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Continuous-flow Synthesis of Aryl Aldehydes by Pd-catalyzed Formylation of Aryl Bromides Using Carbon Monoxide and Hydrogen

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Abstract

A continuous-flow protocol utilizing syngas (CO and H₂) was developed for the palladiumcatalyzed reductive carbonylation of (hetero)aryl bromides to their corresponding (hetero)aryl aldehydes. The optimization of temperature, pressure, catalyst and ligand loading, and residence time resulted in process intensified flow conditions for the transformation. In addition, a key benefit of investigating the reaction in flow is the ability to precisely control the CO to H₂ stoichiometric ratio, which was identified as having a critical influence on yield. The protocol proceeds with low catalyst and ligand loadings, palladium acetate (1 mol% or below) and cataCXium A (3 mol% or below). A variety of (hetero)aryl bromides at a 3 mmol scale were converted to their corresponding (hetero)aryl aldehydes at 12 bar pressure (CO/H_2) = 1:3) and 120 °C reaction temperature within 45 minutes residence time to afford products mostly in good to excellent yields (17 examples). In particular, a successful scale-up was achieved over 415 minutes operation time for the reductive carbonylation of 2-bromo-6methoxynaphthalene to synthesize 3.8 g of 6-methoxy-2-naphthaldehyde in 85% isolated yield. Studies were conducted to understand catalyst decomposition within the reactor by using inductively coupled mass spectrometry (ICPMS) analysis. The palladium could easily be recovered using an aqueous nitric acid wash post reaction. Mechanistic aspects and the scope of the transformation are discussed.

Introduction

Aryl and heteroaryl aldehydes are important intermediates in the synthesis of biologically active molecules (Figure 1). There are a number of synthetic strategies to form aryl aldehydes from their corresponding aryl bromides. One strategy is to use halogen-lithium exchange and subsequently react the lithium intermediate with dimethylformamide (DMF) (Scheme 1a).^[1] However, this protocol requires stoichiometric metal and has limited substrate scope due to the sensitivity of some substrates to decomposition by a strong base such as *n*-butyllithium (*n*-BuLi). Pd-catalyzed formylation of aryl bromides has emerged as a powerful methodology in organic synthesis for the synthesis of carbonyl compounds.^[2] In the case of reductive carbonylations, CO is used in combination with a hydrogen donor source, such as silyl and tin hydrides, or formate salts, to achieve formylation at low pressure (Scheme 1b).^[3,4] However, these protocols often require high catalyst loadings, and silicon and tin hydrides are relatively expensive, which limits their use. In particular, Sn is highly undesirable for pharmaceutical

manufacture due to contamination and toxicity. Whereas, in the case of silvl hydrides, the silvl hydride is typically added in excess (~2 to 3 equivalents) which increases costs and complicates post reaction processing.



Figure 1. Important biologically active molecules containing building blocks derived from (hetero)aryl aldehydes.



Scheme 1. Synthetic approaches for the formation of aryl aldehydes from aryl bromides.

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Anastas developed the 12 principles of green chemistry as a response for the necessity to reduce the environmental impact of chemicals.^[5] Perhaps the greenest and most atom economic source of CO and H₂ is synthesis gas (syngas, CO/H₂). Syngas is a highly abundant and inexpensive feedstock which is available from many sources in the chemicals industry.^[6] Syngas can be produced from the simultaneous splitting of water and activation of carbon dioxide by electrolysis. Furthermore, virtually all hydrocarbons, derived from natural gas, petroleum and coal, can be used as a feedstock for the production of syngas via partial oxidation, steam reforming or gasification. Future sustainable energy policies are likely to see an increase in the use of biomass or municipal waste for syngas production. The first palladium-catalyzed formylation utilizing syngas was reported in 1974 by Schoenberg and Heck using [Pd(PPh₃)₂Cl₂] as catalyst at very high pressures (80 to 100 bar) and elevated temperatures (80 to 150 °C).^[7] The protocol was not widely adopted for conventional organic synthesis due to the high pressures required. In 2006, Beller and co-workers reported the formylation of aryl and heteroaryl bromides by $Pd(OAc)_2$, $P(1-Ad)_2^n Bu$ (cataCXium A), tetramethylethylenediamine (TMEDA) as base, and synthesis gas (CO/H₂ = 1:1) at relatively low pressures (5 to 7 bar) with 16 h reaction time (Scheme 1c).^[8] The protocol utilized very low loadings of catalyst (0.25 mol%) and ligand (0.75 mol%) in most cases and was demonstrated on a wide substrate scope.

There are many process challenges associated with handling gas-liquid transformations in batch reactors, particularly at large scales. The interfacial area between the gas and liquid phases becomes proportionally smaller with increasing reactor size, therefore the reaction is more likely to be mass transfer limited which leads to reproducibility problems during scale-up. In addition, most of the gas is in the headspace and therefore the reactor needs to be pressurized to maximize the amount of gas in solution and reduce mass transfer effects. A large inventory of highly poisonous CO and extremely flammable H₂ needs to be loaded and pressurized into the batch vessel from a gas cylinder. Typical commercial batch reactors can operate between 2 to 6 bar thus higher pressures require more specialized and expensive equipment. These challenges, and that the reaction utilizes toxic and flammable gases unfortunately renders this transformation increasingly unacceptable in contemporary organic synthesis within a batch environment. One solution is to form the gas or gases in situ or ex situ from solid or liquid reagents (gas surrogate) which liberate CO/H₂, therefore addressing some of the challenges associated with handling gases. The problem is that in situ formation generally requires the presence of a transition metal catalyst and strong base in

combination with high temperatures (>100 °C) to release CO, therefore often resulting in compatibility issues between the CO-producing and CO-consuming reaction.^[9] Pioneering research by the Skrydstrup group resulted in the development of a two chamber batch solution for forming gases ex situ.^[10] In particular, 9-methylfluorene-9-carbonyl chloride was employed to generate stoichiometric CO and potassium formate as the hydride source within a two chamber system (COware) for reductive carbonylation of aryl iodides.^[11] Madsen and coworkers also demonstrated a two batch chamber configuration for the ex situ formation CO and H₂ using an iridium-catalysed dehydrogenative decarbonylation of hexane-1,6-diol which was fed into a second chamber for the formylation of aryl bromides.^[12] The Ley group pioneered the tube-in-tube reactor gas-loading concept to enable the safer introduction of gases into the liquid-phase from gas cylinders.^[13] Teflon AF-2400 (a fluoropolymer) is used as a semi-permeable membrane, which is permeable to gases but impermeable to liquids. The tube-in-tube flow reactor was successfully applied for hydroformylation and some carbonylation reactions, but not specifically for reductive carbonylation reactions.^[14] Furthermore, Lev and co-workers have recently shown that oxalyl chloride can be hydrolyzed by using NaOH to form CO in situ in flow and subsequently used the generated CO in carbonylation reactions.^[15] The aforementioned strategies are good options for research scale experimentation, however both approaches suffer from limited scalability in terms of atom inefficiency, poorer performance at scale-up or are simply too expensive.^[16,17]

