W. Han et al.

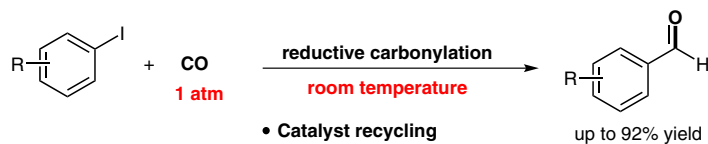# Ligandless Palladium-Catalyzed Reductive Carbonylation of Aryl Iodides under Ambient Conditions

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$R \longleftarrow I$ + **CO** (**1 atm**) → reductive carbonylation, **room temperature** → aldehyde, up to 92% yield

- **Catalyst recycling**
- **No added ligand**
- **Operational simplicity**
- **Broad scope and FG tolerance**
- **Ambient temperature and pressure**

Abstract Ligandless palladium-catalyzed reductive carbonylation of aryl iodides for the synthesis of aromatic aldehydes has been developed. This carbonylation process proceeded effectively even under ambient temperature and pressure. In addition, this method enables successive reductive carbonylation of diiodobenzenes to furnish dialdehydes in satisfactory yields. Finally, the nature of the active catalytic species is discussed.

Key words aromatic aldehydes, aryl iodides, reductive carbonylation, ligandless, ambient conditions

The palladium-catalyzed reductive carbonylation of aryl halide/pseudo-halide using the C1 building block carbon monoxide as carbonyl source is a powerful tool in the synthesis of aromatic aldehydes that are probably the most useful class of products in carbonylations because of the versatile aldehyde group's wide range of further transformations.[1] Since the pioneering work by Heck in 1974,[2] great advances in this transformation have been achieved, particularly in the development of new catalysts, substrate scope, and functional group compatibility. However, the vast majority of these methods require elevated temperatures (≥80 °C) and/or relatively high pressures (≥5 bar).[3] Recently, several groups reported carbon monoxide free reductive carbonylation of aryl halides by using unstable acetic formic anhydrides,[4] *N*-formylsaccharin,[5] 9-methylfluorene-9-carbonyl chloride,[6] paraformaldehyde,[7] and hexane-1,6-diol[8] as carbon monoxide precursors. Although these protocols effectively avoid the difficulty of dealing with gaseous carbon monoxide, all of them require phosphine ligands that are toxic, expensive, and sensitive to air/moisture, and high palladium catalyst loadings (3–10 mol%) to achieve efficient catalysis. Additionally, most of these carbon monoxide pre-

cursors are not terribly atom-efficient, and are expensive in comparison to commonly used gaseous carbon monoxide. All of these disadvantages have impeded the transfer of the advancements to large-scale applications.

Carbon monoxide is a readily available, inexpensive, reactive, and atom-efficient C1 building block, which is most often employed in palladium-catalyzed carbonylations.[3] Additionally, carbon monoxide is chemically inert (bond energy, 257 kcal/mol) and a strong π-acidic ligand, which decreases electron density of low-valent palladium species to hinder oxidative addition of C–X (X = halide or pseudo-halide) to palladium(0).[9] Hence, the development of general room-temperature reductive carbonylation of aryl-X compounds with carbon monoxide that proceeds under ambient pressure without the assistance of a ligand remains an important challenge for organic synthetic chemists.[10] Recently, our group established in situ generated metal-nanoparticles-catalyzed carbonylative cross-coupling reactions of aryl halides in poly(ethylene glycol) (abbreviated to PEG).[11] Notably, some transformations proceed effectively under ambient conditions and even in the absence of an added ligand.

In this contribution, we report a novel and practical method for conducting reductive carbonylation of aryl iodides at room temperature and atmospheric pressure. Notably, the reactions proceed with high selectivity and in high yields even in the absence of an additional ligand. The protocol offers a general, facile, and efficient strategy for the synthesis of aromatic aldehydes.

