Carbonylation

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Palladium-Catalyzed Carbonylations of Aryl Bromides using Paraformaldehyde: Synthesis of Aldehydes and Esters**

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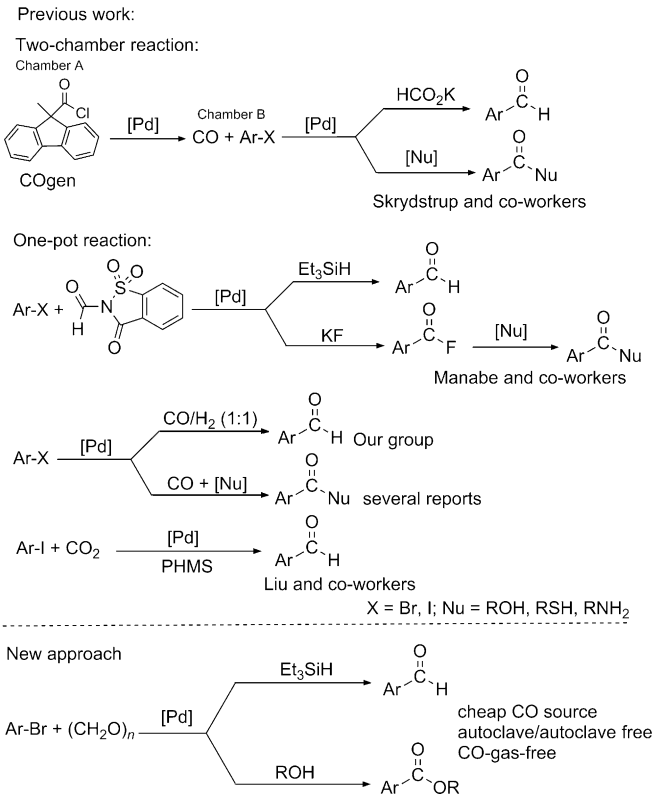
Abstract: *Carbonylation reactions represent useful tools for organic synthesis. However, the necessity to use gaseous carbon monoxide is a disadvantage for most organic chemists. To solve this problem, novel protocols have been developed for conducting palladium-catalyzed reductive carbonylations of aryl bromides and alkoxycarbonylations using paraformaldehyde as an external CO source (CO gas free). Hence, aromatic aldehydes and esters were synthesized in moderate to good yields.*

Aromatic aldehydes carrying additional substituents are an important class of compounds which are widely used in organic synthesis as versatile intermediates. In addition, they are produced on larger scale in the pharmaceutical, agrochemical, and fine-chemical industries as valuable building blocks.[1] Despite their importance, the efficient and selective synthesis of functionalized benzaldehydes are still challenging. In industry, aromatic aldehydes are commonly produced by either oxidations or chlorination/hydrolysis which goes together with significant waste formation. Classical synthetic protocols on laboratory scale such as the Vielsmeier–Haack, Gattermann–Koch, Reimer–Tiemann, and Duff reactions are well known. However, large amounts of reagents, multiple steps, and production of at least a stoichiometric amount of waste, limit these methodologies.[2] Hence, alternative routes have been developed in the past, including the reduction of carboxylic acids and their derivatives, with hydrogen,[3] and the palladium-catalyzed direct formylation of aryl halides.[4]

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylations using CO enabled the synthesis of a variety of carbonyl compounds.[5] Nowadays, these reactions are routinely applied for constructing carbonyl-containing compounds such as aldehydes, amides, esters, etc.[6] Although a variety of palladium-based catalysts is available for alkoxy- and aminocarbonylations of aryl and vinyl halides, there are comparatively few general protocols known concerning the synthesis of interesting benzaldehydes.[6a]

