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Palladium-catalyzed external-CO-free reductive carbonylation of aryl sulfonates

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ABSTRACT

Pd-catalyzed reductive carbonylation of aryl sulfonates using *N*-formylsaccharin as a carbon monoxide (CO) surrogate was developed. This external-CO-free carbonylation provides a safe and practical access to aldehydes from phenol derivatives. The reaction has a broad substrate scope, rendering it an attractive method for synthesizing aldehydes.

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1. Introduction

Aldehydes are one of the most ubiquitous and abundant compounds in nature. Due to their easy availability and appropriate reactivity, they are extensively used as fundamental and useful building blocks in both industry and academia. Therefore, a bunch of synthetic methods for aldehydes have been reported to date [1–6], and undoubtedly, novel ones will be continuously developed.

Transition metal-catalyzed reductive carbonylation using carbon monoxide (CO) and a reductant has been established as a useful and direct method to introduce a formyl group into haloarenes. Use of CO in the industries enables mass production of synthetically important aldehydes [7]. Synthetic gas is easily available and can be used in the reaction as both carbonyl and hydride sources [8]. The combined use of CO gas and hydrosilanes is also an effective strategy for the synthesis of aldehydes from haloarenes [9–11]. Despite the utility of these synthetic methods, tedious reaction procedures involving the use of pressurized and toxic CO gas cause inconvenience and hamper their practical applications, especially in laboratory-scale experiments.

Different from the conventional methods using CO or CO-containing gas, the use of CO surrogates which can generate CO by chemical reaction has gained its utility and practicality in the synthetic community [12–17]. Among the various CO surrogates developed, we have found *N*-formylsaccharin as a stable crystalline CO surrogate that could produce CO under extremely mild conditions and have demonstrated the reductive carbonylation of bromoarenes in the presence of triethylsilane (Et_3SiH) as a reductant using this CO surrogate [18]. We have also shown one example of the reaction of phenyl trifluoromethanesulfonate (triflate) using *N*-formylsaccharin, although the yield of the desired benzaldehyde was low [18].

There is an increasing demand that versatile substrates can be applied for accessing aldehydes either as the final target products or as synthetic intermediates. Furthermore, development of novel transformations using aldehydes as substrates has become a popular research area [19–24]. Nonetheless, there are surprisingly fewer reports on the reductive carbonylation of aryl sulfonates using CO gas [25,26] or CO surrogates [27,28] compared with that of haloarenes. This prompted us to develop a general and convenient method for introducing aldehyde moieties into aryl sulfonates using CO surrogates. The method would provide a safe and practical access to aldehydes, since aryl sulfonates are easily prepared from the corresponding phenols. We report herein the external-CO-free Pd-catalyzed reductive carbonylation of aryl sulfonates using *N*-formylsaccharin as our unique CO surrogate (Scheme 1). Successful scale-up experiments and reaction using ordinary glassware clearly

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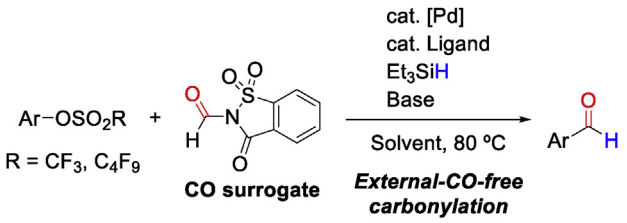


Scheme 1. Pd-catalyzed reductive carbonylation of aryl sulfonates using *N*-formylsaccharin.

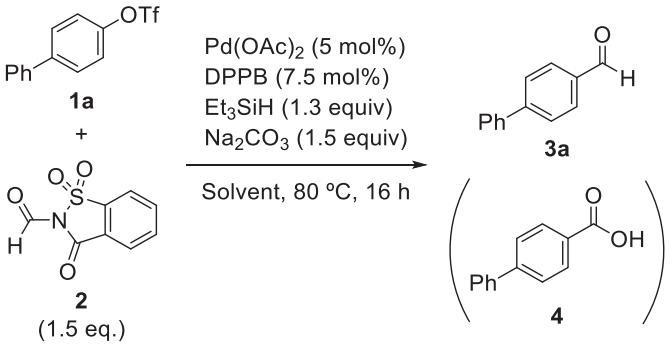
demonstrate the high-safety aspect and practicality of this reaction.

