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Palladium-Catalyzed Synthesis of Aldehydes from Aryl Halides and *tert*-Butyl Isocyanide using Formate Salts as a Hydride Donor

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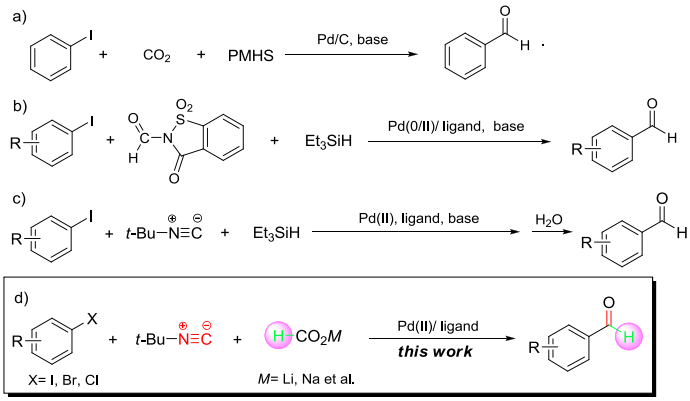
An efficient one-pot palladium-catalyzed hydroformylation of aryl halides to produce aromatic aldehydes has been achieved, employing *tert*-butyl isocyanide as a C_1 resource and formate salt as a hydride donor without any additional bases. Characterized by its mild reaction conditions, easy operation and lower toxicity, this reaction can tolerate a wide array of functional groups with moderate to excellent yields.

Aromatic aldehydes are valuable synthetic intermediates as a platform for further transformations, which could be used not only in forming C—C bond, but also in C—N and C—S coupling reactions. Therefore, aromatic aldehydes occupy an important place in agriculture, materials, perfumery and pharmaceutical industries.[1]

In 1974, R. Heck and co-workers first reported the direct formylation of aryl halides into aromatic aldehydes under carbon monoxide and hydrogen.[2] Since then, several groups have also developed this palladium-catalyzed reductive carbonylation of aryl halides under CO gas, applying tin or silyl hydrides,[3-4] formic acid and its derivatives[5] as reducing agents instead of hydrogen gas. Though research on carbon monoxide as a C_1 source to construct hydroxy-,[6] alkoxy-,[7] and amino-carbonylation[8] molecules as well as reductive carbonylation products has experienced impressive improvements, its generality for industry was severely hampered by its drawbacks such as high pressure, high toxicity and limited tolerance of functional groups.

The key is to find other effective C_1 resources as alternatives to toxic CO gas. For C_1 sources, the application of carbon dioxide (Scheme 1a), formic acid derivatives (Scheme 1b), and metalcarbonyl materials has been reported.[9-11] Moreover, isocyanides can also work as excellent carbonylation species by hydrolysis of imine intermediates. Isocyanides, on one hand, own a set of properties similar to carbon monoxide in that they can react with both nucleophiles and electrophiles on the same carbon atom. On the other hand, isocyanides are more easily handled than carbon monoxide which should be operated under high pressures.[12] Nevertheless, reactions via isocyanide insertion to give aromatic aldehydes have been rarely described (Scheme 1c).[13] We were prompted to investigate whether other hydride donors can be used in aldehyde preparation from aryl halides and isocyanides. Formate salts are stable, nontoxic and economical bases and show high potential as environmentally friendly hydride donors to perform palladium-catalyzed reductive carbonylations.[14] We reasoned that a combination of *tert*-butyl isocyanide and formate salt to give aromatic aldehydes is a more desirable protocal compared to silyl or tin hydrides, for the advantages mentioned above as well as no need of any extra additives owing to simultaneous functions of



Scheme 1. Methods for Synthesis of Aromatic Aldehydes.

