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Reductive carbonylation of aryl and heteroaryl iodides using $Pd(acac)_2$/dppm as an efficient catalyst

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ABSTRACT

Palladium catalyzed simple and efficient protocol for reductive carbonylation of aryl and heteroaryl compounds has been developed. The formylation of aryl and heteroaryl iodides takes place in the presence of $Pd(acac)_2$/dppm catalyst at 10 bar pressure of synthetic gas to give the desired aromatic and heteroaromatic aldehydes in good to excellent yields. Easy work-up, stability of the catalyst, low catalyst loading and less reaction time are the advantages of this method.

Aromatic and heteroaromatic aldehydes are key intermediates in pharmaceuticals, pesticides, perfumery, and dyestuff industries. The presence of highly active formyl group makes aldehyde an important substrate for C–C, C–N, C–S coupling, and for other organic transformation reactions. It has a major application in the synthesis of Schiff bases which are useful in antifungal, antimicrobial, antibacterial, antitubercular, and anticancer applications. In addition it also possesses herbicidal properties. The direct method for synthesis of aromatic aldehyde includes Gattermann–Koch, Gattermann reaction, Reimer–Tiemann, Duff and Vilsmeier reactions where as indirect method includes oxidation and reduction process,[1] which suffers from drawbacks like very low yield, poor selectivity and harsh reaction conditions. They also require environmentally disagreeable reagents and generate excess amount of waste.

The catalytic method involves use of carbon monoxide as a carbonyl source which is an easily available carbonylating agent. The palladium chemistry is well explored for coupling and other organic synthetic reactions.[2] The first palladium catalyzed synthesis of aromatic, heteroaromatic and vinylic aldehydes was effectively achieved by Heck.[3] However, the method required high pressure (80–100 bar), temperature (125–150 °C) and high catalyst loading. The method was further simplified by Stille and co-workers by using tin hydride as reducing agent at low pressure of CO (1 bar).[4] Pri-Bar and Buchman replaced metal hydride by PMHS poly(methylhydroxysilane) as reducing agent.[5] The use of formate salt as reducing agent is also being employed for palladium catalyzed reductive carbonylation.[6] Hitherto the use of formate salt is considered to be the most reliable method for reductive carbonylation. But these reactions are generally accompanied by reductive dehalogenation and require high catalyst loading. The use of CO gas is replaced by acetic formic anhydride as formyl source in the presence of palladium catalyst by Cacchi et al.[7] But the described formylating agent is unstable at room temperature. The comprehensive study on formylation was shown by Barnard and co-workers using Et_3SiH as reducing agent in presence of palladium catalyst and CO gas (3 bar).[8] Beller and co-workers have developed a selective catalytic method for the reductive carbonylation of aromatic, heteroaromatic and vinylic bromide substrates using synthetic gas (CO/H_2 1:1) (5 bar), di-1-adamantyl-*n*-butylphosphine (Cata*CX*ium) as ligand and $Pd(OAc)_2$ as palladium source.[9] This was the first industrially applied, simple, and economically feasible method for the production of aromatic aldehydes on ton scale by using synthetic gas (CO/H_2 1:1).

Despite the potential utility of the described method by Beller and co-workers using synthetic gas at low pressure it suffers from the limitation of high cost of the catalyst. Herein we report a new protocol for reductive carbonylations of aryl and hetero aryl iodides by using simple, low cost, and environmentally benign $Pd(acac)_2$/dppm as a catalyst.

The reaction of iodobenzene with synthetic gas (CO/H_2 1:1) in the presence of palladium source and phosphine ligand was chosen as a model reaction.

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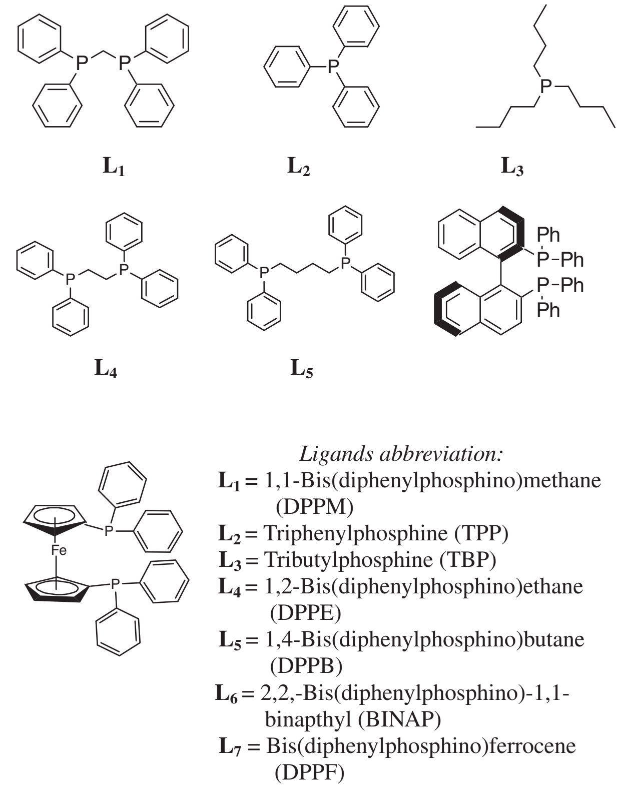
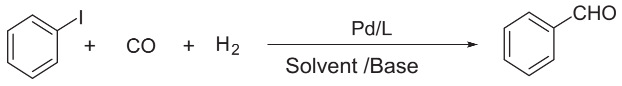