2. Results and discussion

We began our investigation by examining suitable conditions for the reductive carbonylation, using biphenyl-4-yl triflate (**1a**) as a model substrate in the presence of a Pd catalyst and *N*-formylsaccharin (**2**) (Table 1). Solvent screening revealed the formation of an unexpected compound, 4-phenylbenzoic acid (**4**), which was derived from the actual target product, 4-phenylbenzaldehyde (**3a**). Compound **4** could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture; thus, **4** was probably formed via the aerobic oxidation of **3a** during the chromatographic purification on silica gel. Nonetheless, it was revealed that MeCN was the solvent based on the combined yield of aldehyde **3a** and carboxylic acid **4** (entry 4).

For an accurate evaluation of the effect of ligands and bases, product **3a** was converted into 4-phenylbenzyl alcohol (**5**) through one-pot treatment with $NaBH_4$ for every reaction (Table 2). Conversion to product **5** was higher in the presence of bidentate bisphosphines than in the presence of monodentate phosphines; DPPB, DPPPe, and DPPF were found to be the most effective ligands (entries 1–11). Na_2CO_3 was the optimal base, which was similar to that observed for our previously developed reductive carbonylation of bromoarenes (entries 8, 12–17) [18]. While stronger or organic bases could facilitate smooth CO generation from **2**, a fast CO supply was not always effective for Pd-catalyzed carbonylation [29]. Increase in the amount of Et_3SiH was beneficial in promoting the reaction (entry 18).

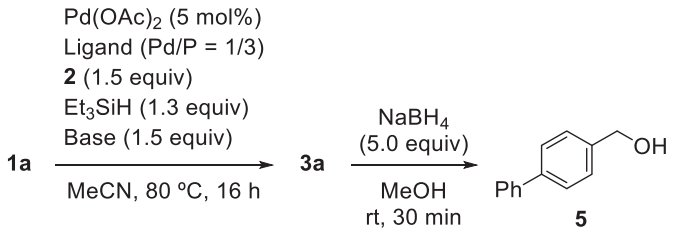
Table 1
Solvent screening.[a]



Entry	Solvent	Isolated yield (%)	
		3a	**4**
1	toluene	trace	–
2	1,2-dichloroethane	trace	–
3	THF	35	15
4	MeCN	77	0
5	DMF	27	20
6	NMP	12	34

[a] DPPB: 1,4-bis(diphenylphosphino)butane.

Table 2
Effect of ligands and bases.



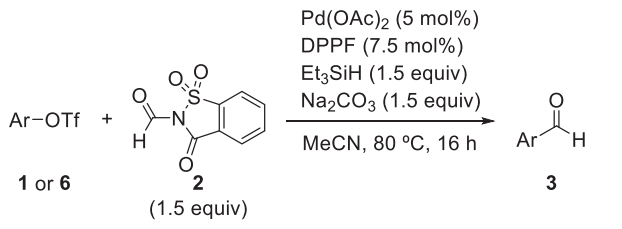
Entry	Ligand[a]	Base	Isolated yield of **5** (%)
1	PPh_3	Na_2CO_3	48
2	PCy_3	Na_2CO_3	5
3	$P(t\text{-}Bu)_3{\cdot}HBF_4$	Na_2CO_3	3
4	DPPE	Na_2CO_3	trace
5	DPPP	Na_2CO_3	26
6	DPPB	Na_2CO_3	77
7	DPPPe	Na_2CO_3	77
8	DPPF	Na_2CO_3	84
9	Xantphos	Na_2CO_3	18
10	DCyPB	Na_2CO_3	12
11	DPEPhos	Na_2CO_3	67
12	DPPF	KOAc	10
13	DPPF	K_2CO_3	54
14	DPPF	Cs_2CO_3	47
15	DPPF	K_3PO_4	59
16	DPPF	NEt_3	29
17	DPPF	DBU	40
18[b]	DPPF	Na_2CO_3	96

