, solvent, temperature, pressure, concentration) for the transformation of (hetero)aryl bromides and iodides. Thus, when Et_3SiH was employed under mild conditions (3 bar CO, 60–120 °C), the $[PdCl_2(dppp)]$/DMF/Na_2CO_3 system gave good results for most of the substrates. In general, the desired aldehydes were obtained in 79–100 % yield. However, the catalyst system failed with aryl chlorides[77] as well as sterically hindered aryl bromides and iodides.

The use of readily available and cheap formate salts is an economically attractive variant of palladium-catalyzed reductive carbonylation.[74c,77a,78] For example, a silica-supported phosphane–palladium complex ("Si"-*P*-Pd) was employed by Cai et al. for the formylation of aryl bromides and iodides with sodium formate (1 bar CO, 90–110 °C).[79] The polymer-bound catalyst could be recovered afterwards, and showed in simple model reactions comparable catalytic activity as homogeneous $[PdCl_2(PPh_3)_2]$.

Cacchi et al. presented two generalized protocols for the synthesis of substituted benzaldehydes **67** from aryl iodides (Scheme 22).[80] The reaction conditions had to be modified depending on the electronic properties of the substrates. Thus,



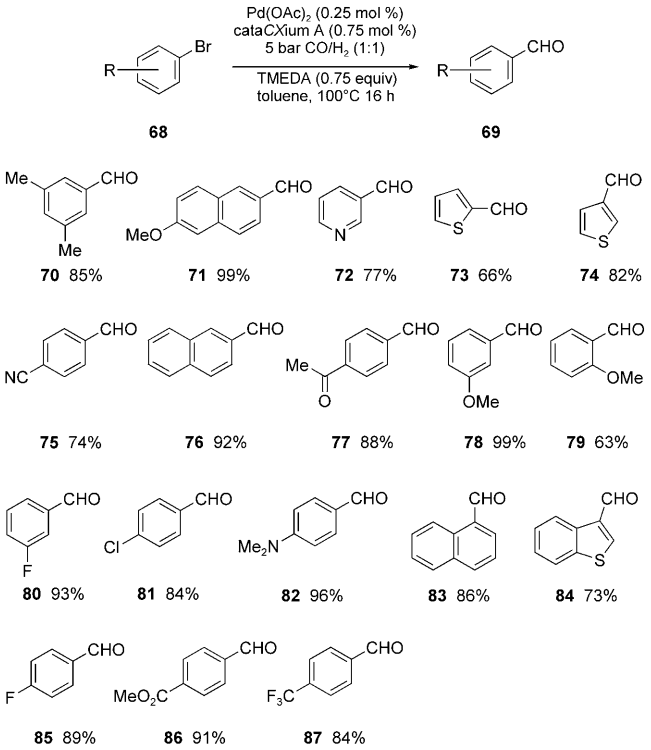
Scheme 22. Palladium-catalyzed synthesis of benzaldehydes from aryl iodides with **66**, the mixed anhydride from acetic and formic acid.[80]

neutral, electron-rich, and slightly electron-deficient aryl iodides were carbonylated in CH_3CN in the presence of $[Pd_2(dba)_3]$, dppe, iPr_2EtN, and Et_3SiH with a mixed anhydride from acetic and formic acid as the CO source. Electron-poor aryl iodides were treated in DMF in an analogous manner; however, the addition of three equivalents of LiCl was required. Good yields were achieved at 60 °C for most starting materials, and several functional groups were tolerated.

A totally different electrochemical approach to aromatic and heteroaromatic aldehydes was presented by Chiarotto et al.[81] Based on preliminary investigations,[82] the formylation of aryl iodides was accomplished in the presence of formic acid and an atmospheric pressure of carbon monoxide.[81b] The necessary formate ions for an efficient formylation were generated from HCOOH in the presence of 10 mol % palladium–phosphane complexes under electrolytic conditions (−1.2 V versus SCE). Here, good yields were achieved for most of the substrates. The analogous electrocarbonylation of iodothiophenes, iodofurans, and iodopyridines in the presence of the phosphane-free palladium catalyst $Pd(OAc)_2$/DABCO proceeded with moderate to good yields.[81a]