As in our previous work of the in situ generated palladium nanoparticles effectively catalyzed carbonylative couplings at ambient conditions and in PEG-400,[11c,d] Preliminary experiments were conducted with aryl iodide **1a** in PEG-400 at ambient conditions to identify optimal conditions for the selective reductive carbonylation (Table 1). From the base screening, Na_2CO_3, $NaHCO_3$, and MeCOONa

(Table 1, entries 1–3) were far more effective than K_2CO_3 and Li_2CO_3 (Table 1, entries 4 and 5). Other bases, including Cs_2CO_3 and DBU resulted in no conversion of **1a** (Table 1, entries 6 and 7). To our delight, the combination of the two better bases, Na_2CO_3 and $NaHCO_3$ proved to be the ideal base (Table 1, entry 15). Reductants other than Et_3SiH[4b,12] were also investigated but found to be hugely less effective: HCOONa (trace), PMHS (< 5%), NaH_2PO_2 (< 5%), and H_2 (–) (Table 1, entries 8–11). Replacing $Pd(OAc)_2$ with Pd/C, $PdCl_2$, or $(PPh_3)_2PdCl_2$ as the catalyst resulted in lower yields (Table 1, entries 12–14). Decreasing the catalytic loading of $Pd(OAc)_2$ to 1.0 mol% had little impact on the yield, albeit with a longer reaction time (Table 1, entry 16). Notably, the in situ generated palladium nanoparticles exhibited far higher catalytic activity than the conventional preformed palladium nanoparticles[13] (Table 1, entry 17).

With conditions for an ambient-condition reductive carbonylation at hand enabled by the use of ligandless palladium, we set out to investigate the scope of this transfor-
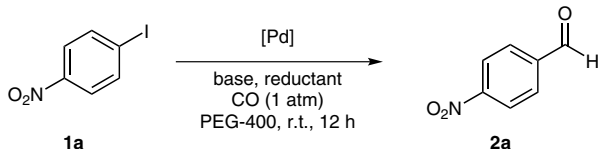
mation (Table 2).[14] A series of electron-poor aryl iodides provided the corresponding aromatic aldehydes in good to excellent yields with high selectivities.

Reactive functional groups, such as nitro, formyl, methoxycarbonyl, phenoxycarbonyl, and chloro, did not compete with the efficacy of the reductive carbonylation event (Table 2, entries 1–6). 3-Fluorobenzaldehyde (**2f**)[15] and 4-trifluoromethylbenzaldehyde (**2g**),[15] which are important intermediates for the synthesis of pharmaceuticals and agrochemicals, were obtained in 92% and 90% yields, respectively (Table 2, entries 7 and 8). However, aryl bromide **1a′**, aryl chloride **1b′**, and aliphatic iodide **1c′** as substrates were totally ineffective under normal conditions or even at a higher temperature (50 °C, Table 2, entries 9–11).

Furthermore, electron-rich aryl iodides were considered and proceeded successfully under the standard conditions (Table 3). An aryl iodide having methyl and fluoro substitutes and iodobenzene provided aldehydes in 87% and 91% yields, respectively (Table 3, entries 1 and 2). Iodotoluenes could undergo the expected carbonylation in excellent yields (Table 3, entries 3–6), regardless of the position of methyl group at phenyl ring. Note that cyano substitution on the aliphatic chain was well tolerated (Table 3, entry 6). An aryl iodide bearing two methyl groups was also reactive and gave the desired product in 87% yield (Table 3, entry 7). Interestingly, the method can move beyond simple aryl group and incorporate heteroaryl iodide. For instance, 1-iodonaphthalene (**1o**) (Table 3, entry 8) could be equally accommodated in a good yield. And heteroaromatic iodides, 2-iodothiophene (**1p**) and 3-iodothiophene (**1q**) underwent successful coupling with yields of 90% and 84%, respectively (Table 3, entries 9 and 10).

To our delight, successive reductive carbonylation of diiodobenzenes, including 1,4-diiodobenzene (**1r**) and 1,3-diiodobenzene (**1s**), furnished dialdehydes in 76% and 71% yields, respectively (Scheme 1).

**Table 1** Palladium-Catalyzed Reductive Carbonylation of **1a**[a]

Entry	[Pd]	Base	Reductant	Yield of **2a** (%)
1	$Pd(OAc)_2$	Na_2CO_3	Et_3SiH	78
2	$Pd(OAc)_2$	$NaHCO_3$	Et_3SiH	75
3	$Pd(OAc)_2$	$MeCO_2Na$	Et_3SiH	63
4	$Pd(OAc)_2$	K_2CO_3	Et_3SiH	13
5	$Pd(OAc)_2$	Li_2CO_3	Et_3SiH	34
6	$Pd(OAc)_2$	Cs_2CO_3	Et_3SiH	trace
7	$Pd(OAc)_2$	DBU	Et_3SiH	–
8	$Pd(OAc)_2$	Na_2CO_3	HCO_2Na	trace
9	$Pd(OAc)_2$	Na_2CO_3	PMHS	<5
10	$Pd(OAc)_2$	Na_2CO_3	NaH_2PO_2	<5
11[b]	$Pd(OAc)_2$	Na_2CO_3	H_2	–
12	Pd/C	Na_2CO_3	Et_3SiH	6
13	$PdCl_2$	Na_2CO_3	Et_3SiH	70
14	$(PPh_3)_2PdCl_2$	Na_2CO_3	Et_3SiH	11
15	$Pd(OAc)_2$	Na_2CO_3 and $NaHCO_3$ (1:1)	Et_3SiH	87
16[c]	$Pd(OAc)_2$	Na_2CO_3 and $NaHCO_3$ (1:1)	Et_3SiH	86
17	nanoPd	Na_2CO_3 and $NaHCO_3$ (1:1)	Et_3SiH	55