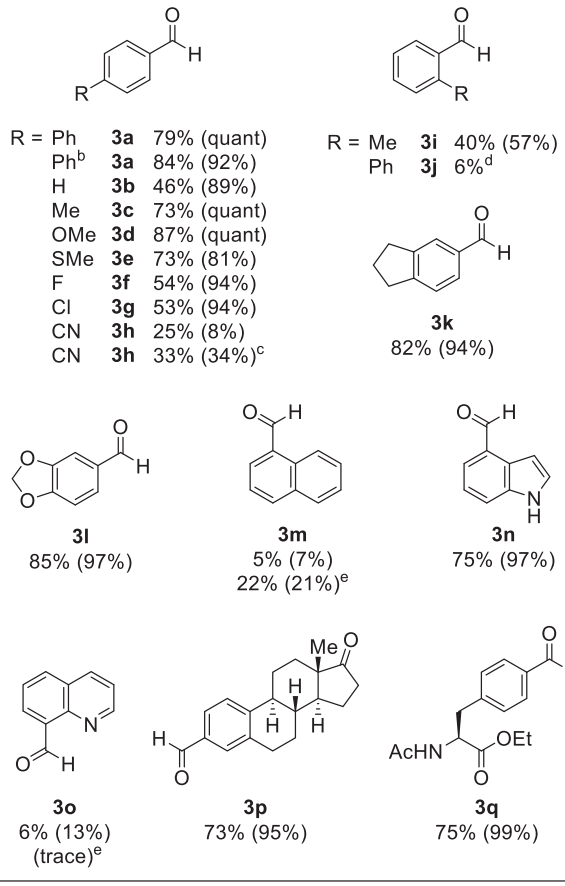
[a] DPPE: 1,2-bis(diphenylphosphino)ethane, DPPP: 1,3-bis(diphenylphosphino) propane, DPPB: 1,4-bis(diphenylphosphino)butane, DPPPe: 1,5-bis(diphenylphosphino)pentane, DPPF: 1,1′-bis(diphenylphosphino)ferrocene, Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DCyPB: 1,4-bis(dicyclohexylphosphino)butane, DPEPhos: 2,2′-bis(diphenylphosphino) diphenyl ether.

[b] Et_3SiH (1.5 eq.) was used.

With the optimal reaction conditions in hand, we investigated the substrate scope of the reaction (Table 3). To obtain the target aldehydes, all the reactions were conducted without $NaBH_4$ treatment. Since some aldehydes are highly volatile, their yields were determined based on both ^{1}H NMR analysis of the crude mixture and the yield after chromatographic separation, with the least possible contact time with SiO_2 (for details, see Experimental section). Phenyl triflate (**1b**) and substrates with electron-donating groups such as **1c** and **1d** afforded the corresponding aldehydes **3b**–**d** in high yields. Methylthio, fluoro, and chloro groups were also compatible with this reaction to generate aldehydes **3e**–**g**. However, a low yield of product **3h** was obtained with cyano-containing substrate **1h**, primarily due to the undesirable formation of benzonitrile as a reduced byproduct. Although using DPPPe as a ligand and reducing the amount of Et_3SiH improved the situation, the formation of benzonitrile was still observed. While **1i** bearing a 2-methyl group was well-tolerated in this reaction to form aldehyde **3i**, **1j** with a 2-phenyl group resulted in low conversion to product **3j**, indicating that the reaction was strongly influenced by the steric effect of the substrates. Substrates with indane structure, **1k**, and catechol-derived acetal **1l** were also well-tolerated and gave aldehydes **3k** and **3l** in high yields. Surprisingly, naphth-1-yl triflate (**1m**) did not show the expected reactivity, probably due to the rapid reduction to form naphthalene. More flexible ligands such as DPPPe could possibly improve the yield of

Table 3
Substrate scope of the reductive carbonylation.[a]