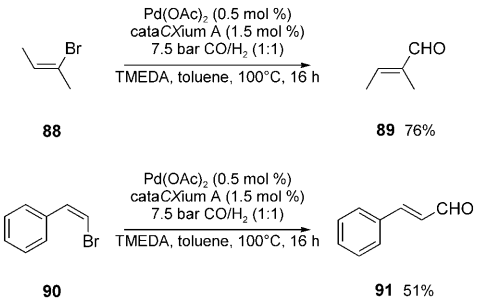
Holzapfel et al. published an alternative synthesis of pyridine and quinoline carboxaldehydes which involved the reductive carbonylation of (hetero)aryl bromides and triflates.[83] Since different hydrogen donors, for example, Bu_3SnH or polymethylhydrosiloxane (PMHS), led to poor results or to significant amounts of by-product resulting from reductive dehalogenation, synthesis gas was used as the formylation source. Thus, carbonylation in the presence of $Pd(OAc)_2/PPh_3$ and 30–40 bar synthesis gas (CO/H_2 1:1) furnished the favored aldehydes in 30–88% yield. However, the protocol was limited to only a few substrates.

Recently, the most general and efficient palladium-catalyzed formylation procedure for the synthesis of aromatic and heteroaromatic aldehydes was developed in our research group (Scheme 23).[84] Several (hetero)aryl bromides were



Scheme 23. Scope of the reductive carbonylation with cataCXium A.[84a]

successfully carbonylated with synthesis gas, a cheap and environmentally benign formyl source, in the presence of $Pd(OAc)_2$/cataCXium A[85] and *N,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% cataCXium A) and at much lower pressures (5 bar) than previously reported catalysts. Furthermore, it was shown that vinyl halides could be formylated under similar conditions to form α,β-unsaturated aldehydes in 41–98% yield.[86] Interestingly, the transformation of (*Z*)-2-bromo-2-butene (**88**) and *cis*-β-bromo-styrene (**90**) resulted in the selective formation of the corresponding *trans* aldehydes (Scheme 24). This efficient, air- and moisture-stable catalyst system is currently employed on a multi-ton scale in the first



Scheme 24. Reductive carbonylation of vinyl halides.[86]

industrial palladium-catalyzed reductive carbonylation of aryl halides.

The application of homogeneous catalysis benefits significantly from advances in organometallic chemistry. Hence, the mechanistic understanding of elementary steps and the synthesis of new organometallic compounds provide a valuable source for inspiration of new catalysts. The mechanism of the reductive carbonylation of aryl bromides with synthesis gas has been investigated in detail because of its industrial importance (Figure 6).[87] This formylation proceeds efficiently in the presence of Pd/PR_2nBu (R = 1-Ad, *t*Bu; 1-Ad = adamantyl) while $Pd/PtBu_3$ catalysts are not efficient. A comparison of stoichiometric and catalytic reactions with P(1-Ad)$_2$*n*Bu (cata*CX*ium A) led to two pivotal results: 1) The carbonylpalladium(0) complex $[Pd_n(CO)_mL_n]$ and the respective bromo(hydrido) 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 the most-active PdL species at a low level during the reaction, thus making oxidative addition the rate-determining step and providing longevity to the catalyst. 2) The product-forming step proceeds by base-mediated hydrogenolysis of the corresponding acyl complex, for example, $[\{Pd(Br)(p\text{-}CF_3C_6H_4CO)[P(1\text{-}Ad)_2nBu]\}_2]$ under mild conditions (25–50°C, 5 bar). Remarkably, reductive dehalogenation of the starting material, which is generally the most important side reaction in the reductive carbonylation, was not observed in the presence of P(1-Ad)$_2$*n*Bu and TMEDA. Stoichiometric studies with the less efficient $Pd/PtBu_3$ catalyst resulted in the isolation and characterization of the first stable three-coordinate neutral acylpalladium complex $[Pd(Br)(p\text{-}CF_3C_6H_4CO)(PtBu_3)]$. Hydrogenolysis of this complex needed significantly more drastic conditions than 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 $Pd/PtBu_3$ catalyst in the formylation of aryl bromides.

