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Communication

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Effective Palladium-Catalyzed Hydroxycarbonylation of Aryl Halides with Substoichiometric Carbon Monoxide

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Supporting Information

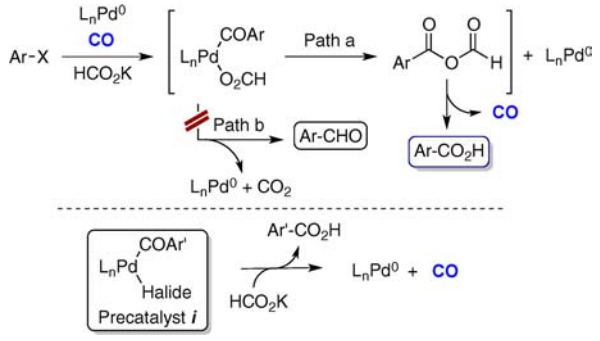
ABSTRACT: A protocol for the Pd-catalyzed hydroxycarbonylation of aryl iodides, bromides, and chlorides has been developed using only 1−5 mol % of CO, corresponding to a p_{CO} as low as 0.1 bar. Potassium formate is the only stoichiometric reagent, acting as a mildly basic nucleophile and a reservoir of CO. The substoichiometric CO could be delivered to the reaction from an acyl-Pd(II) precatalyst, which provides both the CO and an active catalyst, and thereby obviates the need for handling a toxic gas.

Benzoic acids are common structural motifs in many natural products, pharmaceuticals and agrochemicals.[1] Pd-catalyzed hydroxycarbonylation of aryl halides represents a widely used approach for preparing such compounds.[2,3] However, this method suffers from the handling of a highly toxic gas, carbon monoxide, which is typically applied in large excess and high pressures, and therefore requires specific handling measures. Furthermore, the reaction is often conducted with water and strong alkaline bases in polar solvents under elevated temperatures, thereby excluding the presence of certain functional groups. Several protocols have been developed to circumvent these problems. For the latter, this includes the use of nucleophiles of low basicity instead of hydroxide, which leads to the carboxylic acid, but only after an additional hydrolysis step.[4] And for the former, several groups have developed and applied activated formates as a source of *in situ* released CO.[5] Nevertheless, compatibility issues between the CO generating and the CO consuming reactions again reduce the functional group tolerance for this transformation. Moreover, stoichiometric CO is produced under the reaction conditions, and as the two coinciding reactions are not synchronized, the initial CO pressure buildup can lead to overall safety concerns especially with large-scale reactions. Identification of reaction conditions, which address all of these concerns, would be of significant value.

In this Communication, we report the first reaction conditions for the Pd-catalyzed hydroxycarbonylation of aryl halides, which perform well with addition of substoichiometric carbon monoxide as low as only 1−5 mol %. Furthermore, to simplify the operating conditions, we exploit air stable acyl palladium(II) precatalysts, which deliver not only the active catalyst, but also the necessary substoichiometric amount of CO required to initiate the carbonylation reaction.

To promote a carbonylation reaction with substoichiometric addition of CO, it requires that 1 mol of CO is produced for every mole of CO consumed. The hydroxycarbonylation of aryl halides with formate has previously been proposed to proceed through a formic anhydride, which spontaneously decomposes upon heating to the carboxylic acid and CO (Scheme 1, path a).[6] Hence, if reaction conditions can be identified, which are specific for the hydroxycarbonylation step, a protocol running on substoichiometric CO addition should be possible. However, any CO depleting side reactions, such as reductive carbonylation to the corresponding aldehyde (path b), would be detrimental. To initiate the carboxylation reaction, we envisaged that an acyl Pd(II)-complex ***i*** could provide the active catalyst after reductive elimination of the formato intermediate. Furthermore, it would conveniently deliver 1 equiv of CO with respect to the palladium catalyst. Hence, throughout the reaction course, the amount of carbon monoxide should not exceed the catalyst concentration in solution.

Scheme 1. General Considerations for Pd-Catalyzed Hydroxycarbonylations with Substoichiometric CO Addition



Preliminary experiments were conducted with aryl iodide **1** employing the two-chamber system (COware) and 9-methylfluorene-9-carbonyl chloride (COgen) as the stoichiometric CO precursor,[7,8] in order to identify appropriate catalytic conditions for the selective transformation of aryl halides to the corresponding carboxylic acids (Table 1). The reaction conditions used potassium formate and 1.5 equiv of CO. Of the ligands tested, the bulky monodentate phosphine ligands, such as P(*t*Bu)$_3$, P(*o*Tol)$_3$, *t*Bu-Brettphos, or bidentate phosphine ligands, including dppb, dppf, di*P*rpf or *t*Bu-