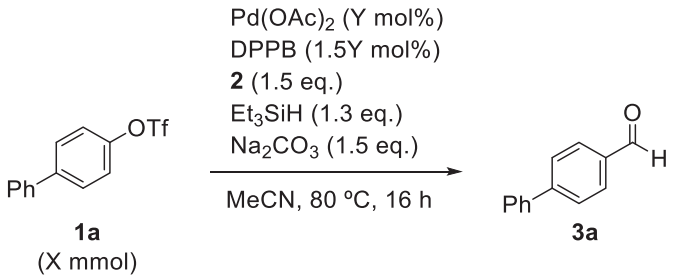
[a]Product yield was determined after chromatographic separation. NMR yield was written in parenthesis. [b]Biphenyl-4-yl nonaflate (**6**) was used as a substrate. [c]DPPPe was used instead of DPPF. **2** (2.0 equiv), Et_3SiH (1.3 equiv), and Na_2CO_3 (2.0 equiv) were used. [d]NMR yield was not determined due to overlapping of peaks derived from impurities. [e]DPPPe was used instead of DPPF. Et_3SiH (1.3 equiv) was used.

aldehyde **3m**. Some heteroaromatic substrates were also examined. Indol-4-yl triflate (**1n**) was smoothly converted into the desired aldehyde **3n** in a high yield. A sharp contrast in the yields of **3m** and **3n** indicated that subtle differences in the steric environments around the reactive sites could strongly influence the substrate reactivity. Electron-deficient quinolin-8-yl triflate (**1o**) failed to afford the corresponding aldehyde **3o**. Similar to the case with cyano-containing **1h**, this substrate mainly afforded quinoline as a reduced byproduct. We were also pleased to find that complex triflates **1p** and **1q** derived from estrone and protected tyrosine successfully afforded the desired aldehydes **3p** and **3q**, respectively. Furthermore, the reaction of biphenyl-4-yl perfluorobutanesulfonate (biphenyl-4-yl nonaflate, **6**), which can be obtained directly from the reaction of 4-phenylphenol and perfluorobutanesulfonyl fluoride, was found to be a good substrate as a triflate.

It is noteworthy that the reaction could be conducted at a 1-mmol scale in a closed test tube with a catalyst loading as low as 1 mol% (Table 4, entries 1 and 2). Furthermore, the 5-mmol scale reaction could also be successfully conducted in a normal two-necked round-bottomed flask with an empty balloon to maintain the atmospheric pressure inside the flask. This clearly indicates the high-safety aspect and potential scalability of this reaction (entry 3).

We have mentioned the reactivity of the reductive carbonylation of aryl sulfonates was influenced by solvents, among which MeCN worked the best (Table 1). This showed a sharp contrast with the reactions of bromoarenes where DMF was the optimal solvent [18]. Therefore, some control experiments were performed under atmospheric CO (Table 5). It was confirmed that the reaction proceeded smoothly under CO gas both in MeCN and DMF, indicating that both solvents were inherently effective for the reductive carbonylation (entries 1 and 2). Considering that sodium saccharinate was gradually generated as the reaction of aryl sulfonates using *N*-formylsaccharin proceeded, we next conducted the

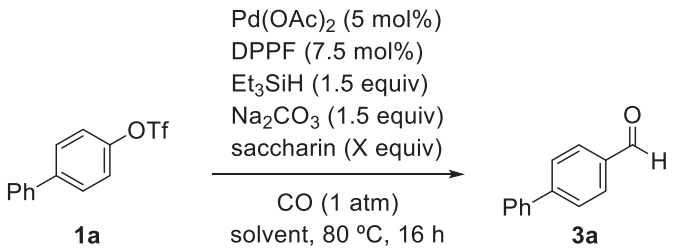
Table 4
Scale-up experiments and reduction of catalyst loading.



Entry	X (mmol)	Y (mol%)	Isolated yield (%)
1[a]	1.0	5	93
2[a]	1.0	1	58
3[b]	5.0	5	74

[a] A screw-capped test tube was used as the reaction vessel.
[b] A two-necked, round-bottomed flask with an empty balloon was used as the reaction vessel.