The first general palladium-catalyzed carbonylation of aryl triflates with synthesis gas was reported in 2007.[88] In contrast to aryl bromides, only the bidentate ligands dppe and dppp led to significant conversion and formation of aldehyde. Various aromatic aldehydes were obtained in 50–92% yield in the presence of 1.5 mol% $Pd(OAc)_2$, 2.25 mol% dppp, and pyridine in DMF under mild conditions. It was also demonstrated that 4-methoxybenzaldehyde (**94**) could be prepared

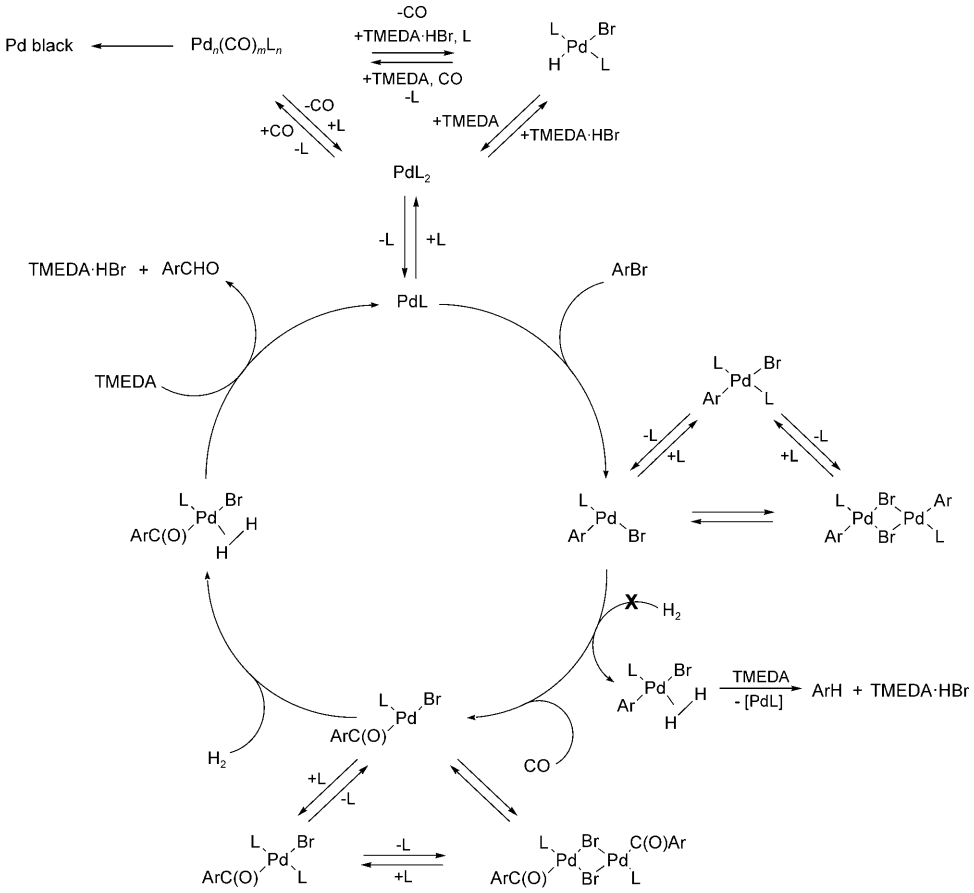
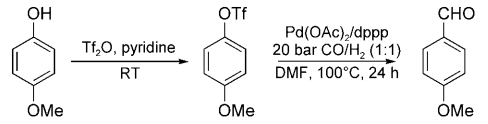


Figure 6. Proposed catalytic cycle for the formylation of aryl bromides with Pd/P(1-Ad)$_2$*n*Bu in the presence of TMEDA.[87]

directly from 4-methoxyphenol (**92**) by a one-pot sulfonylation/carbonylation sequence (Scheme 25).