Tubular plug flow reactors have emerged as a platform for the safe, efficient and scalable utilization of gases direct from gas cylinders by using mass flow controllers.^[17] Gasliquid flow reactions have successfully been applied for API synthesis by using continuousflow reactors.^[18] The improved safety features of continuous-flow reactors enable the safe operation at higher pressures and temperatures, including above the boiling point of the solvent.^[19] A continuous-flow reactor only needs a relatively small pressurized reactor volume containing the reaction mixture, and when properly designed can sustain the pressure of an unexpected combustion.^[20] Gas-liquid segmented (Taylor) flow regimes generated in flow microchannels provide a high interfacial area between the gas and liquid phases within a tubular flow reactor, therefore mass transfer effects are minimized. The utilization of CO in flow for organic synthesis has been demonstrated by a number of groups.^[21] In particular, Ryu and co-workers demonstrated a microflow process for a radical-based carbonylation reaction of alkyl iodides and bromides to aldehydes and ketones.^[22] However, this procedure utilized environmentally unfriendly and expensive Bu₃SnH and very high CO pressures (80 bar). Eli Lilly and Co have successfully demonstrated the successful and safe scale-up of hydroformylation and reductive amination by using CO and H_2 within a large scale tubular reactor, with one example demonstrated at a 2 MT scale.^[23–25]

We were inspired by the low pressure batch protocol reported by Beller and coworkers for the reductive carbonylation of (hetero)aryl bromides with synthesis gas as a sustainable and cost effective reagent.⁸ We herein report the development of a continuousflow protocol for the reductive carbonylation of (hetero)aryl bromides to (hetero)aryl aldehydes using synthesis gas. To our knowledge, this is the first reported flow procedure for the reductive carbonylation of (hetero)aryl bromides using syngas.

Results and Discussion

The gas-liquid continuous-flow reactor setup consisted of two high pressure liquid pumps (HPLC) (P, Uniqsis) for introducing the liquid feeds (see Figure 2a; see also Figure S1 in the ESI). CO gas and H₂ gas were introduced in a controlled manner into the system from gas cylinders via calibrated mass flow controllers (MFC, Bronkhorst-EL). The liquid and gaseous streams were combined in a simple four-way inlet mixer (M) at room temperature. The mixer was connected to the tubular reactor via a fluoropolymer tubing (PFA, 1/8" o.d., 1/16" i.d.). The PFA tubing allowed for visual inspection of the flow profile. The residence time reactor was a 60 mL stainless steel coil reactor (ID: 1/8" o.d., 1/16") heated on an aluminum heating block (Uniqsis FlowSyn). The reaction mixture exited the system through a short cooling loop and an adjustable back pressure regulator (BPR, Swagelok, 0 to 25 bar) which maintained a constant system pressure. A nitrogen purge was installed at the outlet. A pressure sensor (PS1) was integrated directly after one of the liquid pumps before entering the mixer to measure the system pressure.



Figure 2. (a) Continuous-flow configuration for reductive carbonylation optimization; (b) gas-liquid segmented (Taylor) flow regime.

Optimization experiments were performed with 4-bromoanisole (1a) as a model substrate under conditions close to those reported by Beller and co-workers (Table 1) using Pd(OAc)₂ and cataCXium A.^[8] but at residence times more appropriate to flow processing (< 1 h). We expected that 4-bromoanisole (1a) would display relatively low reactivity towards the transformation due to the electron donating effect of the methoxy substituent, because oxidative addition of the aryl bromide to the active palladium(0) species is typically the ratedetermining step in this transformation.^[26] For these reactions, 2.5 mmol of substrate and 0.75 equivalents of base were dissolved in toluene and introduced as one feed, and Pd(OAc)₂ (5 mol%) and cataCXium A (15 mol%) were dissolved in toluene and introduced as the second feed, to provide homogeneous solutions. Pd(0) precipitate formation occurred over time if the palladium catalyst and base were introduced in the same feed, from reduction of Pd(II) to Pd(0) particles.^[14b] Sample loops and injection valves were used to load the liquid feeds. The liquid feeds were each pumped at equal flow rates. When the reaction was started, the injection valves were switched and the feed mixtures were carried into the mixer, where they combined with CO and H₂ to give a segmented gas-liquid (Taylor) flow regime under the flow rates used in this study (Figure 2b).

Initially, the influence of temperature, pressure and gas flow rate were investigated to identify appropriate reaction conditions for the continuous-flow reductive carbonylation of 4bromoanisole (**1a**). For the temperature and pressure optimization (Table 1), CO and H₂ were fed in excess at equal flow rates to give ~2.2 equivalents of each gas relative to the substrate. The flow rates were adjusted at different pressures to provide comparative residence times. The conversion was relatively low at 5 bar pressure (entry 1), which was most likely caused by insufficient mass transfer of CO and H₂ from the gas phase to the liquid phase. However, a drop in conversion was observed at 15 bar, probably due to catalyst deactivation by CO (entry 3). 10 bar pressure was identified providing the best compromise between reaction rate and avoiding unwanted catalyst deactivation (entry 2). The reaction proceeded smoothly giving 95% conversion and 89% desired product yield at 120 °C, 10 bar pressure and 36 min residence time (entry 4). Conversion was significantly lower at 100 °C (entry 5) from a slower reaction rate. A higher reaction temperature resulted in higher conversion but did not improve yield due to the accelerated catalyst decomposition observed (entry 6).

