

Palladium-Catalyzed Reductive Carbonylation of Aryl Halides with *N*-Formylsaccharin as a CO Source**

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Aromatic aldehydes are valuable synthetic intermediates in C–C bond-forming reactions. The reduction of carboxylic acids or esters to aldehydes^[1] is a commonly used synthetic strategy in spite of its drawbacks, that is, the functional groups that it can be applied to are limited, a relatively low temperature is required, and a two-step procedure involving initial activation of the carboxylic acid prior to the reduction is sometimes necessary. Direct formylation of aryl halides is a single-step alternative transformation which can be employed to form aldehydes.^[1] The conventional strategy for this conversion involves halogen–metal exchange by alkyllithium and subsequent addition of formylating agents (e.g., DMF). In this procedure, the reaction requires a stoichiometric amount of the metal reagent, the strong basicity of which limits the scope of functional groups which can be tolerated.

An efficient and complementary methodology is the palladium-catalyzed reductive carbonylation of aryl halides, which employs CO gas. Because of the pioneering work by Heck and Schoenberg in 1974,^[2] several groups have worked on developing this conversion to enhance its utility as a synthetic tool. However, there are still only a few general protocols for reductive carbonylation,^[3,4] especially in comparison to alkoxy- and aminocarbonylations.^[4] Recently Beller et al. reported the first industrially applied and efficient palladium-catalyzed reductive carbonylation at 5 bar of synthesis gas (CO/H₂ 1:1).^[5]

Over the last three decades, CO-free carbonylation chemistry has been the focus of extensive research. Various compounds such as formic acid derivatives and metal carbonyl compounds have already been developed as alternatives to toxic CO gas.^[6] Though some successful reports on hydroxy-,^[7,8] alkoxy-,^[9,10] and aminocarbonylation^[11] have been published, there is still only one report on the reductive carbonylation of aryl halides using an external CO source. Cacchi et al. reported the palladium-catalyzed reductive carbonylation of aryl iodides using thermally unstable acetic formic anhydrides as a CO source.^[12] To the best of our

knowledge, there is no precedent for the reductive carbonylation of electrophiles other than aryl iodide without using CO gas.^[13]

Recently, we developed the alkoxy carbonylation of aryl, alkenyl, and allyl halides, in addition to alkenyl tosylates, with phenyl formates in the presence of a Pd/P(*t*Bu)₃ or xantphos catalyst system.^[10] In this approach, decarbonylation of phenyl formate with a mild base (e.g., NEt₃) generates phenol and CO, which are subsequently used for the palladium-catalyzed alkoxy carbonylation, thus affording the corresponding phenyl esters which can be readily transformed into various carboxylic acid derivatives. Our interest in carbonylation reactions, especially in the conversion of aryl halides into the corresponding aldehydes, prompted us to explore the application of other CO sources to the synthesis of aldehydes. It was hypothesized that σ -acylpalladium species, formed by the reaction of CO generated in situ with σ -arylpalladium species, could be trapped by a hydride donor (e.g., Et₃SiH^[3,12]) to give the desired aldehydes.

Herein, we report a novel and practical method for palladium-catalyzed reductive carbonylation of aryl bromides with *N*-formylsaccharin, which works as an easily accessible and highly reactive crystalline CO surrogate. The reported reactions proceeded with a small excess of a CO source (1.5 equiv) at moderate temperatures and were successfully applied to a wide range of aryl bromides.