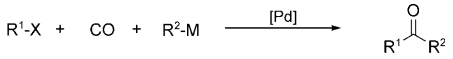


92 **93** **94** 44%

Scheme 25. One-pot sulfonylation and carbonylation for the synthesis of 4-methoxybenzaldehyde (**94**).[88]

4. Carbonylative Cross-Coupling Reactions

While reductive carbonylations make use of hydrogen or hydride as nucleophiles, related carbonylative cross-coupling reactions proceed in the presence of organometallic reagents, with organoboranes or -borates,[89] organoaluminum,[90] organosilane,[91] organoantimony,[92] and organozinc[93] compounds being the most popular. From a synthetic viewpoint, the palladium-catalyzed multicomponent cross-coupling reaction of organic electrophiles, carbon monoxide, and organometallic reagents is a useful method for the preparation of (un)symmetrical ketones (Scheme 26).



95

Scheme 26. General scheme for the three-component cross-coupling reaction.

4.1. Carbonylative Stille Coupling Reactions

The carbonylative Stille reaction between organic halides (or pseudohalides), carbon monoxide, and stannanes has been extensively studied in the past 20 years.[94] In spite of the toxicity of the tin compounds, the Stille carbonylation has found many applications in organic synthesis because of its functional-group tolerance and versatility (Figure 7).

For example, an inverse three-component carbonylative Stille coupling on a solid support was described by Yun et al.[95a] Readily available aryl bromides and iodides were coupled simultaneously with an aryl stannane, which had been immobilized on a Rink amide resin. Diarylketones with a wide range of functional groups were isolated after 18–72 h in good to excellent yields, while direct cross-coupling products were not observed. Very recently, a combinatorial synthesis of conjugated arene systems by sequential palladium-catalyzed coupling reactions on a solid phase, including Stille carbonylation, was also developed.[95b]

The first palladium-catalyzed desulfitative coupling of arenesulfonyl chlorides and organostannanes at a high carbon monoxide pressure (60 bar) was reported by Dubbaka and Vogel (Scheme 27).[96] The reaction was performed in toluene and required CuBr·Me_2S as a co-catalyst. Unfortunately, only moderate yields were achieved under these conditions because of the increased formation of side products arising from the carbonylative homocoupling of the organostannanes. Interestingly, thioesters (R^1-S-CO-R^2) were obtained when the reaction was conducted in THF in the presence of tris(2-furyl)phosphane (TFP) as the ligand.

Furthermore, carbonylative coupling reactions of tributyl(1-fluorovinyl)stannane with 1-iodo-2,4-dimethylbenzene were carried out under an atmospheric pressure of carbon

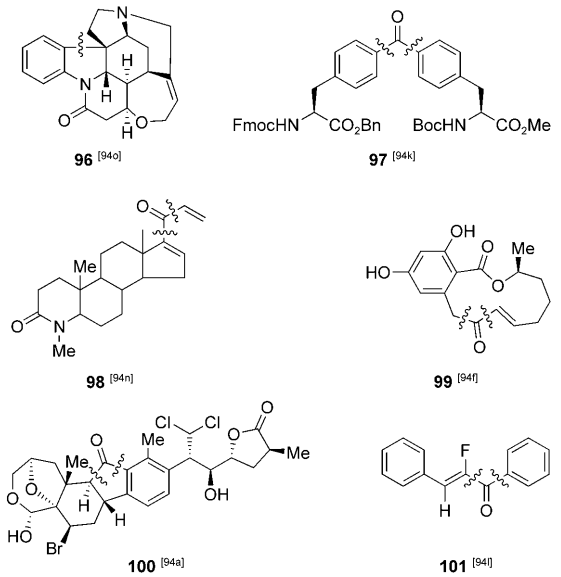
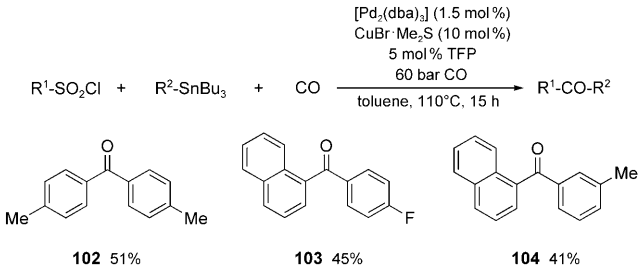


Figure 7. Examples of products from the carbonylative Stille coupling reactions in organic synthesis. (The bonds formed by carbonylation are indicated in each case.) Fmoc = fluorenylmethoxycarbonyl.