In 2006, our group developed a selective protocol for the reductive carbonylation of aromatic, heteroaromatic, and vinylic bromide substrates using syngas (CO/H_2 1:1). This methodology is also applied on an industrial scale for the production of a specific aromatic aldehyde which serves as a drug intermediate.[4a–c] However, with respect to general applications the use of carbon monoxide is not desired because of its toxicity and gaseous nature. Consequently, there is a great interest in CO-free carbonylations and this area has attracted a lot of attention over the last three decades, and become the subject of intense research.[7,6a] More recently, Skrydstrup and co-workers[8] developed an elegant system for ex situ generation of CO in a sealed two-chamber system (COware) by using 9-methylfluorene-9-carbonyl chloride (COgen) as a solid CO precursor (Scheme 1). By using this system they reported several efficient palladium-catalyzed carbonylation reactions, and they also used this technique for selective ^{13}C-isotope labeling. As an example, they demonstrated the reductive carbonylation of aryl iodides with COgen and potassium formate as a hydride source.[8f] Moreover, other research groups used CO



Scheme 1. Palladium-catalyzed carbonylations of aryl halides.

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alternatives such as alkyl and aryl formates for alkoxycarbonylation of olefins and aryl halides.[9] In the last two years, Manabe and co-workers reported an interesting palladium-catalyzed reductive carbonylation of aryl halides using *N*-formylsaccharin and phenyl formate as a CO source.[10a,b] This procedure provides efficient access to the corresponding aldehydes and esters. Also, the synthesis of amides, alkyl esters, and thioesters can be achieved by a two-step process using 2,4,6-trichlorophenyl formate as a reactive intermediate.[10c] It should also be noted that inorganic carbonyl compounds have been employed for in situ CO generation. Nevertheless, they require relatively high catalyst loadings and necessitate the use of stoichiometric amounts of toxic metal carbonyls, thus limiting their application.[11] Most recently, Liu and co-workers[12] reported the Pd/C-catalyzed direct formylation of aromatic iodides to aryl aldehydes using CO_2 and silanes.

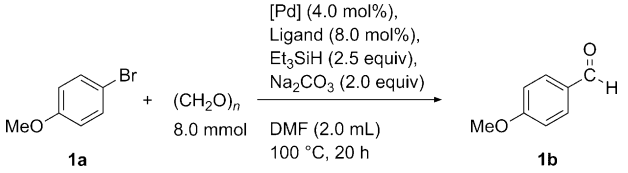
Inspired by the above-mentioned reports and also based on our continuous interest in carbonylation reactions,[13] we recently started to explore carbonylation reactions with alternative CO sources.[9c,13] Herein, we report the first successful application of readily available paraformaldehyde in a CO-gas-free synthetic protocol for the palladium-catalyzed carbonylations of aryl halides (Scheme 1). This novel approach offers a convenient synthesis of a variety of (hetero)aromatic aldehydes and other carboxylic acid derivatives under relatively mild reaction conditions. Notably, paraformaldehyde is a solid, stable, and inexpensive CO surrogate.

In our initial studies, we investigated the formylation of 4-bromoanisole (**1a**) with paraformaldehyde in the presence of silanes as a model system. Preliminary experiments showed that the combination of $Pd(OAc)_2$ and dppf proved to be the optimal catalyst system in the presence of Et_3SiH, DMF (solvent), and Na_2CO_3 (base). As shown in Table 1, 83% of the corresponding aldehyde was obtained under optimized reaction conditions (Table 1, entry 3). Structurally similar and different phosphine ligands as well as other palladium precursors such as $[Pd_2(dba)_3]$ and $[Pd(CH_3CN)_2Cl_2]$ gave significantly lower yields of the desired 4-methoxybenzaldehyde (Table 1, entries 2, 9, 10; see Table S1 in the Supporting Information). Notably, in the presence of most commercially available monodentate and bidendate phosphine ligands no product or very low yield was obtained, thus demonstrating the challenging nature of this coupling reaction (Table 1, entries 4–8, 11; Table S1).

Further optimizations were conducted with different solvents and bases (see Table S1 in the Supporting Information). More specifically, Na_2CO_3 provided the best result compared to all other tested bases, and DMF as solvent gave satisfactory results. Regarding the hydride source, the best product yield was obtained in the presence of 2.5 equivalents triethylsilane.