As an initial test, the reductive carbonylation of 4-bromoanisole (**1a**) was carried out. Here, 1.5 equivalents of formate (butyl, phenyl,^[10a,b] or 2,4,6-trichlorophenyl formate,^[10c] and potassium formate with acetic anhydride^[7]) were used as a CO source, with 2 equivalents of Et₃SiH as a hydride donor under a Pd/xantphos^[10,14] catalyst system at 85 °C (Table 1, entries 1–4). Unfortunately, these experiments resulted in extremely poor yields. The reaction using **2a** mainly afforded the dehalogenated compound, anisole, because of the low reactivity of **2a** as a CO source (entry 1). By employing the more reactive formates **2b** and **2c**, the corresponding phenyl esters, which are alkoxy carbonylation products, were observed as the main products (entries 2 and 3). It was hypothesized that a fragment such as phenol generated from a CO source has higher nucleophilicity to the palladium center compared to silane, thus preventing the conversion of acylpalladium into the desired aldehyde. In agreement with this reasoning, the use of *N*-formylsaccharin (**2d**)^[15] as a CO source resulted in dramatic improvements, thus providing complete conversion of **1a** and a good yield (80 %) of **3a**. Saccharin (p*K*_a = 1.6),^[16] which is generated from **2d** as a result of CO release, has much a lower nucleophilicity than the phenols (p*K*_a = 6–10). *N*-Formylsaccharin (**2d**), developed by Cossy et al. as a new and

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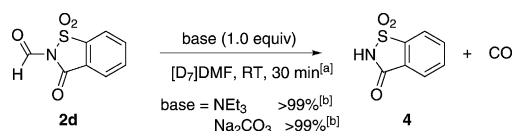
Table 1: Reductive carbonylation of **1a** with various sources of CO.^[a]

Entry	CO source	Conversion [%] ^[c]	Yield [%] ^[c]
1	2a	100	0
2	2b	97	5
3	2c	100	1
4	HCOOK, ^[b] Ac ₂ O	76	2
5	2d	100	80

[a] Reactions were conducted with 0.55 mmol of **1a** and DMF (2 mL).
[b] 1.5 equiv of Ac₂O and 2.5 equiv of HCOOK were used in place of Na₂CO₃. [c] Determined using HPLC. DMF = *N,N*-dimethylformamide.

inexpensive formylating agent for amines, is a highly crystalline compound and can be easily synthesized from saccharin.^[15a]

To confirm the reactivity of **2d** as a CO source, the process of decarbonylation to generate CO and saccharin (**4**) was examined (Scheme 1). As expected, by using a mild base (NEt₃ or Na₂CO₃), rapid decarbonylation was observed at room temperature, thus providing complete conversion of **2d** within 30 minutes.



Scheme 1. Decarbonylation of *N*-formylsaccharin (**2d**). [a] Reactions were conducted with 0.1 mmol of **2d** and [D₇]DMF (1 mL). [b] Conversion was determined using ¹H NMR spectroscopy.

Several ligands were then tested in the reductive carbonylation of **1a** with **2d** (Table 2). Monodentate ligands were found to be ineffective in this reaction (entries 1, 2, 10, 17, and 18). However, dppp, dppb, DCyPB, and dpppe, which have tethers greater than three carbon atoms long, showed excellent catalytic activity, thus affording **3a** in 92–95% (entries 5–7, and 12). In contrast, DCyPP, which has a three-carbon tether and was demonstrated by Buchwald et al. to be a highly active ligand in alkoxy- and aminocarbonylation,^[17] was not particularly effective for this reductive carbonylation (entry 11).

The effects of base and solvent were investigated using dppb as the ligand (Table 3). Na₂CO₃ was found to be the only effective base, thus giving the highest yield out of all the conditions tested (entry 1). When an organic base such as NEt₃ was used, a significant quantity of anisole was produced (entries 3–9). DMF was found to be the optimal solvent for the reaction, with the others tested tending to give poor

Table 2: Ligand screening.^[a]

Entry	Ligand ^[18]	Conversion [%] ^[b]	Yield [%] ^[b]
1	PPh ₃	23	18
2	PCy ₃	28	27
3	dppm	32	9
4	dppe	28	19
5	dppp	98	92
6	dppb	100	95
7	dpppe	99	94
8	dppf	97	56
9	dppBz	20	5
10	P(<i>t</i> Bu) ₃ ·HBF ₄	19	10
11	DCyPP·2 HBF ₄	55	44
12	DCyPB	99	92
13	dpephos	100	36
14	xantphos	100	80
15	<i>rac</i> -binap	85	34
16	Dt-bpf	31	4
17	BuPAD ₂ ·HI	64	62
18	P(<i>o</i> -Tol) ₃	11	0

[a] Reactions were conducted with 0.55 mmol of **1** and DMF (2 mL).
[b] Determined using HPLC.

