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Continuous-Flow Pd-Catalyzed Carbonylation of Aryl Chlorides with Carbon Monoxide at Elevated Temperature and Pressure

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The development of a continuous-flow protocol for a palladium-catalyzed methoxycarbonylation of (hetero)aryl chlorides using carbon monoxide gas and methanol is described. (Hetero)aryl chlorides are the least expensive of the aryl halides, but are underutilized in carbonylation reactions due to their very poor reactivity. The described protocol exploits intensified conditions at elevated temperature and pressure, which are readily accessed within a continuous-flow environment, to provide moderate to excellent product yields (11 examples) in a short 16 min residence time. The continuous-flow protocol enables the safe and potentially scalable carbonylation of aryl chlorides using CO gas.

Palladium-catalyzed carbonylation of aryl halides and vinyl halides using carbon monoxide was discovered by Schoenberg and Heck more than 40 years ago.[1] CO is an inexpensive, atom efficient and synthetically valuable C_1 building block for organic chemistry, and it is readily available in large quantities from the bulk chemical industry.[2] The carbonyl group is a key component in aldehydes, ketones, carboxylic acids and their derivatives. Thus, carbonylation reactions using CO have found widespread application in the chemical industry over recent years.[3–6]

Since the pioneering research by Schoenberg and Heck, researchers have mostly focused on developing carbonylation protocols for aryl bromides and iodides using a wide range of

phosphine ligands.[3,4] Aryl chlorides are the least expensive when compared to other aryl halides.[7] Despite their low cost, aryl chlorides have received far less prominence for Pd-catalyzed carbonylation reactions.[4] Aryl chlorides are relatively inert due to the high stability of the carbon-chlorine bond. The oxidative addition of the aryl chloride to Pd(0) is generally accepted to be the rate limiting step in the catalytic cycle.[8] The utilization of aryl chlorides in carbonylation reactions potentially gives access to a wide range of useful products at low cost (Scheme 1). The procedures reported for the carbonylation of
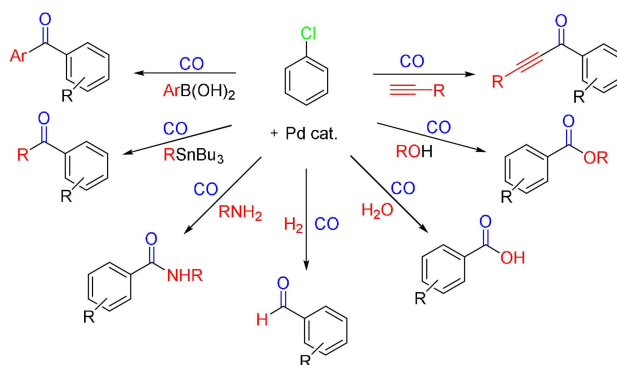
Scheme 1. Possible carbonylation reactions of (hetero) aryl chlorides using CO.

aryl chlorides typically use elevated temperature and pressure, require high catalyst and ligand loadings, and long reaction times are generally necessary.[9] More recently, protocols which use milder conditions have been established, but these generally require more specialized catalyst systems and extended reaction times are still required.[10]

Virtually all of the procedures reported for the carbonylation of aryl chlorides were developed using batch autoclave apparatus.[8,9] There are challenges associated with using batch reactors that prevent the carbonylation of aryl chlorides with CO gas to be widely adopted in organic synthesis, particularly at large scales.[11] Specialized equipment is necessary to handle the elevated temperatures and pressures used. Under batch conditions, a large inventory of highly poisonous CO needs to be loaded and pressurized into a batch vessel to minimize mass transfer effects, with most of the gas remaining in the reactor headspace. In addition, the mass transfer of CO from the gas phase to the liquid phase can result in scalability problems.

