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Advances in the Carbonylation of Aryl Halides Using Palladium Catalysts

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Abstract: The palladium-catalyzed carbonylation of aryl halides is shown to be a versatile tool for the synthesis of various benzoic and heteroaromatic acid derivatives. Recent developments from our laboratories in this area are presented.

Keywords: Benzoic acid derivatives · Carbonylation · Homogeneous catalysis · Palladium

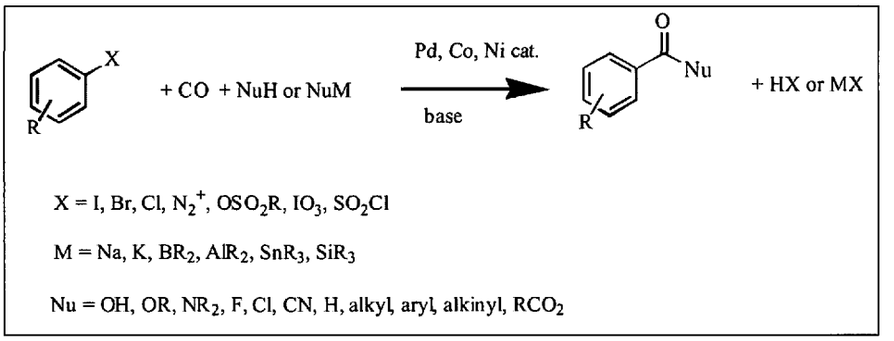
Introduction

Palladium-catalyzed carbonylation reactions of aryl-X compounds leading to carboxylic acid derivatives were established in the mid-seventies by the pioneering work of Heck and co-workers [1]. Since that time these reactions have found a number of applications in organic synthesis, and even some industrial processes (see below) have been realized. However, compared to other palladium-catalyzed coupling reactions such as the Heck and Suzuki reaction or the Buchwald-Hartwig amination reaction, palladium-catalyzed carbonylation still seems somewhat underdeveloped. This review gives an impression of the possibilities of this catalytic multi-component coupling reaction. In addition some of the recent achievements from our groups in this area will be presented.

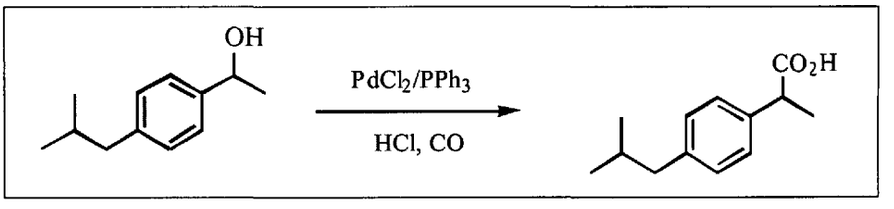
From a general point of view the leaving group of the aryl-X derivative is formally replaced by a nucleophile with incorporation of one or two molecules of CO (Scheme 1). In addition to aryl-, hetero-aryl-, vinyl-, allyl- und benzyl-X compounds can also serve as starting materials in these carbonylations [2]. Two examples for carbonylation reactions of benzyl-X applied on an industrial scale for fine chemical production are the synthesis of Ibuprofen (>3000 to/a) developed by Hoechst-Celanese (Scheme 2) [3] and the carbonylation of 1,2-dixylyldichloride to give isochromanone by Clariant AG [4].

Elegant work by researchers from Hoffmann-La Roche also demonstrated the industrial applicability of such a reaction in the commercial process for Lazabemide, a monamine oxidase B inhibitor. In this process the aminocarbonylation of the commercially available 2,5-dichloropyridine with ethylenediamine is performed with a Pd/dppp catalyst with comparably high catalyst productivity (Scheme 3).

Due to the enhanced reactivity of the 2-position compared to the 3-position of the substituted pyridines, a selective monocarbonylation is possible [5].



Scheme 1. Catalytic carbonylation of aryl-X compounds.