[a] Reaction conditions (unless otherwise noted): **1a** (0.5 mmol), base (1.0 mmol), reductant (1.0 mmol), [Pd] (2 mol%), PEG-400 (2.0 g), CO (1 atm), r.t., 12 h.
[b] CO/H_2 (1:1, 1 atm).
[c] With $Pd(OAc)_2$ (1 mol%), 36 h.
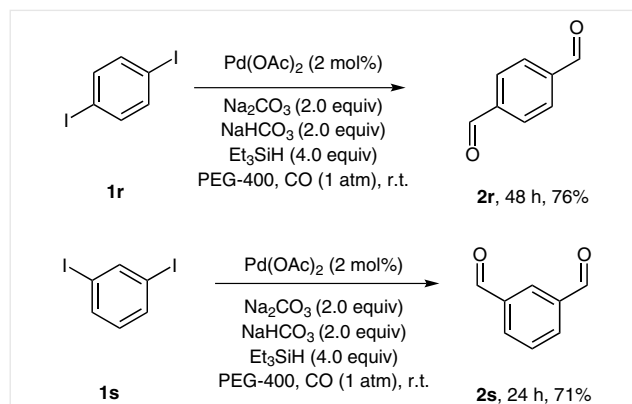
Scheme 1 Successive reductive carbonylation of diiodobenzenes

These products are key intermediates for advanced materials.[16] In addition, a 5 mmol scale of **1a** was conducted and still gave a good yield of **2a** (Equation 1). Furthermore, the recyclability of the catalytic system was tested for the model reaction. The catalytic system maintained its high activity and selectivity for eight consecutive cycles (Figure 1). After the eight run recycling uses, the total leaching of palladium to the diethyl ether extracts was found to be 3.39% by ICP analysis.
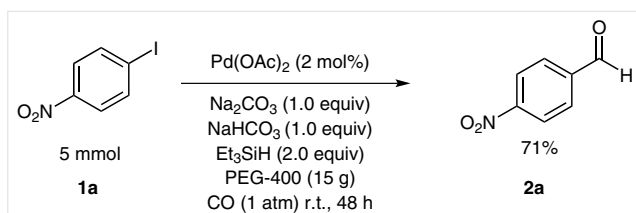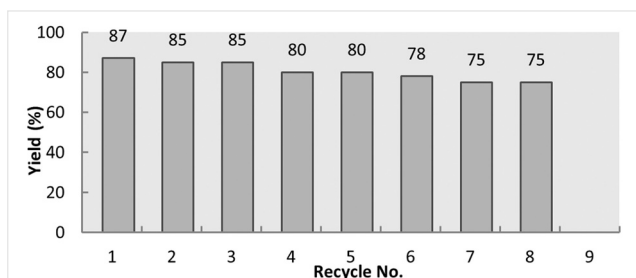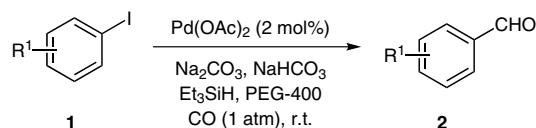

Equation 1

Figure 1 Catalyst reusability study

Table 2 Reductive Carbonylation of Electron-Deficient Aryl Iodides[a]

Entry	Aryl halide	Product	Time (h)	Yield (%)
1	1a	2a	12	87
2[b]	1a	2a	36	85
3	1b	2b	48	84
4	1c	2c	24	83
5	1d	2d	12	81
6	1e	2e	12	85
7[c]	1f	2f	48	92
8	1g	2g	18	90
9[d]	1a′	2a	12	–
10[d]	1b′	2b′	24	–
11	1c′	2c′	24	–

Table 2 (continued)

[a] Reaction conditions (unless otherwise noted): **1** (0.5 mmol), CO (1 atm), Na$_2$CO$_3$ (1.0 equiv), NaHCO$_3$ (1.0 equiv), Et$_3$SiH (2.0 equiv), Pd(OAc)$_2$ (2 mol%), PEG-400 (2.0 g), r.t.. Yields of the isolated products are given.
[b] Pd(OAc)$_2$ (1 mol%).
[c] Based on ^{1}H NMR analysis on the crude reaction mixture with *n*-hexadecane as the internal standard.
[d] 50 °C.