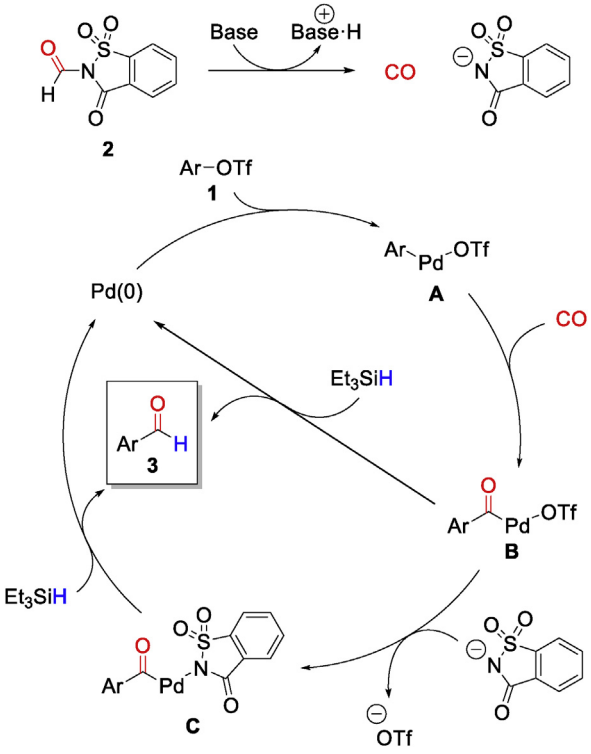
Table 5
Reactions under atmospheric CO with and without saccharin.



Entry	Solvent	X (eq.)	Isolated yield (%)
1	MeCN	0	70
2	DMF	0	64
3	MeCN	1.5	66
4	DMF	1.5	11

reactions in the presence of saccharin. In MeCN, the desired aldehyde was obtained regardless of the presence of saccharin (entry 1 vs. 3). However, an addition of saccharin caused substantial decrease of the yield of the product when DMF was used as a solvent (entry 2 vs. 4). While further studies are needed to clarify the precise mechanism, these results indicate that the formation of sodium saccharinate under the basic conditions have detrimental effects in DMF, thereby resulting in low yield of the product.

A plausible reaction mechanism is shown in Scheme 2. *N*-Formylsaccharin (**2**) reacts with a base to produce CO and saccharinate. Oxidative addition of substrate **1** to Pd(0) generates Pd(II) intermediate **A**, which is followed by coordination and migratory insertion of CO to form intermediate **B**. This intermediate seems to react directly with Et_3SiH to afford the desired product **3**. Another plausible pathway from intermediate **B** to product **3** could be that via the formation of intermediate **C** by the ligand exchange of triflate with saccharinate [18].



Scheme 2. Proposed reaction mechanism.

3. Conclusion

We have developed an external-CO-free method for the Pd-catalyzed reductive carbonylation of aryl sulfonates using *N*-formylsaccharin as a stable crystalline CO surrogate. The reaction has a broad substrate scope and is extremely safe and practical owing to the use of a CO surrogate instead of CO gas. Since aryl sulfonates can be easily obtained from the corresponding phenols via a single-step sulfonylation reaction, the combined sulfonylation and reductive carbonylation can provide a convenient route for the conversion of a phenolic hydroxy group into a formyl group, thereby affording aromatic aldehydes.

4. Experimental section

4.1. General

All the reactions were performed in oven-dried or flame-dried glassware under an argon atmosphere. Reactions were monitored by TLC on Merck silica gel 60 F_{254} plates by visualizing with a UV lamp at 254 nm. Column chromatography was performed on Merck silica gel 60, and preparative TLC was performed on Merck silica gel 60 F_{254} 0.5 mm plates. In the 5-mmol experiment, column chromatography was performed on a Yamazen Smart Flash W-Prep 2XY using Hi-Flash column. Recycling preparative HPLC was performed on a Japan Analytical Industry LaboACE LC-5060 using a JALGEL-2HR column (solvent: ethyl acetate, flow rate: 10 mL/min, detection: 254 nm). NMR spectra were acquired on a JEOL AL-400 NMR spectrometer (400 MHz for ^{1}H spectra) or a JEOL ECX-500 NMR spectrometer (500 MHz for ^{1}H spectra, 125 MHz for ^{13}C spectra, and 470 MHz for ^{19}F spectra) and are quoted in ppm for measurement against tetramethylsilane (TMS) or residual solvent peak as an internal standard. Infrared spectra were acquired on a SHIMADZU IR Prestige-21 spectrometer (ATR). High-resolution mass spectra (HRMS) were acquired on a Bruker MicrOTOF time-of-flight mass spectrometer (ESI).