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Continuous-flow technologies have attracted attention from the scientific community, in particular from the industrial sector due to the safety and scalability benefits when compared to traditional batch processing.[12] The specific characteristics of microreactors in terms of enhanced mass and heat transfer, precise control of reaction parameters and potential scalability enable many of the challenges associated with handling Pd-catalyzed carbonylation reactions to be overcome. Furthermore, the utilization of continuous processing allows the safe access to typically "forbidden chemistry", such as high T/p conditions, operation within explosive regimes, and the handling of hazardous reagents and intermediates.[12,13] Over the past decade, many groups have developed continuous-flow protocols for carbonylation reactions using CO gas.[14] Hence, we envisaged that continuous flow chemistry could be applied to the carbonylation of aryl chlorides under high T/p conditions.

Herein, we describe the preliminary results for a Pd-catalyzed methoxycarbonylation of aryl chlorides using CO gas in continuous-flow mode. To our knowledge, this is the first reported carbonylation utilizing aryl chlorides and CO using continuous processing.[15]

A Phoenix Flow Reactor from ThalesNano, see Figure 1, was assembled consisting of a high pressure pump (P, Knauer), a residence time unit (RTU) equipped with a stainless steel coil (40 mL internal volume) and an adjustable back pressure regulator (BPR2) with a pressure maximum of 100 bar. A mass flow controller (MFC) was used for the introduction of CO in a controlled manner from a cylinder. A BPR (BPR1) was used as a check valve to avoid any possibility of solvent entering the MFC. The mixing of the gas and liquid streams was performed using a static mixer (M). The stream exiting the reactor was cooled down before the BPR by using a heat exchanger (HE).

We commenced our study by using 4-chlorobenzonitrile **1a** as a model substrate to provide methyl 4-cyanobenzoate **2a** as the desired product. We initially undertook a screening campaign to identify reaction conditions amenable to flow processing. High temperatures and pressures were utilized from the outset due to the very poor reactivity of aryl chlorides (Table 1). Batch conditions for the methoxycarbonylation of aryl chlorides typically vary between 100 to 150 °C, 4 to 40 bar, and 1 to 5 mol% catalyst/ligand loading, with reaction times always within the timescale of hours (5 to 24 hours).[4,8] The nucleophile is normally added in high excess because it also functions as the solvent. We encountered difficulties on transferring existing batch conditions directly to flow due to the long reaction times
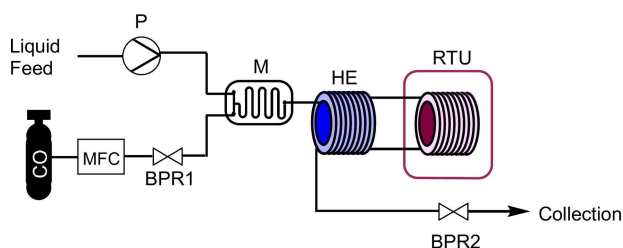
Table 1. Initial optimization of 4-chlorobenzonitrile **1a** methoxycarbonylation under continuous-flow conditions.[a]

Entry	T [°C]	p [bar]	MeOH/MeCN solvent ratio	Cat. loading [mol%]	Conv. 1a [%][b]	Yield 2a [%][b]	Yield 3a [%][b]
1[c,d]	150	20	1:0	5	23	23	–
2[c,d]	150	20	1:0.4	5	23	23	–
3	150	20	1:1	5	22	22	–
4	170	23	1:1	5	62	60	<2
5	170	23	1:1	2.5	53	53	<1
6[e]	180	34	1:1	5	88	86	<2
7[e]	190	43	1:1	5	96	94	<2

[a] Reaction conditions: 4-chlorobenzonitrile **1a** (1 mmol), dppp (10 mol%), Et$_3$N (2 equiv) in solvent (10 mL), liquid flow rate = 2.4 mL min^{-1}, CO flow rate = 12 mL$_n$ min^{-1}, t$_{res}$ = 16 min; [b] Conversion and yields were measured by HPLC-UV area% integration at 254 nm; [c] 4-Chlorobenzonitrile **1a** (5 mmol); [d] A precipitate blocked the reactor; [e] Et$_3$N (4 equiv), CO flow rate = 18 mL$_n$ min^{-1}.