Next, we examined the formylation of bromobenzene in the presence of the $Pd(OAc)_2$/dppf catalyst system. Unfortunately, mainly dehalogenation was observed and only traces of the desired benzaldehyde were obtained. In this experiment it turned out that a significant amount of paraformaldehyde was precipitating on the top of the vessel. Obviously, this decreased the paraformaldehyde concentration in solution, thus inducing the low productivity. To avoid the evaporation of paraformaldehyde from the reaction mixture we pressurized the reaction with 20 bar of N_2.

Table 1: Palladium-catalyzed reductive carbonylation of 4-bromoanisole: Variation of reaction conditions.[a]



1a **1b**

Entry	Ligand	Catalyst	Yields[b] [%]
1	dppe	$Pd(OAc)_2$	5
2	dppb	$Pd(OAc)_2$	40
3	dppf	$Pd(OAc)_2$	83
4	$BuPAd_2$	$Pd(OAc)_2$	12
5	PPh_3	$Pd(OAc)_2$	8
6	PCy_3	$Pd(OAc)_2$	5
7	Xphos	$Pd(OAc)_2$	10
8	Bupox	$Pd(OAc)_2$	5
9	dppf	$[Pd_2(dba)_3]$	35
10	dppf	$[PdCl_2(CH_3CN)_2]$	44
11	dppf	$[PdCl_2(PPh_3)_2]$	traces

[a] Reactions were performed with 0.5 mmol of 4-bromoanisole, 8 mmol of paraformaldehyde, 4 mol% of [Pd], 8.0 mol% of ligand, 2.5 equiv Et_3SiH and 2.0 equiv base at 100°C for 20 h. [b] Yield was determined by GC with hexadecane as the internal standard. Ad = adamantyl, Bupox = 1,2-bis(di-*tert*-butylphosphinomethyl)benzene, dba = dibenzylideneacetonate, dppb = 1,4-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DMF = *N*,*N*-dimethylformamide, Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Indeed, under these reaction conditions formylation of bromobenzene gave 37% (GC yield) of benzaldehyde. However, using a different catalyst (combination of $[Pd(CH_3CN)_2Cl_2]$/dppb) led to 82% yield of the desired product (**3b**; Figure 1, Procedure A:). This promising result encouraged us to study the general scope and limitations for the formylation of different aryl and heteroaryl bromides. In the course of this, different substituted aryl bromides were transformed in moderate to good yields into valuable aldehydes. Notably, functional groups including electron-neutral or electron-donating ones such as methoxy (**4b**), methylene dioxy (**14b**), NMe_2 (**9b**), and thio (**6b**) were tolerated well. In addition, 4-chloro- and 4-fluro-1-bromobenzene are chemoselectively converted into the desired 4-halo-benzaldehydes **7b** and **10b**, respectively. Moreover, electron-withdrawing groups such as CF_3 and CHO on the aryl group (**11b** and **8b**) resulted in similar yields. Moreover, the reaction worked well for a series of bromonapthalenes (**18b**, **19b**, and **20b**). Heterocycles such as **22b**, **23b**, and **24b**, containing sulfur and nitrogen atoms, led to moderate to good yields of the corresponding products.

To make the formylation procedure more versatile we performed some formylation reactions using NMP as the solvent. Indeed, using an inexpensive sealed tube as a reaction vessel bromobenzene resulted in high yield (88%) of benzaldehyde (**3b**; Figure 1, procedure B). Gratifyingly,