We knew from the outset that a well-known phenomenon, and often unavoidable process, is the aggregation of Pd(0) to form clusters, which ultimately and irreversibly precipitate in the form of Pd black, which can then deposit onto the reactor wall.^[27] Deposited Pd can be recovered from a stainless steel coil by washing with 20% aqueous nitric acid solution at 60 °C. The reactor coil was always washed in-between experiments (unless otherwise specified) with aqueous nitric acid solution to remove residual Pd. Washing with aqueous nitric acid solution to remove residual Pd. Washing with aqueous nitric acid solution to remove residual Pd. Washing with aqueous nitric acid solution and deposited onto the reactor wall. No Pd(0) black particles were observed in the collected reaction mixtures, but Pd(0) particles were observed when the solutions were kept overnight indicating not all the Pd was deposited on the reactor channels. Running a reaction without fresh Pd(OAc)₂ and without washing the deposited palladium indicated that the deposited Pd was measured by inductively coupled plasma mass spectrometry (ICPMS) for the optimized conditions (vide infra). No desired transformation occurred in the absence of catalyst (entry 8).

		L/cat =	L/cat = 3:1						
	MeO 1	+ CO +	H ₂ TMED/ PhMe	A N	1eO	1b			
Entry	liq. total flow [mL/min]	CO [mL _n /min]	H ₂ [mL _n /min]	T [°C]	P [bar]	t _{res} [min]	Conv. 1a [%] ^b	Yield 1b [%] ^b	Selec. [%]
1	0.4	5	5	120	5	18	45	38	84
2	0.8	10	10	120	10	18	66	61	92
3	1.10	14	14	120	15	18	63	58	92
4	0.4	5	5	120	10	36	95	89	94
5	0.4	5	5	100	10	40	50	46	92
6	0.4	5	5	140	10	33	96	79	82
7^c	0.4	5	5	120	10	36	1	0	0
8^d	0.4	5	5	120	10	36	0	0	0

Table 1. Initial flow optimization of reductive carbonylation of 4-bromoanisole (1a).^{*a*}

Pd cat.

0

^{*a*} Conditions: **1a** (0.25 M) in anhydrous PhMe, 5 mol% Pd(OAc)₂, 15 mol% cata*CX*ium A, 0.75 equiv. TMEDA, 15 mol% Ph₂O as internal standard (IS). The liquid pumps were set at equal flow rates. Reactor coil was washed with 20% aqueous nitric acid at 60 °C in-between experiments with the exception of entry 7. Conversion and yield determined by GC-FID using Ph₂O as IS, selectivity (%) = [prod. (mol) / 1– SM remaining (mol)] × 100%. ^{*c*} No Pd(OAc)₂ within feed and no pre-reaction wash with aqueous nitric acid from previous run to remove deposited Pd black. ^{*d*} No Pd(OAc)₂ added to feed.

We next investigated different catalyst systems which might provide better performance under the process intensified conditions utilized in a continuous-flow environment (Table S1). Pd(OAc)₂/cata*CX*ium A gave the highest conversion and yield when compared to a selection of other phosphine ligands. The structure of the ligand appears to be very specific to the success of the reaction: two bulky alkyl groups and the long aliphatic tail are very important for the high efficiency of the catalyst system in terms of electron-richness and steric shielding of the complexes.^[28] The catalyst system is critical to the reaction given the limited stability of the corresponding palladium(0) complexes in presence of base and carbon monoxide, especially under high temperatures and pressures.

The solubility of CO and H₂ in toluene is relatively poor 7.59×10^{-3} mol L⁻¹ and 3.31×10^{-3} mol L⁻¹ respectively under standard conditions (20 °C and 1 bar). Thus, elevated pressures are necessary to dissolve a sufficient quantity of the gases in solution to provide a reasonable reaction rate and therefore an appropriate residence time (<1 h) for processing within a tubular reactor. There are a number of reports measuring the solubility of CO and H₂ in organic solvents, however data available for high T/p regimes are limited.^[31] Delmas and co-workers measured the solubility of CO and H₂ in toluene at relative high temperatures (up

to 100 °C) and pressures (up to 15 bar).^[31c] The solubility of each gas in the liquid-phase obeys Henry's law whereby the amount of dissolved gas is proportional to its partial pressure in the gas phase,^[32] therefore the reaction rate should be directly proportional to the amount of gas dissolved in solution. The data from Delmas and co-workers was simulated in DynoChem (Scaleup Systems) to predict the solubility of CO and H₂ as a function of pressure. The solubility of CO in the liquid phase was approximately double than for H₂ (Figure 3a). H₂ is competing with CO for dissolution in the liquid phase and when these are used in equimolar amounts then the amount of H₂ dissolved in solution will be lower than CO, so the effective concentration of CO will be higher. Increasing the reaction temperature would only have a small influence on the amount of dissolved H₂ (Figure 3b), whereas the solubility of CO in the liquid phase displayed only marginal temperature dependence (not shown).



Figure 3. (a) Simulated concentration of H_2 and CO dissolved in the liquid phase as a function of pressure at 120 °C; (b) Simulated concentration of H_2 dissolved in the liquid phase at different temperatures and pressures.

The ability to carefully control the relative stoichiometric ratio of CO to H₂ through varying the gas flow rates by using mass flow controllers is a key benefit of using continuous-flow reactors (Table 2). The influence of gas stoichiometry has not previously been studied for reductive carbonylations. The conversion and yield significantly drops when CO to H₂ was used at a 3:1 ratio, corresponding to 3.3 equiv. of CO and 1.1 equiv. of H₂ (entries 1 and 2). The Pd became easily deactivated by the CO present, because CO is a strong π -acceptor ligand, and therefore forms palladium carbonyl clusters which can irreversibly form Pd black. The rate of oxidative addition is significantly reduced due to the loss of active catalyst. The clustering of Pd atoms is facile in the presence of CO resulting in nonactive palladium carbonyl complexes.^[29] One approach to prevent catalyst deactivation is to utilize CO at a close-to-stoichiometric quantity.^[30] Very good conversion and yields were obtained at a 1:1 CO to H₂ ratio (~2.2 equiv. of each gas). A CO to H₂ ratio of 1:3 resulted in even better results with 99% conversion and 98% yield at 35 min residence time (entry 6). Under these conditions, the system becomes highly starved on CO towards the end of reaction. In these circumstances, at the beginning of the reactor there is a higher CO concentration present while towards the end the concentration is very low because almost all the CO has been consumed, thus improving process safety at the outlet due to the low concentration of CO present.