Scheme 27. Carbonylative Stille coupling reaction of sulfonyl chlorides.[96]

monoxide.[97] The desired aryl 1-fluorovinyl ketone was obtained in quantitative yield under optimized conditions (2.5 mol% $[Pd(PPh_3)_4]$, 80 °C, 2 h). This carbonylative Stille reaction was applied to other 2-, 3-, or 4-substituted aryl iodides, and the corresponding fluorinated α,β-unsaturated ketones were isolated in good yields. In contrast to the protocol of Chen et al.,[94l] the addition of copper(I) iodide or lithium chloride was not required. Some electron-deficient aryl triflates were also coupled in the presence of tetrabutylammonium iodide.

4.2. Carbonylative Suzuki Coupling Reactions

In 1993, Suzuki and co-workers successfully synthesized unsymmetrical biaryl ketones by a palladium-catalyzed cross-coupling reaction of arylboronic acids with iodoarenes in the presence of 1 bar carbon monoxide (carbonylative Suzuki reaction).[98] Boronic acids are gaining increasing importance over tin compounds as they are generally nontoxic, thermally stable, and inert to oxygen and moisture. Several improvements and applications of the original synthetic protocol have been described,[94a,99] but limitations (formation of (biaryl) side products, employment of additives, or restriction to special substrates) often remain.

Andrus et al. have broadened the scope of the Suzuki carbonylation by using aryl diazonium tetrafluoroborate salts as coupling partners.[100] Treatment of aryl and vinyl boronic acids with these electron-rich or -deficient substrates at 1 bar CO and 100 °C in dioxane for 5 h afforded the desired aryl ketones in 76–90% yield; the corresponding biaryl coupling products were isolated in 2–12% yield. The authors generated a novel catalytically active species from a palladium complex and an N-heterocyclic carbene (NHC) in situ from 2 mol% $Pd(OAc)_2$ and 2 mol% *N*,*N*′-bis(2,6-diisopropylphenyl)dihydroimidazolium chloride (**105**; Figure 8). Subsequently, an

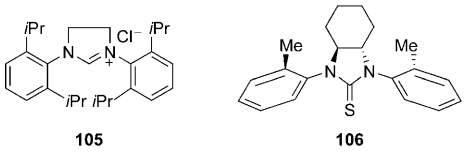
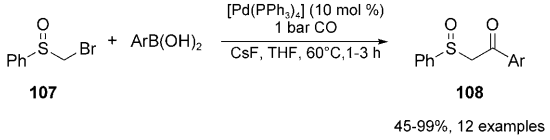


Figure 8. Ligands used for the carbonylative Suzuki cross-coupling of diazonium salts.[100–101]

alternative phosphane-free palladium catalyst was reported for the carbonylative Suzuki reaction of diazonium salts.[101] The use of the C_2-symmetrical and sterically bulky thiourea ligand (**106**; Figure 8) allowed milder reaction temperatures (20 or 50 °C) to be used. However, in some cases, for example, for nitrophenyldiazonium compounds, the yields were lower in comparison to those obtained by the method of Andrus et al.[100] The palladium/thiourea catalyst system was also employed to couple (hetero)aryl iodides in satisfying yields (> 70%).

β-Ketosulfoxides **108** were synthesized for the first time by transformation of α-bromo sulfoxide **107** with (hetero)aryl boronic acids under atmospheric CO pressure (Scheme 28).[102] Neither homo- and cross-coupling side

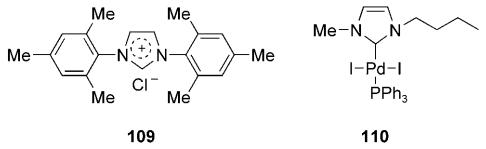


Scheme 28. The first synthesis of β-keto sulfoxides by a palladium-catalyzed carbonylative Suzuki reaction.[102]

products nor sulfoxides resulting from dehalogenation were observed in significant amounts. Under mild conditions, aryl boronic acids with electron-withdrawing substituents were less reactive, and alkyl boronic acids did not react at all. A modified reaction mechanism was suggested for the Suzuki carbonylation of α-bromo sulfoxides.[102]