Our previous studies indicate that palladium nanoparticles are readily generated in situ in palladium–PEG catalytic systems for carbonylations.[11c,d] Indeed, TEM was employed to analyze the sample collected from the mixture of the model reaction under the normal conditions, and revealed palladium nanoparticles formed in situ and well dispersed in PEG consistent with our previous studies (see Scheme S1 in Supporting Information).[11c,d] Despite that the in situ generated palladium nanoparticles showed good catalytic activity, we still did not know whether the catalysis occurred on the cluster surface or by leached palladium species.[17] To gain further insight into the catalytic system, mercury and

carbon disulfide as additives were utilized to examine the homo- or heterogeneous nature of the active nanocatalyst.[18] A large excess of Hg(0) (relative to palladium) was added to the model reaction and had no significant impact on the catalytic activity (Equation 2). In addition, the introduction of 0.70 equivalents of CS₂ (relative to palladium) to the reaction under the standard conditions and did not obviously affect the reaction progress (Table 4, entry 2). However, when CS₂ was increased to 1.0 and 1.5 equivalents, the reactions were completely or almost completely inhibited (Table 4, entries 3 and 4). These poisoning experiments hint that the active catalytic species is very likely to be homogeneous in nature.[18]
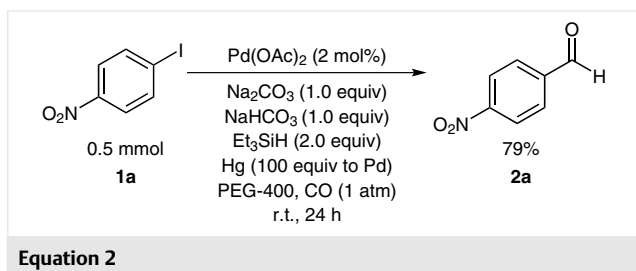
Equation 2

Table 3 Reductive Carbonylation of Electron-Rich Aryl Iodides[a]

Entry	Aryl halide	Product	Time (h)	Yield (%)
1	1h	2h	48	87
2[b]	1i	2i	48	91
3[b]	1j	2j	48	84
4	1k	2k	48	90

Table 3 (continued)

Entry	Aryl halide	Product	Time (h)	Yield (%)
5	1l	2l	48	84
6	1m	2m	24	83
7	1n	2n	33	87
8	1o	2o	36	85
9[b]	1p	2p	24	90
10[b]	1q	2q	48	84

[a] Reaction conditions (unless otherwise stated): **1** (0.5 mmol), CO (1 atm), Na₂CO₃ (1.0 equiv), NaHCO₃ (1.0 equiv), Et₃SiH (2.0 equiv), Pd(OAc)₂ (2 mol%), PEG-400 (2.0 g), r.t. Yields of the isolated products are given.
[b] Based on ¹H NMR analysis on the crude reaction mixture with *n*-hexadecane as the internal standard.

Table 4 CS₂ Poisoning Experiments[a]

Entry	CS₂ (equiv)	Yield of **2a** (%)
1	0	87
2	0.70	80
3	1.0	<5
4	1.5	–

[a] Reaction conditions (unless otherwise stated): **1** (0.5 mmol), CO (1 atm), Na₂CO₃ (1.0 equiv), NaHCO₃ (1.0 equiv), Et₃SiH (2.0 equiv), CS₂, Pd(OAc)₂ (2 mol%), PEG-400 (2.0 g), r.t., 12 h.