Table 3: Effect of base and solvent on the reaction of **1a** and **2d**.^[a]

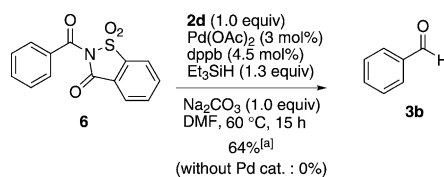
Entry	Solvent	Base	Conversion [%] ^[b]	Yield [%] ^[b]
1	DMF	Na ₂ CO ₃	100	95
2	DMF	Li ₂ CO ₃	69	58
3	DMF	NEt ₃	83	60
4	DMF	DIPEA	84	62
5	DMF	DABCO ^[c]	80	55
6	DMF	TMEDA ^[c]	72	60
7	DMF	<i>N</i> -methylmorpholine	67	50
8	DMF	<i>N</i> -methylimidazole	52	38
9	DMF	pyridine	16	9
10	DMI	Na ₂ CO ₃	97	48
11	NMP	Na ₂ CO ₃	99	58
12	CH ₃ CN	Na ₂ CO ₃	39	29
13	DME	Na ₂ CO ₃	18	7
14	THF	Na ₂ CO ₃	46	30
15	CPME	Na ₂ CO ₃	12	0
16	toluene	Na ₂ CO ₃	7	4
17	EtOAc	Na ₂ CO ₃	14	2
18 ^[d]	DMF	Na ₂ CO ₃	100	87
19 ^[d,e]	DMF	Na ₂ CO ₃	100	92
20 ^[f]	DMF	Na ₂ CO ₃ ^[c]	100	93

[a] Reactions were conducted on a 0.55 mmol scale in **1a** and 2 mL of solvent at 85 °C using 1.5 equiv of **2d**, 2.0 equiv of Et₃SiH, and 2.5 equiv of base in the presence of 3 mol % of Pd(OAc)₂ and dppb. Reaction time was 16 h. [b] Determined using HPLC. [c] Used 1.5 equiv of base. [d] Used 1.5 equiv of Et₃SiH and 1.5 mol % of Pd(OAc)₂ and dppb. [e] Pd/P ratio was 1:3. [f] Used 1.3 equiv of Et₃SiH. CPME = cyclopentyl methyl ether, DABCO = 1,4-diazabicyclo[2.2.2]octane, DIPEA = diisopropylethylamine, DME = 1,2-dimethoxyethane, NMP = *N*-methylpyrrolidone, THF = tetrahydrofuran, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

aldehyde yields while producing an increased amount of anisole (entries 10–17). A further series of experiments showed that even when reduced amounts of Na_2CO_3 (1.5 equiv), Et_3SiH (1.3 equiv), and catalyst (1.5 mol %) were used, the yields of the reaction remained high (87–92 %, entries 18–20). The P/Pd ratio was found to slightly affect the catalytic activity, with the yield increasing to 92 % at P/Pd = 3 (entries 18 and 19).