that would be needed to achieve reasonable conversion and yield, and from the poor solubility of the products formed (entries 1 and 2). The problem associated with solubility was solved through reducing the substrate concentration and by the utilization of MeOH/MeCN at a ratio of 1:1. Changing the concentration and solvent ratio had no apparent influence on reaction rate (entry 3). Gratifyingly, the product was obtained in 60% yield within 16 min residence time on increasing the temperature to 170 °C (entry 4). A drop in conversion and yield was observed when the catalyst loading was decreased to 2.5 mol% (entry 5). The conversion and yield were improved on increasing the temperature to 180 °C (entry 6). The conversion and yield could be successfully increased to 96% and 94%, respectively, when operating the system at 190 °C and by using 4 equivalents of triethylamine (entry 7). At higher pressures, it was necessary to use 3 equivalents of CO to provide a more stable CO flow rate.[16] The expected residence time of 16 min was maintained which indicated all the gas was dissolved in the liquid phase. A benefit of having all the CO dissolved in solution is that the residence time remains constant. The undesired dechlorinated side product **3a** was formed in less than 2% yield in all the initial optimization experiments.

Once the initial conditions were established, we proceeded to investigate the parameter effects on conversion and yield further. The screening of conditions included the evaluation of a range of phosphine ligands (Table 2). The oxidative addition is believed to be the rate determining step, therefore ligands which push electron density onto Pd and stabilize Pd(0) generally perform better in carbonylation reactions.[3–6] At high temperatures, phosphine Pd(0) complexes are usually short-lived with the Pd(0) agglomerating and the irreversibly forming inactive solid (Pd black). The monodentate phosphine ligands trialed did not work (entries 1 and 2). 1,3-Bis(diphenylphosphino)propane (dppp), one of the least expensive bidentate

Figure 1. Continuous-flow setup for Pd-catalyzed carbonylation using CO (for further details, see the Supporting Information).

Table 2. Results of the ligand screening. [a]

$$1a \xrightarrow[\text{MeOH/MeCN}]{\substack{\text{Pd(OAc)}_2 \\ \text{CO, Et}_3\text{N}}} 2a$$

Entry	Ligand	Structure	Yield 2a [%][b]
1	PPh₃		< 1
2	P(C₆H₁₁)₃		< 1
3	(S)-BINAP		< 1
4	dppe		18
5	dppbe		20
6[c]	Xantphos		31
7[d]	Xantphos		32
8	dppp		60

[a] Reaction conditions: 4-chlorobenzonitrile **1a** (1 mmol), Pd(OAc)2 (5 mol%), ligand (10 mol%), Et3N (2 equiv) in MeOH/MeCN 1:1 (10 mL), liquid flow rate = 2.4 mL min⁻¹, CO flow rate = 12 mL$_n$ min⁻¹1, T = 170°C, p = 23 bar; [b] Yields were measured by HPLC area% integration; [c] CO (1.5 equiv); [d] CO (1.2 equiv).

ligands, provided the best results (entry 8). 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) also showed promising results (entries 6 and 7). The ratio of dppp to Pd (OAc)₂ was also investigated. The formation of Pd black was observed for experiments with a dppp to Pd ratio of below 1.25:1 which demonstrated that some of the catalyst was lost from the catalytic cycle, although, no difference in yield was observed (Table S3). The optimal ligand to catalyst ratio was determined to be 1.25:1.

A study of the residence time showed that the conversion halts at ~16 min (Table S4). No Pd black formation was observed in the outlet solution in the experiments with dppp. However, Pd black can deposit onto the reactor wall on its formation.[14i] Pd can be readily recovered from the reactor by washing with 20% aqueous nitric acid solution at 60°C. Inductively coupled plasma mass spectrometry (ICPMS) analysis was used to measure the amount of Pd remaining in solution compared to the amount deposited on the reactor channels. The results showed that nearly all the Pd remained in solution with only 6% of the Pd deposited on the reactor channels

during the experiment (Table S8). Thus, the analysis demonstrated that only a small amount of Pd black was formed. A control experiment demonstrated that the residual deposited Pd was catalytically inactive when a feed solution, in the absence of Pd(OAc)₂, provided a yield below 1%. The results therefore indicated that the active catalyst is converting to an inactive form which is soluble in solution.