Scheme 2. Synthesis of Ibuprofen.

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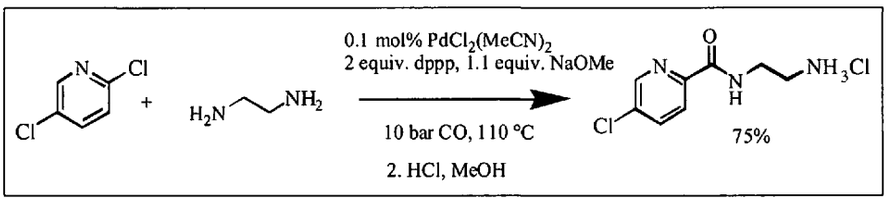


Scheme 3. Carbonylation of 2,5-dichloropyridine leading to lazabemide.

Depending on the nucleophile many useful transformations like hydroxy-, alkoxy- and aminocarbonylations are possible. By far the most frequently employed transition metal catalysts are palladium compounds, but also much cheaper cobalt complexes (like $Co_2(CO)_8$) [6] and – in rare cases – nickel complexes (like $Ni(CN)_2$) [7] have been used. Most of the work on carbonylation of aryl-X derivatives during the last 25 years concentrated on the corresponding halides as starting materials, especially aryl bromides and aryl iodides. Less frequently, substrates with different leaving groups like diazonium salts, triflates, alkyl- or arylsulfonates, fluorosulfonates, aryliodonium salts, iodoxyarenes, or sulfonyl chlorides have been successfully transformed into the corresponding carbonyl compounds.

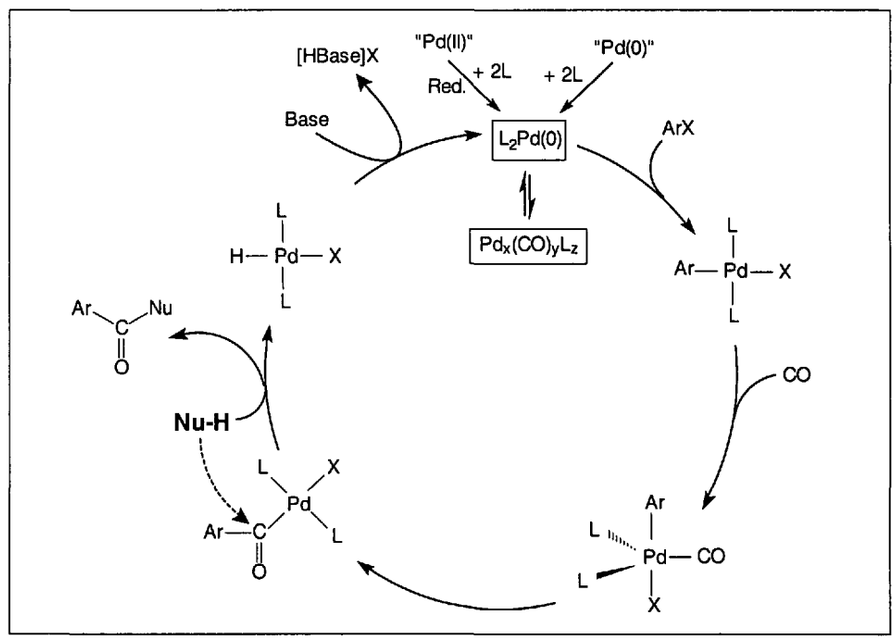
The variety of nucleophiles that can be employed makes the carbonylation of aryl-X derivatives especially valuable for organic synthesis. Hence, a plethora of different compounds can be synthesized from the same starting material. Water, alcohols, primary and secondary amines, carboxylates, even fluorides lead to carboxylic acids, esters, amides, anhydrides, and acid fluorides, respectively. Additionally, aldehydes, ketones, aroyl cyanides, aroyl alkenes and aroyl acetylenes are accessible with suitable nucleophiles. Even anionic metal complexes like $[Co(CO)_4]^-$ can serve as nucleophiles, leading to metal acyl complexes as products [8]. Recently, we were able to prepare amides with a free NH_2 group by aminocarbonylation reaction of aryl halides in high yields (70–90 %) using formamide as the amine source. The reactions require a palladium catalyst in combination with a nucleophilic Lewis base which acts as an acylating catalyst such as *e.g.* imidazole or 4-dimethylaminopyridine. Aryl, heteroaryl and vinyl bromides and chlorides are converted to the primary amides under mild conditions (5 bar, 120 °C) using 1 mol % of a palladium phosphine complex. Best results were obtained in dioxane using triphenylphosphine as the ligand and DMAP as the base [9].