The identified optimal reaction conditions for **1a** (1 equiv of aryl halide, 1.5 equiv of **2d**, 1.3 equiv of Et_3SiH ,^[19] 1.5 equiv of Na_2CO_3 in the presence of 3 mol % of $\text{Pd}(\text{OAc})_2$ and 4.5 mol % of dppb in DMF) were subsequently employed to test the generality of the catalyst system for a variety of aryl halides and triflates (Table 4). It was found that, in addition to bromobenzene (**1b**), iodobenzene (**1c**) afforded **3b** in high yields (entries 1 and 2). Phenyl triflate (**1d**) also reacted, although the yield was modest (entry 3). A variety of functional groups (ether, ester, amide, aldehyde, amine, cyano, and dioxolane) were tolerated (entries 4, 7–12). Although electron-withdrawing groups at the 4-positions promoted reductive debromination, slightly lowering the reaction temperature resulted in a reduced amount of by-products, thus giving the corresponding aldehydes in moderate to good yields (entries 7–9, and 11). Though *ortho*-substituted aryl bromides also gave good results (entries 13 and 14), the steric hindrance of 2,6-disubstitution prevented the reaction from taking place (entry 15). The protocol was found to work well with bromonaphthalene (entries 16 and 17). Reaction of N- and S-containing heteroaromatic bromides proceeded to afford **3r–w** in moderate to good yields (entries 18–23). In addition, reductive carbonylation with Et_3SiD was effective in affording $[\text{D}_1]$ -4-phenylbenzaldehyde **3x** in good yield (entry 24).

The initial hypothesis for the mechanism of these palladium-catalyzed transformations was formed on the basis that owing to the low nucleophilicity of saccharin (**4**) generated from **2d**, the σ -acylpalladium species could be trapped by silane without the participation of the saccharin species (see Scheme 4, path 1). However, we cannot exclude the possibility that acylsaccharin would be formed in situ in the reductive carbonylation by reaction of the σ -acylpalladium species and saccharin. The palladium-catalyzed reduction of the in situ generated acylsaccharin with silane might also give the desired aldehyde (see Scheme 4, path 2). To further elucidate the mechanism, the palladium-catalyzed reduction of *N*-benzoylsaccharin (**6**) was examined.^[20] Surprisingly, the reaction of **6** with Et_3SiH in the presence of a Pd/dppb catalyst system afforded **3b** in 64 % yield (Scheme 2). In the absence of the palladium catalyst, **3b** was not obtained. In



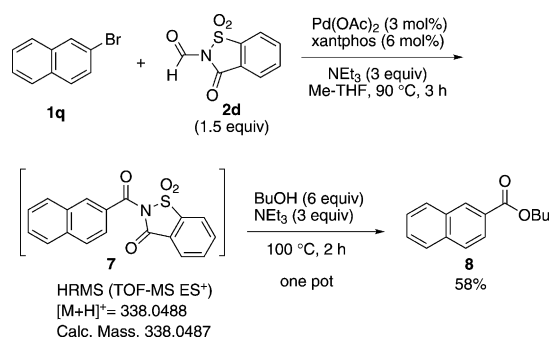
Scheme 2. Palladium-catalyzed reduction of **6** with Et_3SiH . [a] Determined using HPLC.

Table 4: Palladium-catalyzed reductive carbonylation of aryl bromides, iodide, and triflate with **2d**.^[a]