All the solvents and ligands, $Pd(OAc)_2$, and Et_3SiH were purchased from commercial suppliers and used directly without purification. Aryl triflates [30,31] and *N*-formylsaccharin [32] were synthesized from the corresponding phenol derivatives and saccharin, respectively, according to reported procedures.

4.2. General experimental procedure for the reductive carbonylation of aryl triflate **1** using N-formylsaccharin (**2**)

CAUTION! To avoid an unexpected leak of toxic CO and an increase in the internal pressure of the reaction vessel, all reactions should be conducted behind a blast shield in a well-ventilated fume hood.

$Pd(OAc)_2$ (2.2 mg, 10.0 μmol, 5.00 mol%), DPPF (8.3 mg, 15.0 μmol, 7.50 mol%), **2** (63.4 mg, 0.300 mmol, 1.50 equiv), and MeCN (1.00 mL) were added to an oven-dried, 10-mL test tube with a septum containing a magnetic stirring bar. The tube was evacuated and backfilled with Ar three times. Aryl triflate **1** (0.200 mmol), Et_3SiH (47.8 μL, 0.300 mmol, 1.50 equiv), and Na_2CO_3 (31.8 mg, 0.300 mmol, 1.50 equiv) were added to the mixture under Ar flow. The tube was tightly screw-capped and heated to 80 °C in an oil bath. The mixture was stirred for 16 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and H_2O, extracted with CH_2Cl_2 from aqueous layer, washed with brine, dried over Na_2SO_4, filtered, and concentrated. After the ^{1}H NMR analysis of the crude reaction mixture with a small amount of 1,2,4,5-tetramethylbenzene as an internal standard, the obtained residue was purified by preparative TLC (SiO_2, developed with hexane/EtOAc mixture). The desired aldehyde was eluted just after finishing the development of the preparative TLC plate to prevent undesirable oxidation to carboxylic acid on SiO_2. Further purification by recycling preparative HPLC afforded the analytically pure product. The 1-mmol scale experiment was conducted in a 26-mL test tube.

4.2.1. [1,1′-biphenyl]-4-carbaldehyde (**3a**) [33]

A colorless oil; 28.6 mg; 79% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 147.2, 139.7, 135.1, 130.3, 129.0, 128.5, 127.7, 127.3 ppm.

*4.2.2. Benzaldehyde (3**b**) [33]*

A colorless oil; 9.7 mg; 46% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.89 (d, J = 6.9 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 136.4, 134.5, 129.8, 129.0 ppm.

*4.2.3. 4-Methylbenzaldehyde (**3c**) [34]*

A colorless oil; 17.4 mg; 73% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 145.6, 134.2, 129.9, 129.7, 21.9 ppm.

*4.2.4. 4-Methoxybenzaldehde (**3d**) [34]*

A colorless oil; 23.8 mg; 87% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.85 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 164.6, 132.0, 129.9, 114.3, 55.6 ppm.

*4.2.5. 4-(Methylthio)benzaldehyde (**3e**) [35]*

A colorless oil; 22.3 mg; 73% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 2.54 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 147.9, 132.9, 130.0, 125.2, 14.7 ppm.

*4.2.6. 4-Fluorobenzaldehyde (**3f**) [36]*

A colorless oil; 13.5 mg; 54% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.95-7.90 (m, 2H), 7.22 (t, J = 8.6 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 166.5 (d, J = 256 Hz), 132.9 (d, J = 2.5 Hz), 132.2 (d, J = 10 Hz), 116.4 (d, J = 21 Hz) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −102.2 (m) ppm.

*4.2.7. 4-Chlorobenzaldehyde (**3g**) [33]*

A white solid; 15.0 mg; 53% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 141.0, 134.7, 130.9, 129.5 ppm.