It should also be mentioned that intramolecular carbonylations (cyclocarbonylation) reactions leading to various heterocycles are possible if the nucleophile is attached *via* a suitable spacer to the aryl-X substrate. This enables the direct synthesis of aryl-lactones, -lactams, -oxazoles, -thiazoles, -imidazoles, *etc.* Another variant of the discussed carbonylation reactions is the introduction of two CO molecules in a single step leading to derivatives of α-keto carboxylic acids. The reaction only takes place under specific conditions and is always in competition with monocarbonylation. As an example a variety of aryl and alkenyl bromides and iodides were converted into their corresponding α-keto amides with good chemoselectivity by use of secondary amines and alkylphosphines or bidentate phosphines like dppb [10].

Despite the synthetic usefulness of the carbonylation reaction studies, the development of more efficient catalysts has been largely ignored. In this regard we studied the alkoxycarbonylation of 4-bromoacetophenone as a model reaction [11]. It was discovered that an excess of phosphine ligand (P/Pd = 14; P = PPh_3) leads to a significant increase of the catalyst productivity. Best turnover numbers (TON = 6500) were achieved at 130 °C in the presence of $Pd(PPh_3)_4$-catalyst using 1.2 equiv. of NEt_3 as the base.

Carbonylation of Aryl Chlorides

Regarding starting materials, chloroarenes are certainly the most attractive class of aryl halides for carbonylation reactions on an industrial scale, because they are inexpensive and readily available in bulk quantities with different substitution patterns. However, the high stability of the aromatic carbon–chlorine bond (bond dissociation energy for PhCl at 298 K: 402 kJ/mol) remains a major obstacle for their widespread use in this reaction. Initial studies towards the carbonylation of aromatic chlorides employed nickel and cobalt catalysts. Hence, $Ni(CO)_4$ was used to convert 1- and 2-chloronaphthalene into the corresponding naphthoic acids in the presence of $Ca(OH)_2$ in dipolar aprotic solvents at 110–120 °C and atmospheric CO pressure [12]. Another means of activating aryl chlorides utilized a Ni/Pd system containing NaI. In this case a small amount of the aryl chloride is converted into the iodide by nickel catalysis and subsequently reacted with palladium [13]. When using palladium catalysts, the oxidative addition of Pd(0) to the C–Cl bond is assumed to be the rate-determining reaction step in the catalytic cycle (Scheme 4) [14].



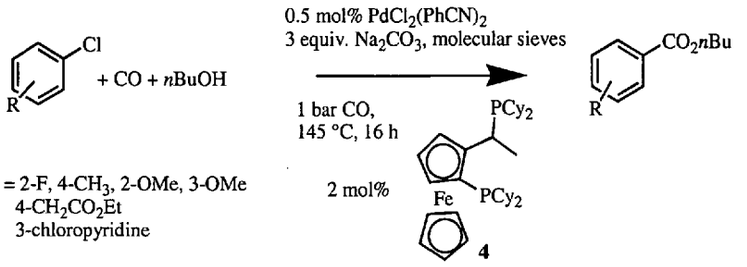
Scheme 4. Proposed mechanism of the palladium-catalyzed alkoxycarbonylation of aryl-X derivatives.