Figure 1. Various phosphine ligands used for model reaction.

Initially our attempt to catalyze the reaction using heterogeneous catalyst like Pd/C or Pd-NHC (palladium *N*-heterocyclic carbene) failed as the reaction is accompanied by reductive dehalogenation leading to the formation of benzene (Table 1, entries 1 and 2). The reaction was further studied using various homogeneous catalysts prepared in situ from Pd-source and the ligand with the ratio of 1:2. It was found that $Pd(acac)_2$ gave the best result (Table 1, entries 3–7). When the reaction was carried out in the absence of phosphine ligand it was observed that only $Pd(TMHD)_2$ and $Pd(acac)_2$ were able to catalyze the reaction with 12% and 20% yields, respectively. Further different ligands were screened and it was observed that reaction of catalyst formed in situ via interaction of $Pd(acac)_2$ with 1,1-bis(diphenylphosphino)methane dppm gave excellent result with 93% yield (Table 1, entry 7). Monodentate phosphines like triarylphosphines (TPP) and tributylphosphine (TBP) were less effective in promoting the reaction towards product formation of desired aldehyde (Table 1, entries 8 and 9). Other bidentatephosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,4-bis(diphenylphosphino)butane (dppb) failed in complete conversion of iodobenzene (Table 1, entries 10 and 11). The results obtained with 2,2-bis(diphenylphosphino)-1,1-binapthyl(BINAP) and bis(diphenylphosphino)ferrocene (dppf) were also not encouraging (Table 1, entries 12 and 13). We observed that the reductive dehalogenation takes place in the reaction where benzene is formed as s by-product of the model reaction (Fig. 1).

Table 1
Screening of different palladium source and ligands for formylation of iodobenzene[a]



Entry	Palladium source	Ligand	Conversion[b] (%)	Select.[b] (%)	Yield[b] (%)
1	Pd/C	--	100	0	0
2	Pd-NHC	--	100	0	0
3	$Pd(Peg)_2$	L_1	10	0	0
4	$Pd(OAc)_2$	L_1	26	90	15
5	$PdCl_2$	L_1	74	95	40
6	$Pd(TMHD)_2$	L_1	100	98	80
7	$Pd(acac)_2$	L_1	100	98	93
8	$Pd(acac)_2$	L_2	12	84	9
9	$Pd(acac)_2$	L_3	15	85	11
10	$Pd(acac)_2$	L_4	86	97	80
11	$Pd(acac)_2$	L_5	88	96	84
12	$Pd(acac)_2$	L_6	02	0	0
13	$Pd(acac)_2$	L_7	39	89	22

[a] Reaction conditions: iodobenzene, (1 mmol), Pd precursor (1 mol %), ligand (2 mol %), base (1 equiv), 50 mg *N*-hexadecane (internal standard), toluene 10 mL, CO/H_2 (1:1) 10 bar, 100 °C, 10 h.
[b] GC yield.

The influence of the different organic and inorganic bases on the reductive carbonylation of iodobenzene was also studied. The inorganic bases like Cs_2CO_3 and K_2CO_3 gave poor yield of the product due to low solubility in organic solvent (Table 2, entries 1 and 2). Among the nitrogen containing various organic bases such as DBU (1,8-diazabicycloundec-7-ene), morpholine, triethylamine, and tetramethylethylenediamine (TMEDA), it was found that TMEDA is the best suited base for the model reaction (Table 2, entries 3–6). Among the different solvents studied, the complete conversion of iodobenzene to benzaldehyde took place in presence of toluene as a solvent (Table 2, entry 6). Other protic and aprotic solvents such as DMF, DMSO, ACN, and THF failed to catalyze the formylation reaction of the iodobenzene to benzaldehyde. The reaction proceeded smoothly in 1,4-dioxane as a solvent, however, due to easy availability and low cost of the solvent we preferred toluene as the best suited solvent for carrying out further reactions of the substrate under similar conditions.