*4.2.8. 4-Formylbenzonitrile (**3h**) [36]*

The reaction was performed with DPPPe instead of DPPF. A white solid; 8.6 mg; 33% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 138.7, 132.9, 129.9, 117.7, 117.6 ppm.

*4.2.9. 2-Methylbenzaldehyde (**3i**) [33]*

A colorless oil; 9.6 mg; 40% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.49 (td, J = 7.4, 1.1 Hz, 1H), 7.37 (d, J = 7.4 Hz, 1H), 7.29-7.26 (m, 1H), 2.68 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 140.6, 134.1, 133.7, 132.1, 131.8, 126.3, 19.6 ppm.

*4.2.10. [1,1′-biphenyl]-2-carbaldehyde (**3j**) [37]*

A colorless oil; 2.2 mg; 6% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.65 (td, J = 7.4, 1.1 Hz, 1H), 7.53-7.43 (m, 5H), 7.41-7.37 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ192.5, 146.0, 137.7, 133.7, 133.6, 130.8, 130.1, 128.4, 128.1, 127.8, 127.6 ppm.

*4.2.11. 2,3-Dihydro-1H-indene-5-carbaldehyde (**3k**) [38]*

A colorless oil; 24.0 mg; 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.73 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 2.97 (t, J = 7.4 Hz, 4H), 2.13 (quint, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 152.1, 145.3, 135.2, 128.9, 125.1, 124.8, 33.1, 32.3, 25.3 ppm.

*4.2.12. Benzo[d][1,3]dioxole-5-carbaldehyde (**3l**) [39]*

A colorless oil; 25.5 mg; 85% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.42 (dd, J = 8.0, 1.1 Hz, 1H), 7.34 (d, J = 1.1 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.08 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 153.1, 148.7, 131.8, 128.7, 108.3, 106.8, 102.1 ppm.

*4.2.13. 1-Naphthaldehyde (**3m**) [40]*

The reaction was performed with DPPPe instead of DPPF. A pale yellow oil; 6.8 mg; 22% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.26 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 6.9 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 6.9 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.60 (t, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 136.7, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.9 ppm (one carbon signal is missing).

*4.2.14. 1H-Indole-4-carbaldehyde (**3n**) [41]*

A white solid; 21.8 mg; 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.70 (br s, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 2.9 Hz, 1H), 7.38−7.32 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 136.5, 128.3, 127.7, 127.6, 125.6, 121.3, 117.5, 103.0 ppm.

*4.2.15. Quinoline-8-carbaldehyde (**3o**) [42]*

A white solid; 1.9 mg; 6% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.47 (s, 1H), 9.07 (dd, J = 4.3, 1.4 Hz, 1H), 8.35 (dd, J = 7.4, 1.1 Hz, 1H), 8.26 (dd, J = 8.3, 1.4 Hz, 1H), 8.11 (dd, J = 8.0, 1.1 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.53 (dd, J = 8.6, 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 151.3, 147.6, 136.3, 134.2, 131.7, 129.4, 128.3, 126.2, 121.8 ppm.

*4.2.16. (8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carbaldehyde (**3p**) [43]*

A white solid; 41.2 mg; 73% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 3.05-2.94 (m, 2H), 2.56-2.44 (m, 2H), 2.37 (td, J = 10.9, 4.0 Hz, 1H), 2.21-1.98 (m, 4H), 1.70-1.44 (m, 6H), 0.93 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.4, 192.2, 147.0, 137.5, 134.2, 130.2, 127.2, 126.0, 50.4, 47.8, 44.8, 37.6, 35.7, 31.4, 29.1, 26.1, 25.5, 21.5, 13.7 ppm.

*4.2.17. (S)-4-(2-acetamido-3-ethoxy-3-oxopropyl)benzoic acid (**3q**)*

A pale yellow oil; 39.4 mg; 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.04 (d, J = 6.9 Hz, 1H), 4.94-4.88 (m, 1H), 4.23-4.14 (m, 2H), 3.25 (dd, J = 13.8, 6.3 Hz, 1H), 3.18 (dd, J = 13.8, 5.2 Hz, 1H), 2.01 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 171.3, 169.6, 143.3, 135.3,130.0, 129.9, 61.8, 52.9, 38.2, 23.1, 14.1 ppm; IR (ATR) 1735, 1697, 1654, 1606, 1535, 1375, 1213, 1170, 1018, 732 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_5$: 302.0999; found: 302.0991.