Based on the above results and previous studies,[5,10d,12a,13,19] we proposed a mechanism for the reductive carbonylation reaction (Scheme 2). Initially, palladium nanoparticles are generated in situ from Pd(OAc)$_2$ and PEG-400.[13,19] And then, the nanoparticles undergo oxidative addition of aryl iodide to form ArPdI intermediate, followed by interception of carbon monoxide to give acylpalladium species (ArCOPdI). Finally, the acylpalladium species is reduced by Et$_3$SiH to afford the aldehyde and regenerate the palladium(0) catalyst.[5,10d,12a]
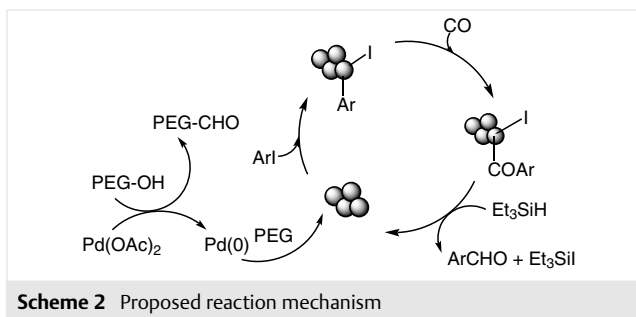
Scheme 2 Proposed reaction mechanism

In summary, a facile and robust method has been demonstrated for reductive carbonylation of aryl iodides to provide aromatic aldehydes in high yields with high selectivities. Noteworthy is that the transformation is conducted under ambient temperature and pressure and even in the absence of an added ligand. In addition, the double reductive carbonylation of diiodobenzenes, which is sparsely reported, can be achieved in our catalytic system. Advantageously, the catalytic system is in situ generated, which obviate cumbersome processes for the preparation of metal nanoparticles, and can be recyclable. Control experiments suggest that a typical heterogeneous reaction process is unlikely to be in operation.

Acknowledgment

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588930.

References and Notes

(1) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Springer: Heidelberg, **2007**.

(2) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

(3) For some recent reviews on Pd-catalyzed carbonylations of aryl halides, see: (a) Wu, X. F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (b) Wu, X. F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (c) Grigg, R.; Mutton, S. P. *Tetrahedron* **2010**, *66*, 5515. (d) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114. (e) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (f) Wu, X. F.; Beller, M. *Transition Metal Catalyzed Carbonylation Reactions-Carbonylative Activation of C–X Bonds*; Springer: Berlin, Heidelberg, **2013**.

(4) (a) Qi, X. X.; Li, C.-L.; Wu, X. F. *Chem. Eur. J.* **2016**, *22*, 5835. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Comb. Chem.* **2004**, *6*, 692.

(5) Ueda, T.; Konishi, H.; Manabe, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 8611.

(6) Korsager, S.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2013**, *78*, 6112.

(7) Natte, K.; Dumrath, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 10090.

(8) Christensen, S. H.; Olsen, E. P. K.; Rosenbaum, J.; Madsen, R. *Org. Biomol. Chem.* **2015**, *13*, 938.

(9) (a) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (b) Barnard, C. F. J. *Org. Process Res. Dev.* **2008**, *12*, 566. (c) Maitlis, P. M.; Haynes, A. *Synthesis Based on Carbon Monoxide, In Metal-Catalysis in Industrial Organic Processes*; Chiusoli, G. P.; Maitlis, P. M., Eds.; RSC Publishing: Cambridge, **2006**.

(10) For selected examples of palladium-catalyzed reductive carbonylation of aryl halides, see: (a) Klaus, S.; Neumann, H.; Zapf, A.; Strubing, D.; Huber, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *45*, 154. (b) Hamasaki, A.; Yasutaka, Y.; Norio, T.; Ishida, T.; Akita, T.; Ohashi, H.; Yokoyama, T.; Honma, T.; Tokunaga, M. *Appl. Catal., A* **2014**, *469*, 146. (c) Hao, W. Y.; Ding, G. D.; Cai, M. Z. *Catal. Commun.* **2014**, *51*, 53. (d) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549. (e) Brennführer, A.; Neumann, H.; Beller, M. *Synlett* **2007**, 2537. (f) Carelli, I.; Chiarotto, I.; Cacchi, S.; Pace, P.; Amatore, C.; Jutand, A.; Meyer, G. *Eur. J. Org. Chem.* **1999**, 1471. (g) Hamasaki, A.; Yasutaka, Y.; Norio, T.; Ishida, T.; Akita, T.; Ohashi, H.; Yokoyama, T.; Honma, T.; Tokunaga, M. *Appl. Catal., A* **2014**, *469*, 146. (h) Neumann, H.; Kadyrov, R.; Wu, X. F.; Beller, M. *Chem. Asian J.* **2012**, *7*, 2213. (i) Singh, A. S.; Bhanage, B. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 2383. (j) Brennführer, A.; Neumann, H.; Klaus, S.; Riermeier, T.; Almena, J.; Beller, M. *Tetrahedron* **2007**, *63*, 6252. (k) Yu, B.; Yang, Z. Z.; Zhao, Y. F.; Hao, L. D.; Zhang, H. Y.; Gao, X.; Han, B. X.; Liu, Z. M. *Chem. Eur. J.* **2016**, *22*, 1097. (l) Yu, B.; Zhao, Y. F.; Zhang, H. Y.; Xu, J. L.; Hao, L. D.; Gao, X.; Liu, Z. M. *Chem. Commun.* **2014**, *50*, 2330.