The influence of catalyst loading of ligand and palladium source was studied. It was found that 1 mol % of $Pd(acac)_2$ and ligand loading of 2 mol % were sufficient to catalyze the reaction. Further increase in catalyst concentration could not lead to increase the product yield. In a typical reaction TON of 100 and TOF of 10 h^{-1} was observed (Table 3).

Considering these optimized reaction conditions the reaction of iodobenzene gave high yield of the desired product (Table 4, entry 1).[11] The electron donating adduct such as 4-iodoanisole and 4-iodotoluene gave remarkable conversion and selectivity (Table 4, entries 2 and 3). As 4-iodotoluene is less active than 4-iodoanisole, the former requires higher temperature for conversion. Though 4-

Table 2
Influence of different bases and solvents on formation of benzaldehyde yield[a]

Entry	Base	Solvent	Conversion[b] (%)	Select.[b] (%)	Yield[b] (%)
1	CS_2CO_3	Toluene	48	78	10
2	K_2CO_3	Toluene	30	45	8
3	DBU	Toluene	10	0	0
4	Morpholine	Toluene	20	0	0
5	Triethylamine	Toluene	69	90	50
6	TMEDA	Toluene	100	98	93
7	TMEDA	DMF	50	0	0
8	TMEDA	DMSO	95	20	6
9	TMEDA	ACN	42	90	33
10	TMEDA	Dioxane	98	96	88
11	TMEDA	THF	9	65	2

[a] Reaction conditions: iodobenzene, (1 mmol), $Pd(acac)_2$ (1 mol %), ligand dppm (2 mol %), TMEDA (1 equiv), 50 mg *N*-hexadecane (internal standard), toluene 10 mL, CO/H_2 (1:1) 10 bar, 100°C, 10 h.
[b] GC yield.

Table 3
Influence of amount of catalyst loading on the yield (GC)[a]

Entry	$Pd(acac)_2$ (mol %)	Conversion[b] (%)	Yield[b] (%)
1	0	0	0
2	0.2	15	10
3	0.4	36	30
4	0.6	58	50
5	0.8	78	70
6	1.0	100	93
7	1.2	100	94

[a] Reaction conditions: iodobenzene, (1 mmol), TMEDA (1 equiv), 50 mg *N*-hexadecane (internal standard), toluene 10 mL, CO/H_2 (1:1) 10 bar, 100 °C, 10 h.

[b] GC yield.

iodoaniline is highly active, it leads to slight decrease in the selectivity of the product (Table 4, entry 4). Even sterically hindered 2-iodoanisole gave complete conversion with 75% yield of the desired product (Table 4, entry 5). With electron withdrawing group as in 4-iodochlorobenzene, the catalyst gave low conversion of the desired product (Table 4, entry 6). However, the catalyst failed to activate the carbonylation of 4-iodonitrobenzene (Table 4, entry 7). This protocol also works successfully for the formylation of iodonapthalene (Table 4, entry 8). Since the heteroaromatic aldehydes are biologically active compounds, their synthesis is also beneficial. The reductive carbonylation of 5-iodoindole was done selectively with 78% isolated yield (Table 4, entry 9). The catalyst was not highly effective in the carbonylation of orthosubstituted heterocycles like 2-iodothiophene. The formylation of 3-iodopyridine took place effectively with 78% yield of the product (Table 4, entry 11). The catalyst was ineffective when formylation of aryl bromide was carried out under similar conditions.

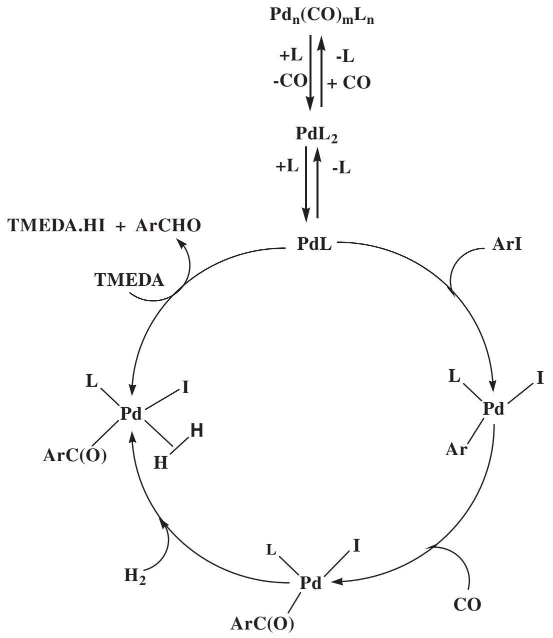
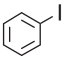
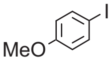
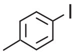
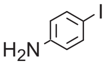
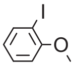
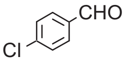
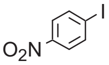
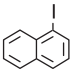
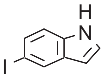
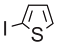
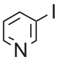


Figure 2. Proposed catalytic cycle for the Pd-catalyzed reductive carbonylation of aryl iodides with synthesis gas.