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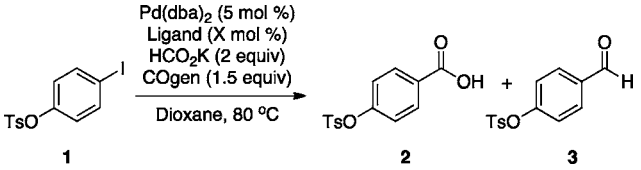
Table 1. Screening Ligands for the Hydroxycarbonylation of Aryl Iodide 1[a]



Entry	Ligand	Conversion (%)[b]	2:3[b]
1	PPh_3	>95	39:61
2	dppe	33	55:45
3	dppp	15	60:40
4	dppb	55	82:18
5	dpppentane	13	<1:99
6	P(*t*Bu)$_3$	>95	96:4
7	dppf	>95	>99:1[c]
8	d*t*bpf	>95	>99:1
9	d*i*Prpf	>95	93:7
10	P(*o*Tol)$_3$	>95	88:12
11	*t*Bu-Brettphos	>95	94:6[c]
12	*t*Bu-Josiphos	>95	97:3

dppe, n = 2; dppp, n = 3; dppb, n = 4; dpppentane, n = 5

dppf, R = Ph; d*i*Prpf, R = *i*-Pr; d*t*bpf, R = *t*-Bu

*t*Bu-Brettphos

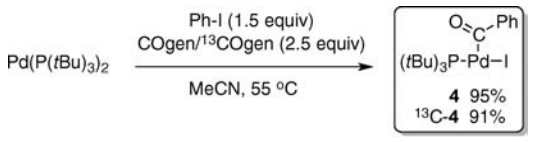
*t*Bu-Josiphos

[a]Chamber 1: **2** (0.5 mmol), Pd(dba)$_2$ (25 μmol), ligand (monodentate: 50 μmol, bidentate: 25 μmol), HCO_2K (1 mmol), TBAI (0.15 mmol, phase transfer catalyst), dioxane (3 mL). Chamber 2: COgen (0.75 mmol), Cy_2NMe (1.5 mmol), Pd(dba)$_2$ (38 μmol), P(*t*Bu)$_3$·HBF_4 (38 μmol), dioxane (3 mL) at 80 °C for 18 h. [b]Based on ^{1}H NMR analysis. [c]The reductive dehalogenation of **2** was observed in 10% with dppf and 22% with *t*Bu-Brettphos.

Josiphos, provided high selectivities for the carboxylic acid **2** over the reductive carbonylation product, aldehyde **3**. However, complete selectivity for **2** and the best yield was secured with d*t*bpf (entry 8).

To investigate the use of an acyl Pd(II) precatalyst, we first prepared complex **4** due to known similar acyl complexes in the literature bearing a P(*t*Bu)$_3$ ligand.[9] This was easily achieved from the reaction of Pd(P*t*Bu$_3$)$_2$ with phenyl iodide and 2.5 equiv of CO or ^{13}CO (generated from COgen and ^{13}COgen, respectively), yielding **4** and ^{13}C-**4** in good yields as air-stable solids (Scheme 2). Synthesis of ^{13}C-**4** allowed for the rapid

Scheme 2. Synthesis of Acyl Pd(II) Complexes 4 and ^{13}C-4



assignment of the *cis*-relationship between the acyl and phosphine ligand as demonstrated by the small coupling constant of 4.9 Hz in the ^{13}C NMR and ^{31}P NMR spectra (Figure 1). This assignment was confirmed by the single crystal X-ray structure of **4** revealing a T-shaped complex as seen for analogous acyl complexes with the P(*t*Bu)$_3$ ligand (Figure 1).[9] Unfortunately, similar attempts to prepare the complex bearing the ligand d*t*bpf were fruitless.

Surprisingly, complex **4** could not catalyze the hydroxycarbonylation of iodide **1** with potassium formate in the

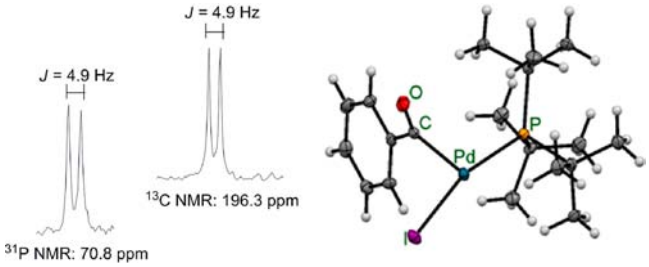
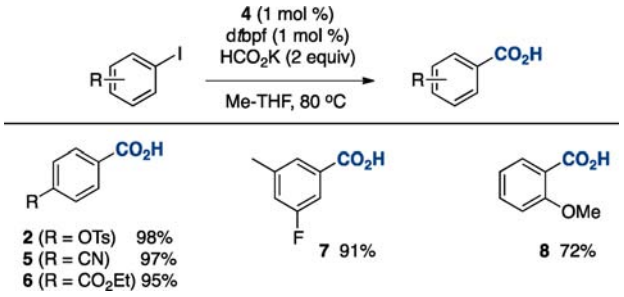