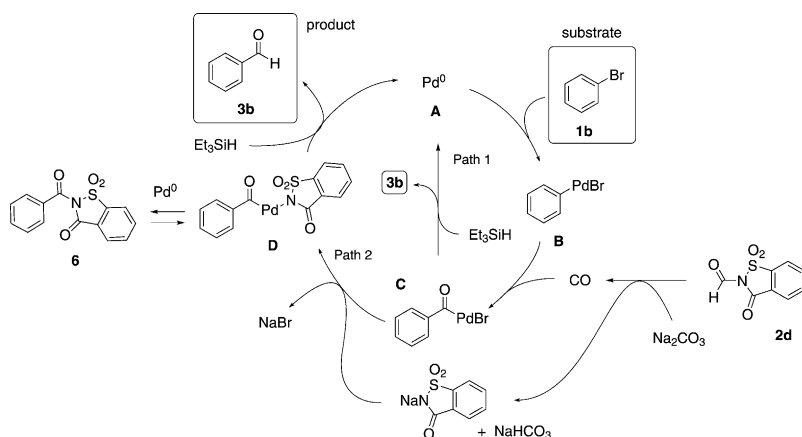
		$\text{R}-\text{C}_6\text{H}_4-\text{X} + \text{H}-\text{C}(=\text{O})-\text{N}(\text{O}_2)-\text{C}_6\text{H}_4-\text{S}-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{H}$ 2d (1.5 equiv)		$\text{Pd}(\text{OAc})_2$ (3 mol %) DPPB (4.5 mol %) Et_3SiH (1.3 equiv) Na_2CO_3 (1.5 equiv)	$\text{R}-\text{C}_6\text{H}_4-\text{CHO}$		
		DMF, 65–90 °C, 16–20 h					
Entry	T [°C]	Substrate	Product	Yield [%] ^[b]			
1	75	1b : X = Br	3b	83 (92) ^[c]			
2	75	1c : X = I	3b	78 (92) ^[c]			
3	75	1d : X = OTf	3b	36 (50) ^[c]			
4	85	1a : R = OMe	3a	87 (93) ^[c]			
5	80	1e : R = Me	3e	78 (93) ^[c]			
6	80	1f : R = Ph	3f	83			
7	75	1g : R = CO ₂ Et	3g	72			
8	75	1h : R = CONMe ₂	3h	77			
9 ^[d]	65	1i : R = CHO	3i	65			
10 ^[e]	85	1j : R = NMe ₂	3j	82			
11	75	1k : R = CN	3k	60			
12 ^[e]	85	1l : R =	3l	80			
13	80	1m : R = Me	3m	72 (87) ^[c]			
14	85	1n : R = OMe	3n	54 (65) ^[c]			
15 ^[d]	90	1o	3o	trace ^[c]			
16 ^[d]	90	1p : X ¹ = Br, X ² = H	3p : R ¹ = CHO, R ² = H	66			
17 ^[e]	85	1q : X ¹ = H, X ² = Br	3q : R ¹ = H, R ² = CHO	77			
18	80	1r : X ¹ = Br, X ² = H	3r : R ¹ = CHO, R ² = H	57 (72) ^[c]			
19	80	1s : X ¹ = H, X ² = Br	3s : R ¹ = H, R ² = CHO	70 (87) ^[c]			
20	80	1t	3t	70			
21 ^[f]	80	1u	3u	45			
22	80	1v : X ¹ = Br, X ² = H	3v : R ¹ = CHO, R ² = H	63 (72) ^[c]			
23	70	1w : X ¹ = H, X ² = Br	3w : R ¹ = H, R ² = CHO	45 (49) ^[c]			
24 ^[g]	80	1x	3x	77			

[a] Reactions were conducted on a 0.5–1.5 mmol scale in substrate and 2–6 mL of DMF. [b] Yield of isolated product. [c] Determined using HPLC. [d] 5 mol % of $\text{Pd}(\text{OAc})_2$. [e] 1.5 equiv of **2d**, 1.5 equiv of Et_3SiH , and 2.5 equiv of base in the presence of 1.5 mol % of $\text{Pd}(\text{OAc})_2$ and 2.3 mol % of dppb. [f] Xantphos was used in place of dppb. [g] 1.3 equiv of Et_3SiD was used in place of Et_3SiH .

addition, palladium-catalyzed carbonylation of **1q** using **2d** without silane produced the acylsaccharin **7** (the corresponding $[\text{M}+\text{H}]^+$ was detected as a major peak on HRMS analysis), which could be converted into the ester **8** in a one-pot procedure (Scheme 3). These observations indicate that the reaction intermediate is likely to be acylsaccharin, the C–N bond of which could oxidatively add to the palladium. A plausible catalytic cycle is shown in Scheme 4. *N*-Formylsaccharin (**2d**) is converted into sodium saccharin and CO by



Scheme 3. Palladium-catalyzed alkoxycarbonylation of **1q** with **2d**.