(11) (a) Zhao, H. Y.; Du, H. Y.; Yuan, X. R.; Wang, T. J.; Han, W. *Green Chem.* **2016**, *18*, 5782. (b) Zhong, Y. Z.; Han, W. *Chem. Commun.* **2014**, *50*, 3874. (c) Zhou, Q.; Wei, S. H.; Han, W. *J. Org. Chem.* **2014**, *79*, 1454. (d) Han, W.; Jin, F. L.; Zhou, Q. *Synthesis* **2015**, *47*, 1861. (e) Zhong, Y. Z.; Gong, X. X.; Zhu, X. S.; Ni, Z. C.; Wang, H. Y.; Fu, J. L.; Han, W. *RSC Adv.* **2014**, *4*, 63216. (f) Cheng, L. J.; Zhong, Y. Z.; Ni, Z. C.; Du, H. Y.; Jin, F. L.; Rong, Q.; Han, W. *RSC Adv.* **2014**, *4*, 44312.

(12) For silanes as hydride source for reductive carbonylation of aryl halides, see: (a) Ashfield, L.; Barnard, C. F. J. *Org. Process Res. Dev.* **2007**, *11*, 39. (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009. (c) Kotsuki, H.; Datta, P. K.; Suenaga, H. *Synthesis* **1996**, 470.

(13) Palladium nanoparticles were prepared according to the reference: Han, W.; Liu, C.; Jin, Z. L. *Adv. Synth. Catal.* **2008**, *350*, 501.

(14) **General Procedure**

The reaction was carried out in a 25 mL flask was equipped with 4-iodo-4-nitrobenzene (**1a**, 0.5 mmol, 127.0 mg), Pd(OAc)$_2$ (0.01 mmol, 2.4 mg), Na$_2$CO$_3$ (0.5 mmol, 53.1 mg), NaHCO$_3$ (0.5 mmol, 42.0 mg), and PEG-400 (2.0 g) before standard cycles of evacuation and back-filling with dry and pure carbon monoxide. Triethylsilane (1.0 mmol, 162.8 µL) was added successively. The mixture was stirred under ambient temperature and pressure for the indicated time. At the end of the reaction, the reaction mixture was poured into a sat. aq NaCl solution (20 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The residue was purified by column chromatography on silica gel (PE–Et$_2$O, 50:1) to afford the corresponding product **2a**, a light yellow solid (66 mg, 87%); mp 105.9–106.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.13 (s, 1 H), 8.36 (d, *J* = 8.9 Hz, 2 H), 8.05 (d, *J* = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 190.3, 151.1, 140.0, 130.4, 124.3 ppm.

(15) (a) Dong, L. C.; Crowe, M.; West, J.; Ammann, J. R. *Tetrahedron Lett.* **2004**, *45*, 2731. (b) Reinhard, E. J.; Wang, J. L.; Durley, R. C.; Fobian, Y. M.; Grapperhaus, M. L.; Hickory, B. S.; Massa, M. A.; Norton, M. B.; Promo, M. A.; Tollefson, M. B.; Vernier, W. F.; Connolly, D. T.; Witherbee, B. J.; Melton, M. A.; Regina, K. J.; Smith, M. E.; Sikorski, J. A. *J Med Chem.* **2003**, *46*, 2152.

(16) Zhuang, X. D.; Zhang, F.; Wu, D. Q.; Feng, X. L. *Adv. Mater.* **2014**, *26*, 3081.

(17) (a) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884. (b) Pachón, L. D.; Rothenberg, G. *Appl. Organomet. Chem.* **2008**, *22*, 288. (c) Thathagar, M. B.; Elshof, J. E.; Rothenberg, G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2886. (d) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *Adv. Synth. Catal.* **2003**, *345*, 979.

(18) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A.: Chem.* **2003**, *198*, 317.

(19) Han, W.; Liu, C.; Jin, Z. L. *Org. Lett.* **2007**, *9*, 4005.