Table 2. Optimization of gas stoichiometry for the reductive carbonylation of **1a**.^{*a*}

Entry	liq. total flow [mL/min]	CO/H ₂ ratio	CO [mL _n /min]	H ₂ [mL _n /min]	t _{res} [min]	Conv. 1a [%] ^b	Yield 1b [%] ^b	Selec. [%]
1	0.8	3/1	15	5	19	32	29	91
2	0.4	3/1	7.5	2.5	37	54	50	93
3	0.8	1/1	10	10	18	66	61	92
4	0.4	1/1	5.0	5.0	36	95	89	94
5	0.8	1/3	5.0	15	17	70	66	94
6	0.4	1/3	2.5	7.5	35	99	98	99

^{*a*} Conditions: **1a** (0.25 M) in anhydrous PhMe, 5 mol% Pd(OAc)₂, 15 mol% cata*CX*ium A, 0.75 equiv. TMEDA, 15 mol% Ph₂O (IS) T = 120 °C, $P_{sys} = 10$ bar, 30 min collection time. The liquid pumps were set at equal flow rates. Reactor coil was washed with 20% aqueous nitric acid at 60 °C in-between experiments. Conversion and yield determined by GC-FID using Ph₂O as IS.

The main limitation of Cata*CX*ium A is that it is a proprietary ligand and therefore relatively expensive compared to many other phosphine ligands. Consequently, it was important to identify flow conditions that provided low ligand loadings to reduce costs and minimize waste. The catalyst and cata*CX*ium A loadings were lowered to more commecially-viable levels, 1 mol% and 3 mol% respectively, for subsequent optimization. The conversion and yield dropped signicantly on reducing the catalyst and ligand loadings which could be improved by increasing the base to 3 equivalents (Table S2, entry 6). Further optimization at a lower catalyst loading demonstrated that increasing the pressure from 10 to 12 bar resulted in a significant improvement in conversion and yield (Table 3, entries 3 and 5). However, there was a drop in conversion at 14 bar, indicating elevated catalyst deactivation from CO poisoning at higher pressures (entry 6). The optimal system pressure was identified as 12 bar (entry 7). The ratio of CO to H₂ became even more important when the catalyst and ligand loadings were lowered to more commecially viable levels, 1 mol% and 3 mol% respectively

(entries 1 to 3). For the reaction in a segmented gas-liquid flow pattern, only a small excess of CO (1.1 equiv.) and H₂ (3.3 equiv.) are needed, whereas the reaction in a batch autoclave would require much more (ca. more than 90 equiv. of CO and 280 equiv. of H₂) due to the reactor headspace.^[8] The low dosing of gases using continuous-flow reactors is a key benefit of continuous-flow reactors in terms of reducing usage and wastage, and improving safety.

Entry	CO/H ₂ ratio	Liq. total flow [mL/min]	CO [mL _n /min]	H ₂ [mL _n /min]	P [bar]	t _{res} [min]	Conv. 1a $[\%]^b$	Yield 1b [%] ^b	Selec. [%]
1	3/1	0.8	15	5	12	23	34	26	76
2	1/1	0.8	10	10	12	22	48	44	92
3	1/3	0.8	5	15	12	22	80	76	95
4	1/5	0.8	5	25	12	17	55	53	96
5	1/3	0.8	5	15	10	19	60	57	96
6	1/3	0.8	5	15	14	24	78	75	96
7	1/3	0.4	2.5	7.5	12	44	87	86	99

Table 3. Influence of CO/H₂ ratio, pressure and residence time on conversion and yield.^{*a*}

^{*a*} Conditions: **1a** (0.25 M) in anhydrous PhMe, 1 mol% Pd(OAc)₂, 3 mol% cata*CX*ium A, 3 equiv. TMEDA, 15 mol% Ph₂O (IS) T = 120 °C Reactor coil was washed with 20% aqueous nitric acid at 60 °C in-between experiments. ^{*b*} Conversion and yield determined by GC-FID using Ph₂O as internal standard.

Another strategy to prevent deactivation by CO is to utilize phosphine ligands at high ligand–Pd ratios (Table 4).^[33] A ligand to catalyst ratio of 2:1 resulted in a drop in conversion and yield (entry 1), probably due to catalyst poisoning from overcoordination of CO. The utilization of a ligand to catalyst ratio of 4:1 only resulted in a marginal improvement in yield (entry 4) from a 3:1 ratio. In contrast, an increase in the ligand to catalyst ratio to 5:1 retards the reaction and decreased the aldehyde yield to 71% (entry 5). The slight increase in yield obtained when using a ligand to catalyst ratio of 4:1 compared to 3:1 often cannot be justified based on the increase in cost associated with using a higher ligand excess. We also investigated the use of stabilizing solvents to prevent the formation of black Pd(0) particles. Even though environmentally their use should be minimized,^[34] polar aprotic solvents DMF and (dimethylacetamide) DMA, can stabilize Pd(0) species in solution.^[27b] However, using these solvents as co-solvents did not improve conversion or yield (Table S3), therefore were not investigated further.

Entry	Cat. [mol%]	Ligand [mol%]	L/C ratio	t _{res} [min]	Conv. 1a [%] ^b	Yield 1b [%] ^b	Selec. [%]	
1	1	2	2	44	72	70	97	
2	1	3	3	45	90	86	96	
3	1	4	4	46	91	89	98	
4	1	5	5	46	74	71	96	
5	0.5	2	4	47	58	53	91	

Table 4. Optimization of catalyst and ligand loadings for reductive carbonylation.^{*a*}

^{*a*} Conditions: 1a (0.25 M) in anhydrous PhMe, 3 equiv. TMEDA, 15 mol% Ph₂O (IS) T = 120 °C, $P_{sys} = 12$ bar, 30 min collection time. Reactor coil was washed with 20% aqueous nitric acid at 60 °C in-between experiments. ^{*b*} Conversion and yield determined by GC-FID using Ph₂O as internal standard.

The applicability of the continuous-flow protocol for the Pd-catalyzed reductive carbonylation of aryl bromide substrates with syngas was demonstrated on a 3 mmol scale and is shown in Table 5 (18 examples). 4-Bromobenzotrifluoride, possessing an electron deficient trifluoromethyl group, displayed high reactivity giving full conversion and 97% product yield (entry 2). The catalyst and ligand loadings could be lowered to 0.5 mol% and 1.5 mol% respectively to afford the product in 78% yield. 1-Bromo-4-chlorobenzene also showed high reactivity giving quantitative conversion and 97% product yield (entry 3). Whereas, 1-bromo-4-fluorobenzene (entry 5) displayed slightly lower reactivity than 1-bromo-4-chlorobenzene. Aryl bromides bearing electron donating alkyl groups in the para position displayed moderate reactivity (entries 6 and 7). In particular, 4-isobutylbenzaldehyde, an intermediate in the synthesis of ibuprofen, was afforded in 53% yield (entry 7). 4-Bromo-N-N-dimethylaniline (entry 8), possessing an electron donating group, showed similar reactivity to 4-bromoanisole. Heteroaryl bromides proved to be more challenging than bromobenzene substituted compounds (entries 9 to 12). Beller and co-workers proposed that, in the case of 2bromopyridine, the catalyst was deactivated through the formation of inactive dimers after the oxidative addition step.^[8] We attempted to synthesize pyrimidine-5-carbaldehyde as a precursor compound for a myeloperoxidase (MPO) inhibitor.^[35] but only a poor 13% yield was obtained (entry 10). In the instance of 3-bromoguinoline, full conversion and 75% yield were obtained but dehalogenation of the starting material was also observed (entry 11). As the CO insertion step into the Pd-Aryl bond can be slow with aromatic ring systems possessing electron-deficient substituents, this resulted in the competitive reduction of the aryl bromide in some cases (entries 11 to 18).^[36] A reduction in catalyst loading did not decrease the selectivity for the dehalogenated product. Aryl bromides containing carbonyl compounds