Scheme 4. Plausible mechanism for reductive carbonylation.

Na_2CO_3 . This then intercepts the acylpalladium species **C**, which results from the oxidative addition of **1b** and insertion of CO, thus leading to the formation of **D**. Palladium-mediated reversible reductive elimination/oxidative addition occurs between **6** and **D**, and then reacts with Et_3SiH to form **3b** and the active palladium species **A** (path 2). However, the alternative mechanism which was part of the original hypothesis (path 1) cannot be ruled out. In this case, **C** is directly reduced by Et_3SiH to afford **3b** without the participation of sodium saccharin.

In summary, we have reported a novel and practical method for palladium-catalyzed reductive carbonylation of aryl bromides with *N*-formylsaccharin (**2d**) without using CO gas. The reported reactions proceeded with a small excess of a CO source (1.5 equiv) at moderate temperatures and were successfully applied to a wide range of aryl bromides. Compared to other existing CO sources for palladium-catalyzed reactions, **2d** has a great number of advantages, including low cost, good availability, ease of handling, stability, and high reactivity as a CO source. Further investigations concerning the application of this methodology to other CO-free, palladium-catalyzed reactions will be carried out in due course.

Experimental Section

A typical experimental procedure for reductive carbonylation of **1b** with *N*-formylsaccharin.

$\text{Pd}(\text{OAc})_2$ (10.1 mg, 0.045 mmol, 3.0 mol %), **dppb** (28.8 mg, 0.068 mmol, 4.5 mol %), **2d** (475 mg, 2.25 mmol, 1.5 equiv), and Na_2CO_3 (238 mg, 2.25 mmol, 1.5 equiv) were added to a 30 mL test tube, which was then evacuated and backfilled three times with N_2 . A degassed solution of **1b** (158 μL , 1.50 mmol) and Et_3SiH (311 μL , 1.95 mmol, 1.3 equiv) in DMF (6 mL) was added to the test tube under N_2 . The tube was immediately sealed by a plastic screw cap and the mixture was stirred for 10 min at RT (this stirring is critical for the selectivity of the reaction). The mixture was subsequently warmed to 75 °C and stirred for a further 16 h. The reaction mixture was cooled to RT, then diluted with Et_2O (15 mL), and washed with H_2O (15 mL). The aqueous layer was extracted two times with Et_2O (15 mL). The combined organic layer was dried over MgSO_4 , filtered, and concentrated. The obtained residue was purified by flash column chromatography on silica gel (3–5 % Et_2O in *n*-pentane) to provide **3b** as a colorless oil (132 mg, 83 %).

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- [18] Cy = cyclohexyl, *o*-Tol = 2-methylphenyl, dppm = bis(diphenylphosphino)methane, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, dpppe = 1,5-bis(diphenylphosphino)pentane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppBz = 1,2-bis(diphenylphosphino)benzene, DCyPP = 1,3-bis(dicyclohexylphosphino)propane, DCyPB = 1,4-bis(dicyclohexylphosphino)butane, dpephos = bis(2-(2-diphenylphosphino)phenyl) ether, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, binap = bis(diphenylphosphino)-1,1'-binaphthyl, Dt-bpe = 1,1'-bis(di-*tert*-butylphosphino)ferrocene.
- [19] Other silanes, including PhMe₂SiH, Ph₂MeSiH, Ph₃SiH, polymethylhydrosiloxane, *i*Pr₃SiH, and (EtO)₃SiH were tested in the reaction of **1k**, but only gave poor yields of **2k** (3–50%).
- [20] The preparation of **6** was performed according to: T. Imai, T. Okunoyama, M. Okoshi, *J. Chem. Soc. Jpn.* **1975**, 123. See the Supporting Information for details.