Castanet and co-workers introduced $[PdCl_2(PPh_3)_2]$[103,104] as an efficient catalyst for carbonylative Suzuki cross-coupling reactions of 2- or 4-substituted iodo- and bromopyridines. Thus, phenyl pyridyl ketones were obtained in high

yield and selectivity at 5 bar CO. Dibromopyridines furnished the corresponding dibenzoylpyridines when $[PdCl_2(PCy_3)_2]$ was used.[103,104] Shortly afterwards, the authors succeeded in extending the scope of the reaction to chloropyridines and chloroquinoline.[105] For the first time, activated aryl chlorides were directly converted into the desired benzoylpyridines by an in situ generated palladium complex based on $Pd(OAc)_2$ and imidazolium salt **109** (Figure 9). The reactions were

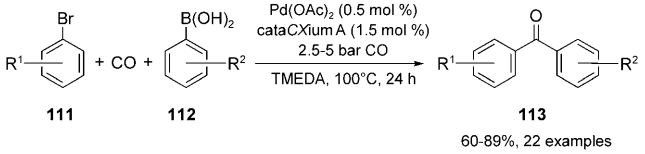


109 **110**

Figure 9. N-Heterocyclic carbene precursor **109** and the palladium–carbene complex **110** used for Suzuki carbonylations.[105,107]

conducted in dioxane in the presence of Cs_2CO_3 under 50 bar CO at 140 °C to improve the reactivity. A detailed investigation of the influence of the catalyst precursor, solvent, temperature, time, and CO pressure on the Pd/NHC-catalyzed Suzuki carbonylation of pyridine halides was published recently.[106] Another Pd/NHC/phosphane complex **110** (Figure 9) was used for the carbonylative reaction of electron-rich and electron-deficient aryl iodides with phenylboronic acid or $NaBPh_4$ as the phenylating agent.[107] Excellent yields were achieved with K_2CO_3 as the base already after 5 h under 1 bar CO at 100 °C.

A general method for the synthesis of diaryl and aryl heteroaryl ketones by palladium-catalyzed Suzuki carbonylation was also developed in our research group (Scheme 29).[108] A broad range of aryl and heteroaryl



111 **112** **113**

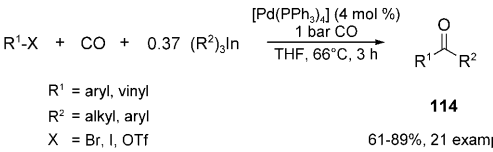
60-89%, 22 examples

Scheme 29. General synthesis of diarylketones in the presence of $Pd(OAc)_2$ and cata*CX*ium A.[108]

bromides were coupled with different aryl boronic acids at low pressure in the presence of $Pd(OAc)_2$/cata*CX*ium A to give the corresponding ketones **113** with high selectivity.

4.3. Indium Organometallic Reagents in Carbonylative Cross-Coupling Reactions

In 2003, Lee et al.[109] (Scheme 30) and Sarandeses and coworkers[110] published independently the first examples of palladium-catalyzed carbonylative cross-coupling reactions of organic electrophiles and triorganoindium compounds in the presence of carbon monoxide. Unsymmetrical ketones **114** were produced in good yields and with high atom efficiency,



114

61-89%, 21 examples

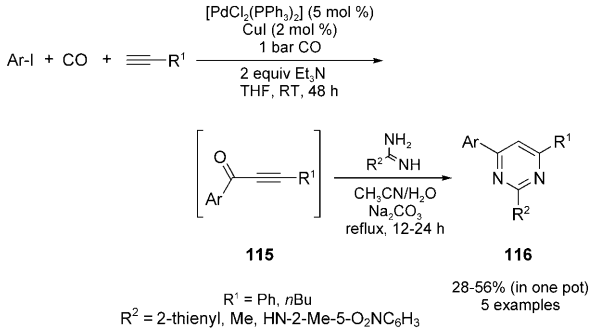
Scheme 30. Carbonylative cross-coupling with triorganoindium compounds according to Lee et al.[109]

since all the organic groups attached to the metal center were transferred onto the electrophile. Double carbonylative coupling reaction provided 1,4-diacylbenzenes in 54–68% yield. The methodology was later extended by using tetraorganoindates as nucleophilic cross-coupling partners. In addition to aryl and vinyl halides, aryl triflates, benzyl bromide, and benzoyl chloride were successfully treated with CO and various organoindates.[111] Hence, organoindium derivatives have become useful alternatives to other organometallic reagents in organic synthesis, since they are relatively readily available and can be conveniently handled. Furthermore, they show good reactivity and selectivity, operational simplicity, and low toxicity.[112]