displayed good reactivity under the flow protocol (entries 16 to 18). The conversions and yields were relatively stable for a 30 min operation time (Tables S2 and S3). Overall the conversions and yields compared favorably to other reductive carbonylation batch protocols, see Table S6.

Entry	Substrate (a)	Product (b)	Pd(OAc) ₂ [mol%]	cata <i>CX</i> ium A [mol%]	Conv. [%] ^[b]	Yield [%] ^[b]	Select. [%] ^[b]	Dehal. (c) [%] ^[b]
1	MeO	Мао	1	3	90	86	96	_
	Br	CHO	1	3	100	97	97	_
2	F ₃ C	F ₃ C	0.5	1.5	81	78	96	_
2	Br	СНО	1	3	100	96	97	-
3	ci	ci	0.5	1.5	58	56	97	-
	Br	CHO	1	3	100	98	98	-
4	MeO	MeO	0.5	1.5	99	95(84)	97	_
5	F	СНО	1	3	88	86	98	-
6	Br	СНО	1	3	70	69(61)	99	-
7	Br	СНО	1	3	55	53	96	_
8	N Br	CHO	1	3	74	73(67)	99	_
9	S Br	СНО	1	3	100	45	45	-
10	N Br	N CHO	1	3	99	13	13	-
11	Br	СНО	1	3	100	75	75	23
11	N	[™] N	0.5	1.5	92	71(66)	77	19
12	∬ Br N	CHO N	1	3	100	0	0	33
13	O ₂ N Br	O ₂ N CHO	1	3	100	18	18	20
14	NC	NC	1	3	100	69(47)	69	28
15	Br	CHO	1	3	100	65(59)	65	34
16	O Br	СНО	1	3	100	85(59)	85	12
17	OHC	онс	1	3	100	78(70)	78	20
18	EtOOC	EtOOC	1	3	100	87(84)	87	12

Table 5. Scope and limitations of reductive carbonylation flow protocol.^{*a*}

^{*a*} Reaction conditions: 3 mmol scale (hetero)arylbromide (0.25 M solution in anhydrous toluene), TMEDA (3 equiv.), Ph₂O (internal standard, 15 mol%), CO:H₂ = 1:3, CO flow rate = 2.5 mL_n/min, H₂ flow rate = 7.5 mL_n/min, catalyst feed flow rate = 0.2 mL/min, substrate feed flow rate = 0.2 mL/min, P_{sys} = 12 bar, T = 120 °C, t_{res} ~45 min. ^{*b*} outlet was fractionated at 10 min intervals over a 30 min period, yields and conversion are average from 30 min collection time and determined by GC-FID, see Tables S4 and S5 for conversions and yields for individual fractions. Molecular weights were confirmed by GC-MS. Values given in parentheses are isolated yields after silica gel chromatography. The somewhat lower isolated yields compared to the GC yields in some cases may be due to the volatility of the product.

A scale-up experiment was conducted for the reductive carbonylation of 2-bromo-6methoxynapthalene (**4a**) to 6-methoxy-2-naphthaldehyde (**4b**). 6-methoxy-2-naphthaldehyde (**4b**) is a possible intermediate in the synthesis of Naproxen, a nonsteroidal anti-inflammatory drug.^[37] The total operation time was 415 minutes (from start-up to shutdown) with the product collected over 370 minutes (Figure 4). It was necessary to submerge the outlet tubing and BPR within an ultrasound bath and heat at 80 °C to prevent accumulation of a white solid near-or at- the BPR, which was from TMEDA–HBr salt precipitation. No pressure increase or fluctuations were observed for the duration of the experimental run. Only a very marginal drop in conversion or yield was observed for the first ~170 minutes of runtime. However, the conversion and yield slowly decreased over the course of the run, with a drop of approximately 15% over 350 min of runtime. The crude product was purified by column chromatography to give pure product in 85% isolated yield which enabled preparation of 3.8 g of product giving a throughput of 0.7 g/h from the continuous-flow process.



Figure 4. Long run profile. For reaction conditions and analytics, see Table 4, entry 4, with $0.5 \text{ mol}\% \text{ Pd}(\text{OAc})_2$ and 1.5 mol% cata*CX*ium A used for the long run. No samples were taken until color (reaction mixture) was observed at the BPR. Samples were fractionated at 20 min intervals. The first and last samples were less concentrated due to dilution by the "pushout" solvent.

Reactor contamination (fouling) is a critical issue in flow chemistry that is often overlooked.^[38] As discussed above, Pd(0) species aggregate to generate Pd clusters, which ultimately irreversibly precipitate in the form of Pd black which deposits on metal surfaces. ICPMS analysis was conducted to measure the amount of Pd deposited on the reactor walls compared to the amount of Pd remaining in solution and to obtain a more thorough understanding of the slow decrease in conversion and yield over operation time for some substrates. ICPMS analysis was conducted on samples fractionated at 20 min intervals for a separate experimental run for the reductive carbonylation of 2-bromo-6-methoxynapthalene (4a) over ~2 hours. Control experiments confirmed that the untreated steel material itself cannot catalyze the reductive carbonylation (videa supra). The amount of Pd measured in the collected reaction solution decreased over operation time which indicated that the presence of existing "inactive" deposited catalyst accelerated the deposition of further catalyst (Table 6). ICPMS measurements, along with the slow decrease in conversion and yield through the run, demonstrated that the rate of decomposition of catalyst increases over the duration of the run. The catalyst can either enter the catalytic cycle or aggregate to form initially soluble palladium clusters, which at some point will turn into insoluble palladium black. ICPMS analysis confirmed that ~80% of the Pd was deposited on the walls over the duration of the experiment and that Pd is easily recovered by washing the reactor with 20% aqueous nitric acid. The formation of Pd black is self-catalyzed and leads to the withdrawal of Pd from the catalytic cycle. ICPMS analysis also confirmed that no Fe or Co leached from the stainless steel into the reaction solution or from the aqueous nitric acid wash (Table S5).