Subsequently, the influence of the base type on the reaction was studied (Table S5). Several organic soluble bases were screened with triethylamine affording the best yield. The influence of equivalents of base was also studied (Table S6). By doubling the equivalents of base from 2 to 4 at 5 mol% catalyst loading, the yield was improved to 78%. However, when performing the same increase in base equivalents at 2.5 mol% catalyst loading, no change in yield was observed. These results indicate that the optimal amount of base is not related to the substrate but to the catalyst, a ratio of 80 between base to catalyst was determined to be optimal.

The influence of CO stoichiometry was investigated by varying the CO flow rate (Figure 2). The utilization of substoichiometric amounts of CO resulted in the formation of large quantities of the dechlorinated side product **3a**. However, the equivalents of CO did not influence the reaction when used in excess to the substrate. It is important to note that over a prolonged operation time a more reproducible pressure control could be achieved by using 2 equiv. of CO when operating at 23 bar and 3 equiv. of CO at higher pressures.

The general applicability of the continuous-flow protocol for the carbonylation of aryl chloride substrates is shown in Table 3. Electron poor aromatics displayed the highest reactivity, with substrates possessing an electron withdrawing group or electron deficient N-heterocycles affording the highest yields. N-heterocycles gave higher conversions than benzene derivatives with 100% conversion at 170°C observed in most cases (entries 7 to 12). The reactivity of the benzene derivatives could be increased through the utilization of higher temperatures and pressures as shown with the model substrate **1a**. 2-Chlorobenzonitrile **1b** displayed poorer reactivity than 4-chlorobenzonitrile **1a**. 4-Chloronitrobenzene **1e** did not react to give the desired product, but the nitro group was reduced to the corresponding amino derivative **4**. The Pd-catalyzed reduction
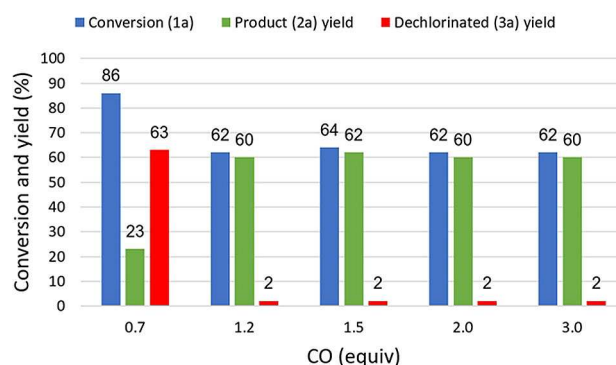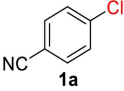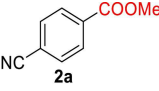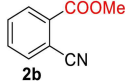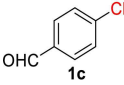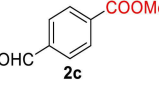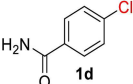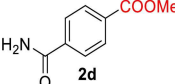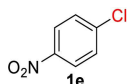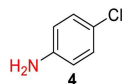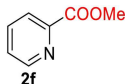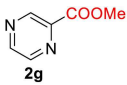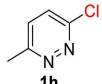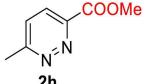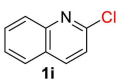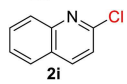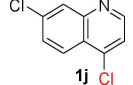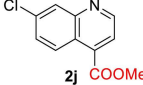

Figure 2. Influence of CO equivalents on the reaction outcome. Reaction conditions are described in Table 2, entry 8, CO (1 equiv) = 6 mL$_n$ min⁻¹.