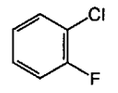
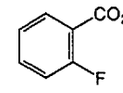
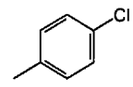
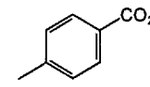
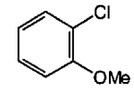
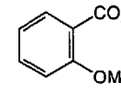
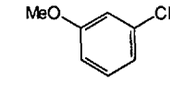
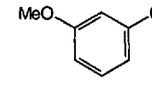
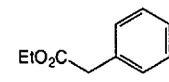
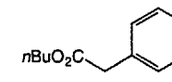
Two strategies have been pursued to increase the rate of this step: a) reduction of the π-electron density of the aromatic chloride and b) enhancement of the nucleophilicity of the palladium(0) catalyst by use of strongly basic ligands. The first approach was successfully employed by Basset *et al.* by converting the chloroarenes stoichiometrically in their respective tricarbonylchromium complexes. The various η^6-RC_6H_4Cl chromium complexes (R = H, 4-Me, 4-OMe, 4-CF_3) were carbonylated at 130 °C/25 bar to the corresponding esters or aldehydes in the presence of 2 mol% $PdCl_2(PPh_3)_2$/5 PPh_3 in moderate to good yields, the hydrocarbonylation being less effective [15].

The second approach [16] was employed most successfully by Milstein and co-workers, who used a palladium catalyst based on the highly electron-rich and bulky chelating ligand 1,3-bis(diisopropylphosphino)propane (dippp). Thus, carboxylic acids, esters and amides were synthesized in excellent yields [17]. The same catalyst also turned out to be active in the formylation of aryl chlorides to aldehydes using sodium formate as the reducing agent. The drawbacks of this catalyst system, however, are the difficult synthesis and the high sensitivity of this pyrophoric phosphine along with the comparatively low turnover numbers of the catalyst (1 mol% of palladium needed). The aminocarbonylation of activated aryl chlorides proceeds with high yields in the presence of a palladium catalyst based on 1,2-bis(diphenylphosphino) ethane, when sodium iodide is used to activate the catalyst [18].

Very recently, we examined the palladium-catalyzed alkoxycarbonylation reaction of activated and deactivated aryl chlorides with regard to the influence of critical reaction parameters, product selectivity, and the performance of various catalyst ligands. Our investigations resulted in the development of a new efficient catalyst system based on cyclohexyl-substituted ferrocenylphosphine ligands for the carbonylation of aryl chlorides [19]. A considerable advantage is that these ligands are air stable and commercially available. With the $PdCl_2(PhCN)_2$/**4** catalyst (0.5 mol% Pd) in the presence of sodium carbonate as a base, chlorobenzene was converted to n-butyl benzoate in an essentially quantitative yield within 16 h (130–145 °C). The CO pressure can be as low as 1 bar. After optimization, a catalyst turnover number of almost 1600 was observed at a Pd loading of only 0.05 mol%, underlining the high productivity of the catalyst system. The observed catalyst productivity is almost one order of magnitude higher than previously reported results with non-activated chloroaromatics, reducing the otherwise high catalyst cost significantly. The applicability of the carbonylation protocol to a variety of aryl chloride substrates as well as other nucleophiles such as amines or water was demonstrated (Table 1).

Table 1. Butoxycarbonylation of various aryl chlorides[a].



Entry	Aryl Chloride	Conversion [%]	Product Yield [%][b]	Chemoselectivity [%][c]
1		100	 100 (76)	95
2		100	 98 (80)	92
3		100	 95 (91)	100
4		100	 95 (68)	84
5		>99	 93 (68)	86[d]

[a] 7 mmol aryl chloride, 14 ml n-butanol. [b] Yield (GC) of all carbonylation products (ester + acid). GC-Yield of product was determined by using diethyleneglycol di-n-butylether as internal standard. Isolated yield of product in brackets. [c] Chemoselectivity = GC-yield of product/yield of carbonylation products. [d] Mixture of 80% (4-carboxyphenyl)acetic acid and 20% (4-butoxycarbonylphenyl)acetic acid.