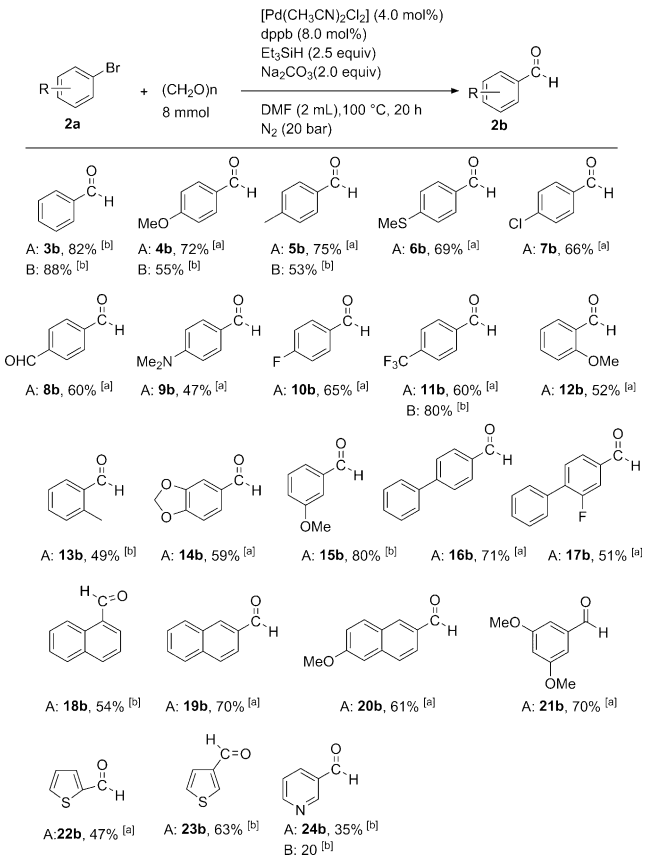


Figure 1. Substrate scope of the various aryl bromides. Reaction conditions: Procedure A: Substrate (0.5 mmol), paraformaldehyde (8 mmol). Procedure B: NMP (2 mL) in sealed tube. [a] Yields of isolated products are shown. [b] Yield was determined by GC with hexadecane as an internal standard.

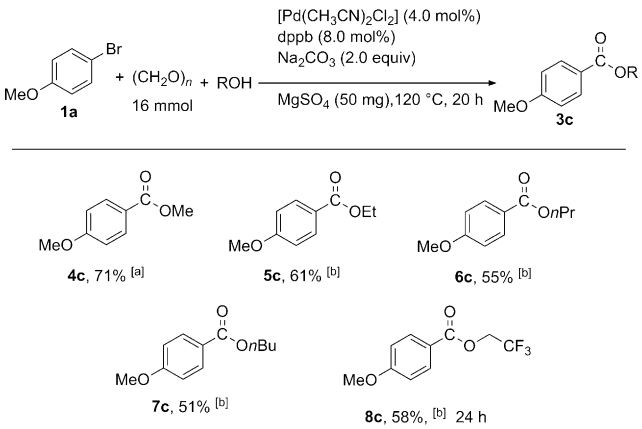


Figure 2. Palladium-catalyzed alkoxycarbonylation of 4-bromoanisole with paraformaldehyde and various alcohols. Reaction conditions: Substrate (0.2 mmol), paraformaldehyde (16 mmol), ROH (0.5 mL). [a] Yield was determined by GC with hexadecane as the internal standard. [b] Yields of isolated products are shown.

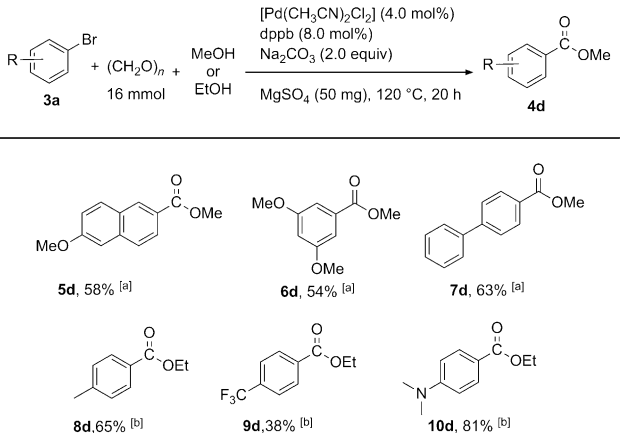


Figure 3. Palladium-catalyzed alkoxycarbonylation using various aryl bromides. Reaction conditions: Substrate (0.2 mmol), paraformaldehyde (16 mmol), MeOH or EtOH (0.5 mL). [a] Yields of isolated products are shown. [b] Yield was determined by GC with hexadecane as the internal standard.

a number of other substrates can be converted into the desired aldehydes with good yields (**4b**, **5b**, **11b**; procedure B).