Table 3. Scope and limitations of flow protocol.[a]

$$\text{(Het)Ar-Cl} \quad \xrightarrow[\text{MeOH/MeCN}]{\substack{\text{Pd(OAc)}_2 \\ \text{CO, Et}_3\text{N}}} \quad \text{(Het)Ar-CO}_2\text{Me}$$

1a-l → 2a-l

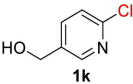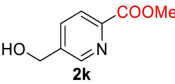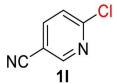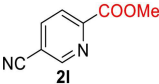| Entry	Substrate 1	Product 2	Conv. 1 [%][b]	Yield 2 [%][c]
1[d]	1a	2a	96	81
2	1b	2b	45	45[b]
3	1c	2c	91	70
4	1d	2d	80	20[b]
5	1e	4	100	–
6[g]	1f	2f	100	96
7[e,f]	1g	2g	100	61
8[f]	1h	2h	100	87
9	1i	2i	100	84
10[f]	1j	2j	90	70
11[g]	1k	2k	100	73
12[h]	1l	2l	100	82

[a] Reaction conditions: substrate **1 a–l** (2.5 mmol), Pd(OAc)$_2$ (5 mol%), ligand:catalyst 1.25:1, Et$_3$N (4 equiv) in MeOH/MeCN 1:1 (25 mL), liquid flow rate = 2.4 mL min^{-1}, CO flow rate = 12 mL$_n$ min^{-1} (2 equiv), T = 170 °C, P = 23 bar. [b] Determined by NMR. [c] Isolated yield. [d] T = 190 °C, p = 43 bar, CO flow rate = 18 mL$_n$ min^{-1} (3 equiv). [e] T = 180 °C, p = 34 bar, CO flow rate = 18 mL$_n$ min^{-1}. [f] MeOH/MeCN 1:9. [g] Pd(OAc)$_2$ (2.5 mol%), Et$_3$N (2 equiv). [h] Pd(OAc)$_2$ (1.25 mol%), Et$_3$N (1 equiv).

of nitro groups to amino groups by CO is well known, and was the focus of a recent study by our group.[17] The reactions for chloropyrazine **1 g** and 3-chloro-6-methylpyridazine **1 h** resulted in the formation of solids which blocked the reactor, which could be prevented by using MeOH/MeCN at a 1:9 solvent ratio. Full conversion of 2-chloropyrazine **1 g** could be achieved at 180 °C and 34 bar pressure. The reaction of 4,7-dichloroquinoline **1 j** resulted in significant formation of the double substituted derivative. The selectivity for the monosubstituted

product **2 j** was improved by changing the MeOH/MeCN solvent ratio to 1:9. The catalyst loading could be lowered for more reactive substrates, for instance full conversion was achieved for 2-chloro-4-hydroxymethylpyridine **1 k** at 2.5 mol% and 2-chloro-5-cyanopyridine **1 l** at 1.25 mol% Pd(OAc)$_2$ loading.

The scalability of the continuous-flow protocol was demonstrated through a scale-out experiment using 2-chloro-5-cyanopyridine **1 l** as the substrate and 1.5 mol% Pd(OAc)$_2$ loading. The system was operated over a period of 100 min (5

reactor volumes worth), with the output fractionated at 25 min intervals. Analysis of the fractions demonstrated that the system could be operated consistently over a longer operation time (Figure S5), thus the protocol can be used to synthesize larger quantities. The collected output solutions were combined and purified by column chromatography to afford pure methyl 5-cyanopicolinate **2l** in 84 % isolated yield.

In conclusion, we have described a continuous-flow protocol for the carbonylation of aryl chlorides using CO gas under high T/p conditions. Among all the catalytic systems studied, Pd (OAc)$_2$/dppp provided the best performance due to its high stability under high T/p conditions. The flow protocol uses 5 mol % catalyst loading. This loading is higher than in some batch protocols, however the reaction time is significantly reduced to only 16 min in flow compared to the long reaction times necessary under typical batch conditions. The protocol was most successful for the carbonylation of electron deficient aromatics, in particular N-heterocycles. The catalyst and ligand loadings could be decreased further for more reactive substrates through the utilization of high T/p conditions which are readily accessed in a continuous-flow environment. In contrast to operation within batch, there was no vapor phase or headspace in flow because all of the gas was dissolved in solution, since a very low amount of CO (2 to 3 equiv) could be utilized, thus improving the inherent safety and potential scalability of the developed protocol.

Conflict of interest

The authors declare no conflict of interest.

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