Entry	Sample [mg]	Pd determined [mg/kg]	Pd determined [mg]	Pd expected [mg]	Pd determined [%]
Fraction 1	253	2352	0.594	0.929	64
Fraction 2	303	811	0.245	0.929	26
Fraction 3	342	366	0.125	0.929	13
Fraction 4	611	117	0.071	0.929	8
Fraction 5	111	194	0.053	0.929	5
Aq. HNO3 wash	12 (mL)	290 (mg/L)	3.48		
		Sum	4.57	4.65	98

Table 6. ICPMS analysis of a flow experiment for the formylation of 2-bromo-6-methoxynapthalene.^a

^{*a*} For reaction conditions and analytics, see Table 4, entry 4, with 0.5 mol% $Pd(OAc)_2$ and 1.5 mol% cataCXium A. Samples were fractionated at 20 min intervals.

The catalytic cycle for Pd-catalyzed formylation between aryl bromides and synthesis gas (CO/H₂ 1:1) proposed by Beller and co-workers is shown in Scheme 2.^[26] The catalytic cycle involves the oxidative addition of the aryl bromide with the active palladium(0) species, migratory insertion of CO into the Ar-Pd bond, coordination of a hydrogen molecule, and subsequent base-mediated hydrogenolysis of the resulting acyl complex to give the desired aldehyde. The catalytic cycle is completed by the reaction of the palladium hydrobromide complex with base to regenerate Pd(0). In the study by Beller and co-workers, the carbonylpalladium(0) complex $[Pd_n(CO)_mL_n]$ and hydrobromide complex $[Pd(Br)(H)L_2]$ were identified as catalytic resting states, these complexes were not directly involved in the catalytic cycle. Consequently, the active catalyst [PdL] is always at low levels throughout the reaction, thus making the oxidative addition the rate-determining step, therefore aromatics containing an electron donating group are slower to react than the corresponding aromatics containing an electron withdrawing group. The efficiency of the Pd(0) catalyst is dependent on the relative rate of the oxidative addition to the decomposition of Pd(0), the agglomeration eventually leads to the formation of palladium black which coats the reactor channels. The rate of the agglomeration process is second order in Pd or higher, whereas oxidative addition is usually first order in palladium(0), therefore the rate of Pd decomposition accelerates throughout over operation time due to the presence of Pd on the reactor channels. The ICPMS showed that increasing amounts of catalyst were lost from solution over operation time, therefore indicating the presence of existing deposited Pd catalyzes the agglomeration process. The very slow decrease in conversion and yield which was observed over time for some substrates is caused by the increasing rate of catalyst decomposition over operation time.

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Scheme 2. Mechanism for the Pd-catalyzed reductive carbonylation of aryl bromides.

Conclusion

Green and sustainable chemical processes rely not only on effective chemistry but also on the implementation of reactor technologies, which enhance reaction performance and overall safety. We have developed a continuous-flow protocol for Pd-catalyzed reductive carbonylation of (hetero)aryl bromides to aldehydes, with syngas as an inexpensive, atom economic and environmentally friendly source of CO and H₂. Relatively low catalyst loadings (0.5 mol% to 1 mol%) and ligand loadings (1.5 to 3 mol%) provided moderate to excellent product yields. The reaction consumes only carbon monoxide, hydrogen, and base as stoichiometric reagents. The continuous-flow protocol enabled the reaction time to be significantly reduced compared to the batch protocols available. For continuous flow reactions, gaseous reagents can be easily and accurately dosed into the system by using mass-flow controllers, therefore enabling precise control over the CO to H₂ stoichiometric ratio. The investigation of gas stoichiometric ratio demonstrated that using CO/H₂ at a 1:3 ratio prevented the formation of non-active Pd carbonyl clusters and therefore increased product yield. The flow reaction uses pure gases as feedstock to generate gas–liquid segmented flow patterns which allows the reaction to be completed within 45 min residence time with much

smaller excess (1.1 equiv of CO, 3.3 equiv of H₂) of gases than batch. Under the flow conditions, at the end of the reactor the CO concentration is very low because almost all the CO has been consumed, thus improving process safety at the outlet due to the low amount of CO present. The presence of deposited catalyst within the reactor was shown to have a negative effect on the reductive carbonylation. ICPMS analysis demonstrated that the amount catalyst deposition on the reactor channels increased over the duration of run. The deposited catalyst could be recovered using an aqueous nitric acid wash. In order to improve safety, recent batch examples have attempted to use liquid and solid reagents as gas surrogates for CO and H₂. The continuous-flow protocol with H₂ and CO offers a safe, atom economic and environmentally benign alternative to these gas surrogate procedures. The developed process is especially appealing for industrial applications, where atom economy, sustainability, reagent cost and reagent availability and safety are important factors. Several key API intermediates were synthesized in a continuous and environmentally benign manner. In particular, a continuous-flow protocol was operated for a 6 hour run time to produce 3.8 g of an important active pharmaceutical intermediate. A major advantage of the continuous flow protocol is the ability to handle pure H₂ and CO under process intensified conditions in a safe and scalable manner. Nevertheless, the long run and ICPMS analysis demonstrated that there are challenges associated with catalyst decomposition over time. Further work is necessary to find improved catalyst systems that allow reaction to occur without any decomposition over time under process intensified conditions.

Experimental

General Methods. NMR spectra were recorded on a 300 MHz instrument (75 MHz for ¹³C). Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m stand for singlet, doublet, triplet, quadruplet and multiplet. GC-FID analysis was performed using a HP5 column (30 m × 0.250 mm × 0.025 µm). After 1 min at 50 °C the temperature was increased in 2 °C min⁻¹ stepped up to 80 °C, then in 25 °C min⁻¹ stepped up to 300 °C and kept at 300 °C for 4 minutes. The detector gas for the flame ionization is H₂ and compressed air (5.0 quality). GC–MS spectra were recorded using a HP5-MS column (30 m × 0.250 mm × 0.25 µm) with helium as carrier gas (1 mL/min constant flow) coupled with a mass spectrometer (EI, 70 eV). After 1 min at 50°C, the temperature was increased in 25 °C/min steps up to 300 °C and kept at 300 °C and kept at 300 °C for 1 min. All solvents and

chemicals were obtained from standard commercial vendors and were used without any further purification. All compounds synthesized herein are known in the literature.