Figure 1. ^{13}C- and ^{31}P NMR spectra of complex ^{13}C-**4** and single crystal x-ray structure of complex **4**.

absence of external CO,[10] in light of the high selectivity for carboxylic acid formation observed for entry 6 in Table 1 with 1.5 equiv of CO. However, to our delight, the addition of a stoichiometric amount of d*t*bpf with respect to the Pd-acyl complex **4** provided a highly active catalyst, which performed the carbonylation reactions without CO addition. Changing the solvent to Me-THF remarkably allowed the carboxylation to be run *at only a 1 mol % catalyst loading* with a 98% isolated yield of **2** (Table 2).[11] Other iodides tested also performed admirably providing carboxylic acids **5**–**8** in good yields.

Table 2. Synthesis of Carboxylic Acids 2, 5–8 from Aryl Iodides[a]



[a]Aryl iodide (0.50 mmol), **4** (5.0 μmol), d*t*bpf (5.0 μmol), HCO_2K (1 mmol), Me-THF (3 mL) at 80 °C for 18 h.

A series of aryl bromides operated well using this precatalyst (Table 3). For substrates with electron donating substituents, a higher catalyst loading (5 mol %) was required to reach full conversion. Gratifyingly, *ortho*-substituents on the aromatic ring, such as methoxy, fluorine, or methyl, were also tolerated (compounds **8**, **15**, **18** and **25**). In addition, heterocyclic compounds were equally adaptable to the applied reaction conditions as illustrated with compounds **13**, **14**, **16**, and **22**–**24**.

Finally, Table 4 reveals that aryl chlorides with electron withdrawing groups can be transformed to their corresponding carboxylic acids **5**, **6**, and **26** in near quantitative yield. To obtain full conversion, the reaction temperature was raised to 120 °C and a higher boiling solvent, diglyme, was applied.[12] Lastly, benzyl chloride proved to be a good substrate for these transformations generating phenylacetic acid (**27**) in an 85% yield.

Several observations suggested that the conversion from aryl halides to benzoic acids was indeed a carbonylation reaction. First, transformation of aryl iodide **1** to carboxylic acid **2** could be run using a catalyst generated from Pd(dba)$_2$ and d*t*bpf with 5 mol % carbon monoxide generated from COgen applying the two chamber system. Again, only the use of d*t*bpf proved

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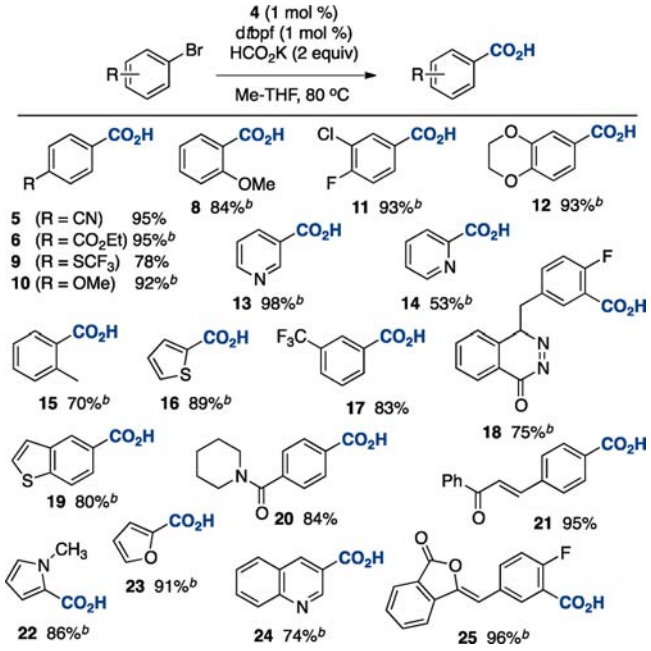
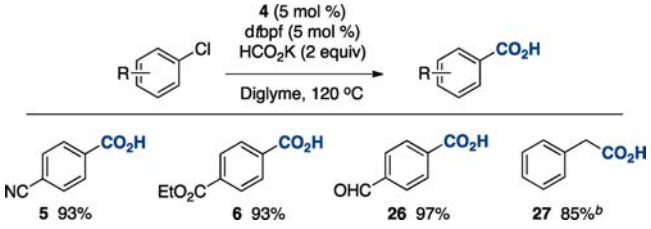
Table 3. Synthesis of Carboxylic Acids 5, 6 and 8−25 from Aryl Bromides[a]



[a]Aryl bromide (0.50 mmol), **4** (5.0 μmol), dtbpf (5.0 μmol), HCO_2K (1 mmol), 2-Me-THF (3 mL) at 80 °C for 18 h. [b]**4** (25 μmol), dtbpf (25 μmol).