Table 4
Reductive carbonylation of various aryl and heteroaryl iodides[a]

Entry	Substrate	Temp (°C)	Conversion[b] (%)	Select.[b] (%)	GC (isolated) yield[b] (%)
1		100	100	98	93 (91)
2		100	100	99	95 (92)
3		120	95	98	88 (84)
4		100	100	80	80 (75)[c]
5		100	100	75	75 (71)
6		120	65	89	56 (50)[d]
7		120	10	90	5
8		100	100	77	77 (72)
9		100	100	95	82 (78)[e]
10		120	48	100	33 (29)
11		100	90	81	81 (78)

[a] Reaction conditions: substrate (1 mmol), $Pd(acac)_2$ (1 mol %), ligand (2 mol %), TMEDA (1 equiv), 50 mg *n*-hexadecane (internal standard), toluene 10 mL, CO/H_2 (1:1) 10 bar, 10 h.

[b] Isolated yield.

[c] Melting point of 4-aminobenzaldehyde: 71 °C.

[d] Melting point of 4-chlorobenzaldehyde: 47 °C.

[e] Melting point of indole5-carboxaldehyde: 10 °C.

The rationale behind this comprehensive catalytic cycle was first revealed by Beller and co-workers.[10] The rate determining step of this cycle is the oxidative addition of aryl iodide to palladium species, which is then followed by CO insertion and finally with the help of base, the hydrogen halide was removed there by generating product and maintaining the concentration of active palladium species throughout this catalytic cycle (Fig. 2).

In conclusion, an efficient protocol for reductive carbonylation of aryl and heteroaryl iodide by using Pd(acac)$_2$/dppm has been developed. The commercially available synthesis gas is used as carbonylation source. The reaction was optimized under various parameters like catalyst concentration, effect of solvent and base. The developed method is chemo selective for the conversion of aromatic iodide in presence of aromatic bromide.

References and notes

1. (a) Aldabbagh, F. *Comp. Org. Funct. Group Transform. II* **2005**, *3*, 99–133; (b) Crawford, L. P.; Richardson, S. K. *Gen. Synth. Methods* **1994**, *16*, 37–91; (c) Ferguson, L. N. *Chem. Rev.* **1946**, *38*, 227–254; (d) Fetter, J.; Bertha, F.; Poszavacz, L.; Simig, G. *J. Heterocycl. Chem.* **2005**, *42*, 137–139.
2. Negishi, E. *Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002.
3. Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.
4. (a) Baillardgeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452–461; (b) Baillardgeon-Geon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175–7176.
5. (a) Kikukawa, K.; Totoki, T.; Wada, T.; Matsuda, T. *J. Organomet. Chem.* **1984**, *207*, 283–287; (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009–4011.
6. (a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc. Chem. Commun.* **1989**, *23*, 1816–1817; (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624–626; (c) Okano, T.; Harada, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2329–2332; (d) Cai, M. Z.; Zhao, H.; Zhou, J.; Song, C. S. *Synth. Commun.* **2002**, *32*, 923–926.
7. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Comb. Chem.* **2004**, *6*, 692–694.
8. Ashfield, L.; Barnard, C. F. J. *Org. Pro. Res. Dev.* **2007**, *11*, 39–43.
9. (a) Klaus, S.; Neumann, H.; Zapf, A.; Strubing, D.; Hubner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154–158; (b) Brennfuhrer, A.; Neumann, H.; Klaus, S.; Riermeier, T.; Almena, J.; Beller, M. *Tetrahedron* **2007**, *63*, 6252–6258.
10. Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.
11. *General experimental procedure for reductive carbonylation of (hetero)aryl iodides*: The reaction was performed in high pressure autoclave of 100 mL capacity manufactured by M/s Amar Industries. Toluene (10 mL), Pd(acac)$_2$ (3 mg, 1 mol %), and dppm (7.7 mg, 2 mol %) were added to the autoclave reactor. To this solution iodobenzene (204 mg, 1.0 mmol), *n*-hexadecane (50 mg, internal GC standard), TMEDA (*N,N,N′,N′*-tetramethylethylenediamine, 1 equiv) were added. The mixture was flushed twice with CO/H$_2$ 1:1, then synthetic gas pressure was adjusted to 10 bar and the mixture was heated at 100 °C for 10 h. After completion of reaction, the reaction mixture was cooled to room temperature. The light yellow colored solution was evaporated and residue obtained was purified by column chromatography (silica gel, mesh size 60–120) using pet ether/ethyl acetate (95:05) as eluent to get the desired formylated product. The products were confirmed by GC–MS, ^{1}H NMR, and ^{13}C NMR techniques. The purity of compounds was determined by GC–MS analysis.