4.4. Carbonylative Sonogashira Coupling Reactions

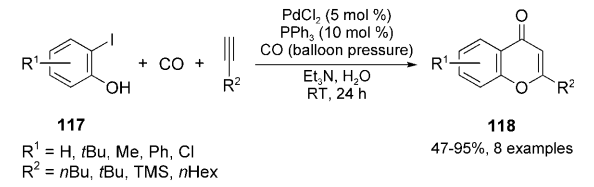
The carbonylative three-component cross-coupling of aryl halides with terminal alkynes in the presence of amines as the base to give alkynyl ketones is known as the carbonylative Sonogashira reaction.[113] Typically, this reaction requires anhydrous/anaerobic conditions, relatively high CO pressures, and a copper(I) co-catalyst. For these reasons, a variety of modifications and new procedures have been developed over the last few years: A notable example was reported in 2003 by Mohamed Ahmed and Mori. They demonstrated the direct carbonylative coupling of phenylacetylene with aryl iodides by using 1 mol% $[PdCl_2(PPh_3)_2]$ and 0.5 M aqueous ammonia in THF.[114] Reactions under mild conditions (25 °C, 1 bar CO) and in the absence of copper led to the isolation of α,β-alkynyl ketone derivatives in 50–81% yield, whereas noncarbonylative coupling products were not observed. Since the reaction was slower for alkynes bearing an alkyl substituent, higher amounts of catalyst and the addition of CuI were necessary.

Carbonylative Sonogashira reactions have been successfully employed in natural product syntheses. For example, 2,4,6-trisubstituted pyrimidines **116** have been prepared from (hetero)aryl iodides, alkynes, carbon monoxide, and amidines by a consecutive four-component carbonylative alkynylation/cyclocondensation reaction sequence in one pot (Scheme 31).[115] Again, CuI had to be added to achieve moderate yields at room temperature. The authors also presented a two-step synthesis of pharmaceutically active meridianins and their derivatives. Carbonylative coupling of Boc-protected 3-iodoindole derivatives and trimethylsilylacetylene afforded trimethylsilylalkynones, which were subsequently treated with guanidine to give the desired indole alkaloids.



Scheme 31. One-pot route to the synthesis of pyrimidines by carbonylative coupling and cyclocondensation.[115]

The first copper-free $PdCl_2/PPh_3$-catalyzed carbonylative Sonogashira reaction of aryl iodides using water as the solvent was published by Yang and co-workers.[116] Both aryl- and alkyl-substituted alkynyl ketones were obtained in good to excellent yields when Et_3N was used as the base at 1 bar CO. The superior performance of the water/Et_3N system led to the proposal that Et_3N not only acted as the base but also as the co-solvent in the reaction. This protocol was applied successfully to the synthesis of naturally occuring flavones **118**. Here, sequential carbonylative coupling of iodophenols with alkyl-substituted terminal acetylenes followed by intramolecular cyclization gave the desired natural products in 47–95% yield (Scheme 32).

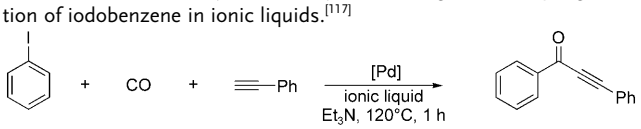


Scheme 32. Synthesis of flavones by carbonylation.[116]

An alternative copper-free approach to alkynyl ketones is the palladium-catalyzed carbonylative alkynylation of aryl iodides in ionic liquids.[117] The reaction of iodobenzene with phenylacetylene in the presence of CO proceeded smoothly in [bmim][PF_6] (Table 2). Thus, acetylenic ketone **120** was produced in 82% yield under 20 bar carbon monoxide (Table 2, entry 1). A reduced pressure or amount of base and modification of the palladium species or ionic liquid did not lead to improved yields (Table 2, entries 4–7). The catalyst and solvent could be recycled and reused with a slight decrease in efficiency (Table 2, entries 1–3). A superior selectivity and higher yields for the Sonogashira carbonylation in ionic liquids have been achieved even at low CO pressures when reactions were carried out in a continuous microflow system instead of a batch reactor.[118]