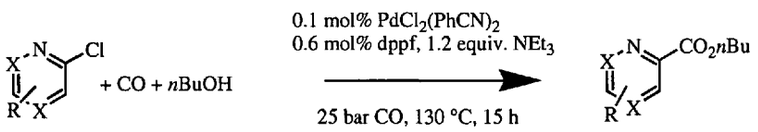
It is interesting to note that chloroarenes activated by electron-withdrawing groups can be carbonylated (at reasonable temperatures and Pd concentrations) in the presence of Pd catalyst systems based on the PCy_3 and similar ligands. Also more reactive heteroaryl chlorides might be activated efficiently in the presence of well-known 'standard ligands' such as dppf (1,1'-bis(diphenylphosphino)ferrocene) or dppb (1,4-bis (diphenylphosphino)butane) (Table 2) [20]. For example good to excellent yields of a number of N-heterocyclic carboxylic acid esters were realized by carbonylation of N-heteroaryl chlorides applying the appropriate ligand in the right concentration at low catalyst loadings (0.005–0.5 mol% Pd).

Here catalyst turnover numbers of up to 13,000 were obtained for the carbonylation of 2- or 4-substituted chloropyridines. The carbonylation of heteroaryl halides is of special interest to fine chemical synthesis, since there are many examples of heteroaromatic substructures in agrochemical and pharmaceutical agents.

Conclusion

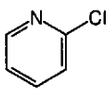
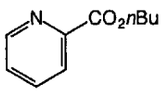
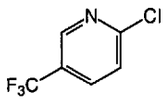
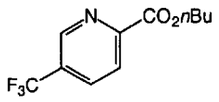
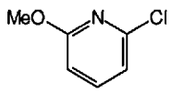
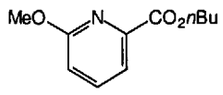
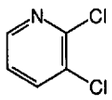
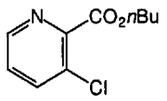
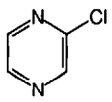
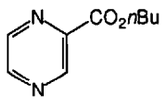
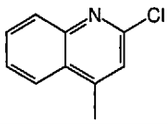
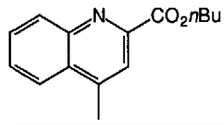
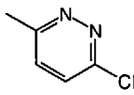
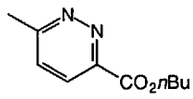
It is obvious that organic halides in comparison to toluenes are less attractive starting materials for the industrial synthesis of bulk benzoic acid derivatives. Nevertheless, the application of the carbonylation of aryl halides and similar starting materials is of importance for the synthesis of higher value fine chemicals and organic building blocks. In general it is nowadays possible by careful optimization of the catalyst system and the reac-

Table 2. Butoxycarbonylation of N-heteroaryl chlorides[a].



X = CH or N

R = CF_3, OMe, Cl, CH_3

Entry	Substrate	Product	Yield[%][b]
1			95
2			94
3			83
4			73
5			82
6			74
7			83

[a]7.0 mmol N-heteroaryl chloride, 14 ml n-butanol, 1.2 equiv. NEt_3, 0.1 mol% $PdCl_2(PhCN)_2$, 0.6 mol% dppf, 130 °C, 25 bar CO, 15 h. [b]isolated yield.

tion conditions to perform such reactions in an economically sensible way. Hence, further applications of carbonylations are foreseen due the numerous possibilities for the selective synthesis of various aromatic carboxylic acid derivatives and the often existing high pressure equipment in industry.

Apart from this aspect, there are interesting research goals for academia and industry. Further catalyst improvements are desirable, and regarding reductive carbonylation (synthesis of aldehydes) there is a need for more general methods. In addition, efficient asymmetric carbonylations of benzyl- and allyl-X derivatives have not achieved so far.

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