CAUTION: CO is highly toxic and flammable, therefore extreme care must be taken when handling. H_2 is extremely flammable. CO alarms must be installed and N_2 purge used at the outlet. All equipment must be set up in a well-ventilated fume hood. A thorough safety assessment should be made before conducting any experiments.

Representative Procedure for Reductive Carbonylation of (Hetero)aryl Bromides **Reported in Table 7.** Flow experiments were performed using the continuous-flow setup depicted in Figure 2 (also see Figure S1 for a labeled image). The continuous-flow setup is described in detail in the Results and Discussion section. The solution of substrate (0.5 M in PhMe), corresponding to 0.25 M within the reactor, tetramethylethylenediamine (TMEDA) (3 equiv.) and diphenylether (15 mol%) as an internal standard (stream 1) and Pd(OAc)₂ (1 mol% or 0.5 mol%) and cataCXium A (3 mol% or 1.5 mol%) in PhMe (stream 2) were loaded into their corresponding sample loops. The liquid feeds were pumped using two high pressure liquid pumps (HPLC) (P, Uniqsis) with a flow rate of 0.2 mL/min for each pump, using toluene as a carrier solvent. The flow rates of the gas streams were measured and controlled by two calibrated mass flow controllers (MFCs) using $CO = 2.5 \text{ mL}_n/\text{min}$, $H_2 = 7.5$ mL_n/min. The system was maintained at 120 °C and 12 bar pressure to provide ~45 min residence time. The residence time was measured from the four streams mixing at the mixer until color was observed at the BPR. The liquid pump flow rates, temperature and pressure were measured and monitored by the control platform of the pumping system. Once color was observed at the BPR, fractions were collected for 10 min intervals over a 40 min period. Collection was stopped once no color was observed at the BPR. Yields and conversion were determined by GC-FID using diphenylether as internal standard and the reported values are an average from 30 min collection time. In some cases fractions were combined for purification by silica gel chromatography.

4-Methylbenzaldehyde (6b). The title compound was prepared according to the general procedure as a colorless oil in 61% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 99/1 then isocratic petroleum ether/EtOAc: 99/1). ¹H NMR (300 MHz, CDCl₃) δ : 9.96 (s, 1H), 7.83-7.72 (m, 2H), 7.33 (d, *J* 8.0 Hz, 2H), 2.44 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ : 192.1, 145.7, 134.3, 130.0, 129.8, 22.0 (lit.^[39]).

4-Dimethylaminobenzaldehyde (8b). The title compound was prepared according to the general procedure as white crystals in 67% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 85/15 then isocratic petroleum ether/EtOAc: 85/15). m.p 74.2-74.6 °C (lit.^[41] 72-73 °C); ¹H NMR (300 MHz, CDCl₃) δ : 9.74 (s, 1H), 7.78-7.68 (m, 2H), 6.76-6.65 (m, 2H), 3.08 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 190.5, 154.4, 132.1, 125.3, 111.1, 40.2 (lit.^[39]).

Quinoline-3-carbaldehyde (11b). The title compound was prepared according to the general procedure as an off-white solid in 66% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 80/20 then isocratic petroleum ether/EtOAc: 80/20). m.p 69.6-69.9 °C (lit.^[39] 70 °C); ¹H NMR (300 MHz, CDCl₃) δ : 10.26 (s, 1H), 9.37 (d, *J* 1.8 Hz, 1H), 8.64 (d, *J* 1.8 Hz, 1H), 8.20 (d, *J* 8.5 Hz, 1H), 8.00 (d, *J* 8.1 Hz, 1H), 7.89 (ddd, *J* 8.5, 7.0, 1.5 Hz, 1H), 7.67 (ddd, *J* 8.1, 7.0, 1.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 190.9, 150.7, 149.3, 140.3, 132.8, 129.8, 129.6, 128.7, 128.0, 127.2 (lit.^[39]).

4-Cyanobenzaldehyde (14b). The title compound was prepared according to the general procedure as white crystals in 47% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 92/8 then isocratic petroleum ether/EtOAc: 92/8). m.p 100.8-101.3 °C (lit.^[42] 100-101 °C); ¹H NMR (300 MHz, CDCl₃) δ : 10.09 (s, 1H), 8.05-7.94 (m, 2H), 7.89-7.80 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ : 190.8, 138.8, 133.0, 130.0, 117.9, 117.7 (ref.^[39]).

1-Naphthaldehyde (**15b**). The title compound was prepared according to the general procedure as a yellow liquid in 59% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 99/1 then isocratic petroleum ether/EtOAc: 99/1). ¹H NMR (300 MHz, CDCl₃) δ : 10.41 (s, 1H), 9.26 (d, *J* 8.8 Hz, 1H), 8.11 (d, *J* 8.2 Hz, 1H), 8.00 (dd, *J* 7.0, 1.3 Hz, 1H), 7.93 (d, *J* 8.2 Hz, 1H), 7.70 (ddd, *J* 8.5, 7.0, 1.5 Hz, 1H), 7.67-7.62 (m, 1H), 7.62-7.56 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 193.7, 136.8, 135.4, 133.9, 131.5, 130.7, 129.2, 128.6, 127.1, 125.1, 125.0 (lit.^[39]).

4-Acetylbenzaldehyde (16b). The title compound was prepared according to the general procedure as a pale yellow low melting solid in 59% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 91/9 then isocratic petroleum ether/EtOAc: 91/9). ¹H NMR (300 MHz, CDCl₃) δ : 10.10 (s, 1H), 8.14-8.05 (m, 2H), 8.01-7.94 (m, 2H), 2.66 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ : 197.5, 191.7, 141.3, 139.2, 130.0, 128.9, 27.1 (lit.^[40]).

Benzene-1,4-dicarboxaldehyde (17b). The title compound was prepared according to the general procedure as white crystals in 70% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 90/10 then isocratic petroleum ether/EtOAc: 90/10). m.p 116.8-117.3 °C (lit.^[39] 115 °C); ¹H NMR (300 MHz, CDCl₃) δ : 10.13 (s, 2H), 8.05 (s, 4H); ¹³C NMR (75 MHz, CDCl₃) δ : 191.7, 140.1, 130.3 (lit:^[39]).