Recently, new phosphane-free, heterogeneous catalytic systems were investigated for carbonylative Sonogashira reactions.[119] Pd/C-Et_3N[119a] efficiently catalyzed the coupling reaction of various aryl halides with terminal alkynes and was easily recycled up to three times with no significant loss of

Table 2: Palladium-catalyzed carbonylative Sonogashira coupling reaction of iodobenzene in ionic liquids.[117]



Entry	[Pd]	Run	CO [bar]	Et_3N [equiv]	Ionic liquid	Yield [%][b]
1	$[PdCl_2(PPh_3)_2]$	1	20	3.6	[bmim][PF_6]	82
2		2	20	3.6	[bmim][PF_6]	68
3		3	20	3.6	[bmim][PF_6]	61
4[c]	$[PdCl_2(PPh_3)_2]$	1	20	2.0	[bmim][PF_6]	48
5	$[PdCl_2(PPh_3)_2]$	1	10	3.6	[bmim][PF_6]	52 (21)
6	$[PdCl_2(PPh_3)_2]$	1	20	3.6	[bmim][Tf_2N]	58 (24)
7	$Pd(OAc)_2$	1	20	3.6	[bmim][PF_6]	60

[a] Reaction conditions: 1 mmol iodobenzene, 1.2 mmol phenylacetylene, 1 mol% [Pd], 3 mL ionic liquid, 120°C, 1 h. [b] Yield of isolated product. The yield of diphenylacetylene is shown in parantheses. [c] The reaction was carried out for 2 h.

catalytic activity. Only small amounts (<1%) of competing noncarbonylative Sonogashira coupling products were observed. A magnetically separable palladium catalyst (Pd/Fe_3O_4)[119b] was reused seven times with similar selectivity and activity. A turnover number of about 500 was achieved for the reaction of iodobenzene with phenylacetylene in the presence of carbon monoxide.

The first palladium-free, copper-catalyzed carbonylative Sonogashira coupling reaction of aliphatic and aromatic alkynes with iodoaryls was explored quite recently by Tambade et al.[120]

5. Summary and Outlook

We have summarized in this Review the recent developments in the area of palladium-catalyzed carbonylation reactions of aryl halides and related starting materials. Since the original work of Heck and co-workers, various catalytic carbonylation reactions have been developed over the past decades, and nowadays a plethora of palladium catalysts are available for these transformations. Moreover, the advancements in cross-coupling chemistry have made it possible that some carbonylations of aryl halides are efficient enough to be run in industry on a ton scale.

There is no doubt that cross-coupling reactions have become reliable transformations for all kinds of complex natural product syntheses. However, this is only in part true for catalytic carbonylation reactions. The use of gaseous carbon monoxide still hinders the application of these reactions, because synthetic organic chemists are reluctant to use high-pressure equipment, alhough carbonylative coupling reactions can be carried out at ambient or low pressure (1–5 bar). Often it is even advantageous to work under these mild conditions, since a high CO pressure retards the oxidative addition of the aryl–X compound to the palladium center because of the π-acidic nature of CO as a ligand. It should also be noted that commercially available

apparatuses exist nowadays which allow for parallel carbonylations, typically 6–16 parallel reactions.

What are the goals for the coming years? For example, catalyst efficiency (activity and productivity) in carbonylative coupling reactions is still comparably low compared to Suzuki or Heck reactions. In addition, substrates such as (nitrogen)heteroarenes and more-functionalized coupling partners represent significant challenges. Here, the development of better ligands will be a key issue. Clearly, such new catalyst systems should be initially tested in simpler benchmark reactions; however, this should be only the start and not the end of the development of a catalyst!

With regard to sustainability, a major challenge will be the development of catalytic carbonylation reactions which do not use aryl halides as substrates, but directly employ arenes. The advantages of such methods are clear: cheaper substrates and less waste. Such reactions would also be of central interest to bulk chemicals, for example, terephthalic acid derivatives.

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