Table 4. Synthesis of Carboxylic Acids 5, 6, 26 and 27 from Aryl Chlorides and Benzyl Chloride[a]

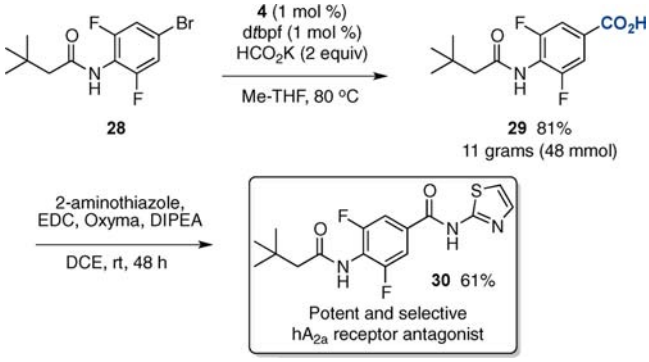


[a]Aryl chloride (0.50 mmol), **4** (25 μmol), dtbpf (25 μmol), HCO_2K (1 mmol), diglyme (3 mL) at 120 °C for 18 h. [b]80 °C for 18 h.

effective with the addition of low CO loadings. And second, the volume of the headspace in the reaction flask proved important for an efficient reaction suggesting that CO dissociates from the Pd complex and diffuses into the headspace. Through pressure measurements, we have observed that for effective transformation the partial pressure should reach a minimum of 0.1 bar. Reducing the CO partial pressure leads to lower conversions. As predicted, the same measurements revealed that the increase in the pressure of the overall system corresponds to the amount of **4** added, which is maintained throughout the reaction course (see Supporting Information).[13]

This carboxylation protocol was next applied to the gram scale synthesis of benzamide **30**, a potent and selective human A_{2A} receptor antagonist (Scheme 3).[14] Prodrug derivatives of **30** are currently under evaluation as drug candidates for the treatment of Parkinson's disease.[14] Hydroxycarboxylation of aryl bromide **28** was successfully performed on a 60 mmol scale providing carboxylic acid **29** in an 81% isolated yield (11 g). **29** could readily be transformed into the corresponding amide **30** with 2-aminothiazole in the presence of EDC/Oxyma. It should be noted that the hydroxycarbonylation was run with only 14.5

Scheme 3. Scale-Up Experiments



mL of CO present at all times, corresponding to a CO partial pressure of only 0.1 bar.

In conclusion, a mild protocol for the Pd-catalyzed hydroxycarbonylation of aryl halides has been developed using only 1−5 mol % loadings of carbon monoxide. This transformation works well with a number of aryl iodides and bromides, as well as aryl chlorides possessing electron poor substituents. The substoichiometric amounts of CO could be delivered to the reaction using an acyl-Pd(II) precatalyst, such as complex **4**, which also provides the active metal catalyst. This approach obviates the need for handling gaseous CO from a cylinder. Further work is in progress to examine other carbonylation reactions, which can run with the addition of only substoichiometric carbon monoxide.

CCDC 905027 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all the coupling products, as well as details on experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Only the deiodinated product was observed using precatalyst **4** without the addition of d*t*bpf.

(11) The boiling point of Me-THF is 80 °C. Alternatively, this solvent could be substituted for isopropyl acetate (bp 89 °C), which also provided full conversion.

(12) Aryl chlorides with electron donating groups did not undergo hydroxycarbonylation with these reactions conditions.

(13) Pressure measurements for the hydroxycarbonylation of *p*-cyanophenyl chloride at 120 °C in diglyme revealed a pressure build-up to 5 bar over a reaction period of 16 h in the glass equipment used (see Supporting Information). This is most likely due to the slow decomposition of formate to carbon dioxide and hydrogen at this temperature. Decomposition to carbon monoxide did not occur, as no product was observed when the same reaction was run with 5 mol % of $Pd(dba)_2$ and d*t*bpf instead of **4**. It should be noted that a similar pressure build-up was not observed under the hydroxycarbonylation conditions used for the aryl iodides and bromides (Me-THF at 80 °C).

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