4-Ethoxycarbonylbenzaldehyde (18b). The title compound was prepared according to the general procedure as a colorless oil in 84% yield after silica gel chromatography (petroleum ether/EtOAc: 100/0 to 95/5 then isocratic petroleum ether/EtOAc: 95/5). ¹H NMR (300 MHz, CDCl₃) δ : 10.09 (s, 1H), 8.23-8.14 (m. 2H), 7.98-7.88 (m, 2H), 4.40 (q, *J* 7.1 Hz, 2H), 1.40 (t, *J* 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ : 191.8, 165.7, 139.2, 135.5, 130.2, 129.6, 61.7, 14.4 (ref.^[39]).

Long Run Procedure for the Preparation of 6-Methoxy-2-naphthaldehyde (4b) Using Continuous-flow.

Preparation of catalyst feed: $Pd(OAc)_2$ (42.1 mg, 0.188 mmol, 0.5 mol%) and cata*CX*ium A (201.7 mg, 0.563 mmol, 1.5 mol%) were weighed into 100 mL two-necked round bottom flask containing a magnetic stirrer. The flask was enclosed with a rubber septa and a balloon filled with argon was attached. Anhydrous toluene (75 mL) was added to the flask and the mixture was stirred for 15 minutes to provide a homogeneous yellow solution (75 mL).

Preparation of substrate feed: 2-bromo-6-methoxynaphtalene (**4a**) (7.113 g, 30 mmol, 1 equiv.) was weighed into a 100 mL two-necked round bottom flask containing a magnetic stirrer. The flask was enclosed with rubber septa and a balloon filled with argon was attached. Subsequently, Ph₂O (709 μ L, 4.5 mmol, 15 mol %), TMEDA (13.5 mL, 90 mmol, 3 equiv.) and anhydrous toluene (60 mL) were added under argon atmosphere. The resulting mixture was stirred for 15 minutes to provide homogeneous pale yellow solution (80.5 mL).

Flow procedure: Flow experiments were performed using the continuous-flow setup depicted in Figure 1 (also see Figure S1 for a labeled image). Before the reaction, the entire flow system was washed with 20% aqueous nitric acid solution at 60 °C to ensure no residual Pd deposited on the reactor channels, and then subsequently washed with acetonitrile and then toluene. Calibrated mass flow controllers (MFC, EL-Bronkhorst) were set to the desired flow rates, $CO = 2.5 \text{ mL}_n/\text{min}$, $H_2 = 7.5 \text{ mL}_n/\text{min}$, and gases started to flow into the reactor. The pressure was slowly increased at the BPR (Swagelok). The gas flow rate was measured in units of mL_n/min (n represents measurement under standard conditions: $T_n = 0$ °C, $P_n = 1.01$

bar). When the system reached 3 bar, the liquid pumps were started P1 = 0.2 mL/min and P2 = 0.2 mL/min, with both pumping toluene. The pressure was slowly increased to 12 bar and the temperature set to 120 °C. Once at the desired temperature and pressure, the streams were switched to the feed solutions. The feeds were introduced directly through the pumps. The streams were mixed using a four-way inlet mixer at room temperature to give a segmented flow regime and then flowed through the reactor. The residence time ~45 min was the time measured from the four streams mixing at the mixer until color was observed at the BPR. The tubing after the stainless steel coil and the Swagelok BPR were immersed in an ultrasound bath and heated at 80 °C to prevent of accumulation solids in front of- and within- the BPR. The feed solutions were pumped for 350 min, then toluene was pump for the remaining time as a carrier solvent. A total of 18 fractions were collected, a fraction was collected every 20 minutes (approx. 8 mL) and conversion and yield measured by GC-FID using diphenylether as an internal standard (see Fig. 4 for conversion and yield over operation time).

Isolation procedure. All fractions were combined (except the first and last) to give 128 mL (max. yield would give 23.9 mmol based on 64 mL substrate feed) and the volatiles were removed under reduced pressure. The residue was dissolved in EtOAc and absorbed on silica gel (43 to 60 μ m particle size). Purification of the crude product by silica chromatography (petroleum ether/EtOAc 100/0 to 95/5 then isocratic petroleum ether/EtOAc 95/5). Subsequent removing of solvent under reduced pressure afforded 6-methoxy-2-naphthaldehyde (**4b**) (85% yield, 3.77 g, 20.2 mmol) as white crystals. m.p 83.4-83.8 °C (lit.^[43] 80-82 °C); ¹H NMR (300 MHz, CDCl₃) δ : 10.01 (s, 1H), 8.17 (d, *J* 1.7 Hz, 1H), 7.84 (dd, *J* 8.5, 1.7 Hz, 1H), 7.81 (d, *J* 9.0 Hz, 1H), 7.73 (d, *J* 8.5 Hz, 1H), 7.16 (dd, *J* 9.0, 2.5 Hz, 1H), 7.10 (d, *J* 2.5 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ : 192.2, 160.4, 138.4, 134.4, 132.5, 131.2, 128.1, 127.9, 123.8, 120.1, 106.2, 55.6 (lit.^[39]).

ICPMS. The amount of Pd deposited within the reactor compared to remaining in solution was determined by ICPMS analysis. The crude reaction solution was collected from the reactor was evaporated under reduced pressure to remove all volatile compounds. The resulting residue was dissolved in acetonitrile/concentrated nitric acid to give a homogeneous solution. The deposited Pd from the reactor channels was collected by washing with 20% aqueous nitric acid at 60 °C. The solutions were diluted with nitric acid to 40 mL and placed in a vial for microwave digestion. Microwave-assisted acid digestion was carried out in an MLS UltraClave IV instrument. The temperature was ramped up in 30 min to 250 °C and kept at this temperature for a further 30 min. After appropriate dilution Pd was quantitatively

determined at m/z 105 with an Agilent 7500ce inductively coupled plasma mass spectrometer. A calibration was performed with an external calibration curve established from 1.000 g of Pd/L standard (CPI International). Indium served as the internal standard.

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Keywords: reductive carbonylation; formylation; aldehydes; Pd-catalyzed; continuous-flow; carbon monoxide; gas-liquid transformation.

Text for TOC: The development of a continuous-flow protocol for a Pd-catalyzed formylation of (hetero)aryl bromides using carbon monoxide and hydrogen is described. The applicability of the continuous-flow protocol is demonstrated on several (hetero)aryl bromide substrates. The intensified continuous-flow process enables safe and scalable Pd-catalyzed formylation using gases.

Graphical Contents Entry