Among the possible carbonylation products resulting from aryl halides, esters represent another important class of compounds in organic synthesis, and this structural motif is found in numerous pharmaceuticals, agrochemicals, fragrances, and polymers.[14] Specifically, substituted benzoic acid esters are used as valuable building blocks in the fine- and bulk-chemical industries. In this context, it is also interesting to synthesize aromatic esters under CO-gas-free conditions. Initially, we adapted the reaction conditions from Figure 1 by using methanol instead of Et_3SiH. However, only 15% of the desired ester was generated (see Table S2 in the Supporting Information). Increasing the amount of paraformaldehyde (from 8 mmol to 16 mmol) improved the yield of methyl 4-methoxybenzoate to up to 38%.

Further optimization showed that the best results (71% yield) were obtained using $[Pd(CH_3CN)_2Cl_2]$ (4 mol%), dppb (8 mol%), paraformaldehyde (16 mmol), Na_2CO_3 (2 equiv), and $MgSO_4$ (50 mg) at 120°C for 20 hours (see Table S2). Under these reaction conditions reaction of 4-bromoanisole with five different alcohols gave the corresponding esters in moderate to good yields (Figure 2). Moreover, alkoxycarbonylation of six substituted aryl bromides proceeded smoothly under identical reaction conditions (38–81%; Figure 3).

To understand the nature of this novel carbonylation process involving paraformaldehyde and to gain insight into the reaction mechanism, several labelling experiments, with 4-bromoanisole as a substrate were performed (Figure 4). Using ^{13}C-labelled paraformaldehyde, the ^{13}C-carbonyl-labelled aldehyde and ester are formed predominantly. In addition, using $^{13}CH_3OH$ and CD_3OD afforded the expected labelled products (see Scheme S7 for MS (EI) spectra).

Next, we investigated the reactivity of paraformaldehyde in the presence of the catalyst system ($[Pd(CH_3CN)_2Cl_2]$, dppb) and base (Na_2CO_3) in DMF at 100°C (Scheme 2). Here, we were especially interested to know if CO gas is formed and if so in what amounts (for experimental details and GC spectra see Scheme S4). Indeed, within 2 hours 4% of the paraformaldehyde was converted into CO (550 ppm of the gas phase), thus demonstrating the slow release of CO.

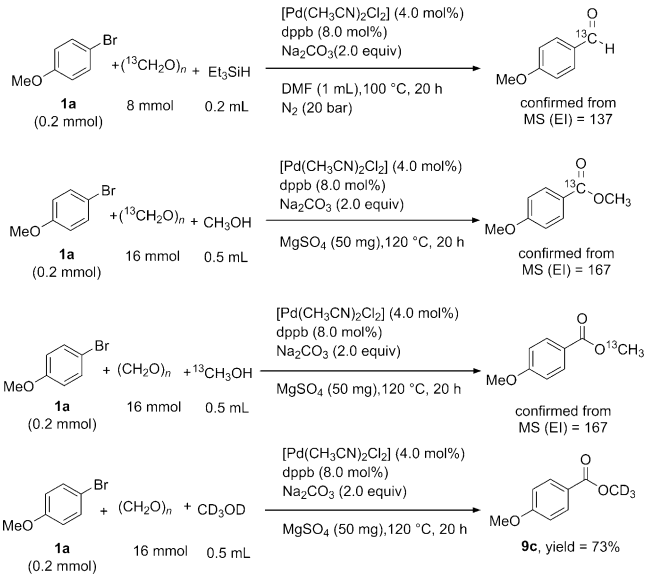
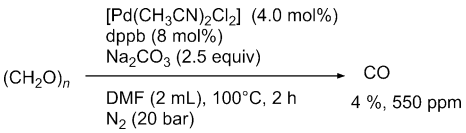