*4.2.18. [1,1′-biphenyl]-4-carboxylic acid (**4**) [44]*

This compound was obtained during the purification process of the **3a** in the reaction of **1a** (Table 1, entries 3, 5, 6). A white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.4 Hz, 2H), 7.50 (t, J = 6.9 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H) ppm (carboxy proton signal is missing); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.2, 144.4, 139.1, 130.0, 129.7, 129.2, 128.4, 127.0, 126.9 ppm.

*4.2.19. [1,1′-biphenyl]-4-ylmethanol (**5**) [45]*

This compound was obtained after the treatment of the crude reaction mixture with $NaBH_4$ (37.8 mg, 5.0 equiv) in MeOH at rt for 30 min, which was followed by the same purification process as that of aldehyde **3a** (Table 2). A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.57 (m, 4H), 7.46-7.42 (m, 4H), 7.35 (t, J = 7.5 Hz, 1H), 4.74 (s, 2H), 1.79 (br s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 140.6, 139.8, 128.8, 127.4, 127.3, 127.1, 65.1 ppm (one carbon signal is missing) ppm.

*4.3. Five-mmol experiment for the synthesis of [1,1′-biphenyl]-4-carbaldehyde (**3a**)*

$Pd(OAc)_2$ (56.1 mg, 0.250 mmol, 5.00 mol%), DPPF (208 mg, 0.375 mmol, 7.50 mol%), **2** (1.85 g, 7.50 mmol, 1.50 equiv), and MeCN (25.0 mL) were added to an oven-dried, 100-mL round-bottomed flask with a reflux condenser, Ar balloon, and a septum containing a magnetic stirring bar. The flask was evacuated and backfilled with Ar three times. Biphenyl-4-y triflate **1a** (1.51 g, 5.00 mmol), triethylsilane (1.20 mL, 7.50 mmol, 1.50 equiv), and Na_2CO_3 (795 mg, 7.50 mmol, 1.50 equiv) were added to the mixture under the flow of Ar. The Ar balloon and the septum were replaced to an empty balloon (Fig. 1 (a)) and a glass stopcock, respectively, and the flask was warmed to 80 °C in an oil bath. The mixture was stirred for 16 h. A balloon was inflated due to CO generation and evaporation of MeCN on the course of the reaction (Fig. 1). After cooling to rt, the mixture was diluted with CH_2Cl_2 and H_2O, extracted with CH_2Cl_2 from aqueous layer, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was purified by column chromatography (performed by Smart Flash W-Prep 2XY using Hi-Flash column, hexane/AcOEt = 100/0 to 85/15) to afford [1,1′-biphenyl]-4-carbaldehyde (**3a**, 677 mg, 3.71 mmol, 74%).

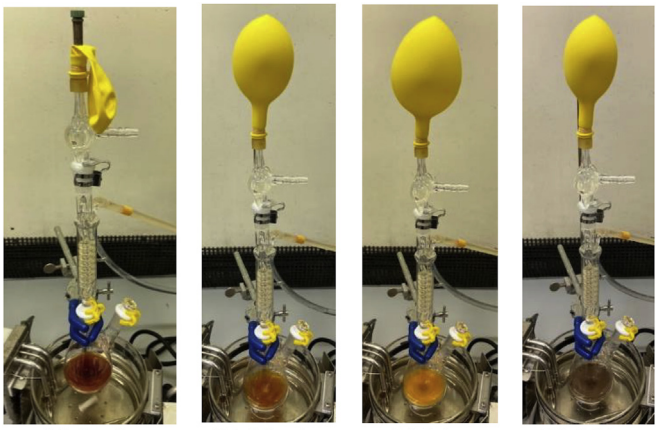


Fig. 1. Pictures of the 5-mmol experiment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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