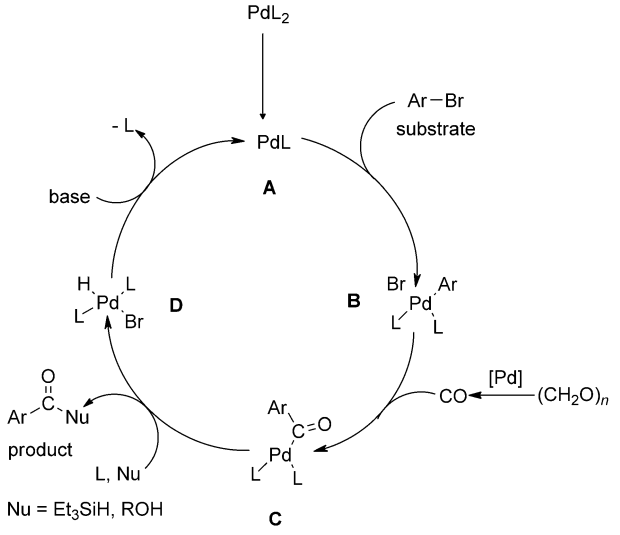
Figure 4. Alkoxycarbonylation of 4-bromoanisole with labelled compounds.



Scheme 2. Palladium-catalyzed CO formation from paraformaldehyde.

Furthermore, traces of carbon dioxide were also found in the gas phase.

As a result of these observations, we propose the mechanism shown in Scheme 3. After formation of the active palladium(0) species **A**, oxidative addition of the aryl bromide takes place to form the complex **B.** Then, migratory insertion of CO into the Ar–Pd bond (**C**), and hydrogenolysis of the resulting acyl complex or nucleophilic attack of the alcohol give the desired product (aldehyde or ester). Finally, the active palladium complex is regenerated from the palladium hydrobromide complex via reaction with base.



Scheme 3. Proposed catalytic cycle for the palladium-catalyzed carbonylation of aryl bromides with paraformaldehyde as CO source.

In conclusion, we developed novel CO-free carbonylation protocols for the palladium-catalyzed reductive carbonylation and alkoxycarbonylation of aryl bromides. Notably, paraformaldehyde is readily available and constitutes an inexpensive formylating reagent. This synthetic approach offers a convenient alternative compared to conventional carbonylations using syngas or CO directly. Advantageously, most of the reactions can be performed in conventional glassware and does not require high-pressure equipment. Currently, we are expanding this work to other kinds of carbonylation reactions.

Experimental Section

Procedure A: The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for six 4 mL Wheaton vials. $[Pd(CH_3CN)_2Cl_2]$ (5 mg, 4 mol%), dppb (17 mg, 8 mol%), paraformaldehyde (120 mg, 8 mmol), Na_2CO_3 (106 mg, 1.0 mmol, 2.0 equiv), and a magnetic stir bar were placed in each of the vials, which were then capped with a septum equipped with an inlet needle and flushed with argon. Then, Et_3SiH (200 μL, 1.25 mmol, 2.5 equiv), and 4-bromoanisole (62 μL, 0.5 mmol) in DMF (2 mL) was added to the vial with a syringe. The vials were placed in an alloy plate, which was then placed in the autoclave. Once sealed, the autoclave was purged several times with argon, then pressurized to 20 bar of N_2 at room temperature and heated at 100 °C for 20 h. It was then cooled to room temperature and vented to discharge the N_2. The product was extracted with ethyl acetate (5 × 3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. Purification by flash chromatography on silica gel (eluent: heptane/EtOAc 70:30) gave the product **4b** (72%) as a colorless oily liquid.

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