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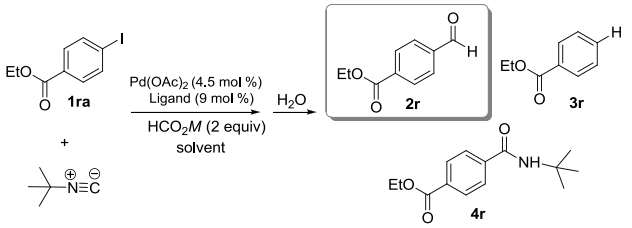
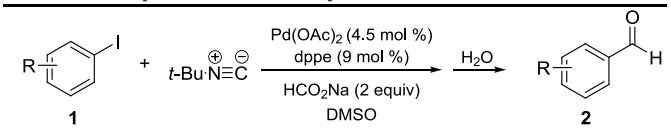
Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Ligand	Formate salt	T [℃]	Yield (%) **2r** : **3r**: **4r**
1	DMF	PPh_3	HCO_2Na	65	21 :10 : 54
2	DMF	PPh_3	HCO_2Na	100	42 : 0 : 41
3	DMF	PPh_3	HCO_2Na	120	53 :4 : 38
4	CH_3CN	PPh_3	HCO_2Na	120	0 : 0 : 0
5	DMSO	PPh_3	HCO_2Na	120	64 : 0 : 25
6	THF	PPh_3	HCO_2Na	120	0 : 0 : 0
7	toluene	PPh_3	HCO_2Na	120	5 : 0 : 0
8	dioxane	PPh_3	HCO_2Na	120	0 : 0 : 0
9	DMSO	PCy_3	HCO_2Na	120	37 : 5 : 32
10	DMSO	TFP	HCO_2Na	120	41 : 49 : 0
11	DMSO	$BuPAd_2$	HCO_2Na	120	89 : 8 : 0
12	DMSO	JohnPhos	HCO_2Na	120	56 : 8 : 19
13	DMSO	dppm	HCO_2Na	120	34: 12: 0
14	**DMSO**	**dppe**	**HCO_2Na**	**120**	**94 : 0 : 0**
15[b]	DMSO	dppe	HCO_2Na	120	79 : 2 : 0
16	DMSO	dppp	HCO_2Na	120	90 : 0 : 5
17	DMSO	dppb	HCO_2Na	120	82 : 3 : 0
18	DMSO	dpppe	HCO_2Na	120	80 : 2 :6
19	DMSO	DPEphos	HCO_2Na	120	81 : 0 : 5
20	DMSO	*R*-BINAP	HCO_2Na	120	6 : 0 : 0
21	DMSO	xantPhos	HCO_2Na	120	10 : 0 : 90
22	DMSO	dppf	HCO_2Na	120	17 : 0 : 1
23	DMSO	none	HCO_2Na	120	23 : 0 : 28
24	DMSO	dppe	HCO_2Li	120	90 : 4 : 0
25	DMSO	dppe	HCO_2K	120	81 : 6 : 7
26	DMSO	dppe	$(HCO_2)_2Ca$	120	9 : 0 : 0

[a] Reaction conditions: **1ra** (0.4 mmol), *tert*-butyl isocyanide (0.48 mmol), formate salt (0.8 mmol), catalyst (0.018 mmol), ligand (0.036 mmol), and 2.0 mL of solvent under nitrogen in a sealed tube. Reaction time was 6 h; Isolated yield.[b] with 1.5 mol % of catalyst and 3 mol % of ligand.

Table 2. Formylation of different aryl halides[a]



1ra, X = I
1rb, X = Br
1rc, X = Cl

Entry	Substrate	Time(h)	Yield(%)
1	**1ra**	6	94
2	**1rb**	30	trace
3[b]	**1rb**	30	83
4[b]	**1rc**	30	11

[a] Reaction conditions: **1** (0.4 mmol), *tert*-butyl isocyanide (0.48 mmol) HCO_2Na(0.8 mmol), $Pd(OAc)_2$ (0.018 mmol), dppe (0.036 mmol), and 2.0 mL of solvent under nitrogen in a sealed tube; Isolated yield.[b] HCO_2K instead of HCO_2Na.

formate salt as a base and hydride donor.

As an initial test, we began our exploration by examining the formylation of ethyl 4-iodobenzoate. The reaction was carried out using 1.2 equivalents of *tert*-butyl isocyanide and 2 equivalents of sodium formate under a palladium(II)/PPh_3 catalyst system at 65 ^oC for 6 h (Table 1, entry 1). Unfortunately, only a small amount of desired aldehyde (21 %) could be isolated. Instead, amide **4r** formed from intermediate **B** (Scheme 3) by reacting with water, was obtained in good yield (Table 1, entry 1). Another byproduct was ethyl benzoate **3r** as showed in Table 1. In order to suppress the conversion of **3r** and **4r**, several aspects of this transformation were observed. In contrast with Bar's results,[5b] whose experiments indicated that raising the temperature tended to avoid aldehyde formation, a significant increase in the aldehyde yield (53 %) was achieved at an elevating temperature (120 ^oC) in this report (Table1, entry 3). Then, a series of solvents were changed to find a better condition. Solvents screening showed that a solvent of higher polarity conduced to the hydroformylation of ethyl 4-iodobenzoate. DMSO was optimal for this reaction (Table 1, entry 5), no hydrogenolysis product ethyl benzoate (**3r**) and only 25% of ethyl 4-(*tert*-butylcarbamoyl)benzoate (**4r**) were detected. Other solvents gave no or low aldehyde yields (Table 1, entries 4, 6-8).

Almost 15 phosphine ligands were examined in our study (Table1, entries 9-22). Only a very low yield of aldehyde could be isolated without any ligands, which were usually essential for the stability of the catalyst (Table 1, entry 23). Classic bidentate ligands such as dppe, dppb, and DPEphos, gave good to excellent results (Table 1, entries 14 and 16-19). Ligands which had tethers less than three carbon atoms long could afford **2r** in 90-94 % yields (Table 1, entries 14 and 16), and dppe was most efficient for the reductive formylation of ethyl 4-iodobenzoate (Table 1, entry 14). Meanwhile, monodentate ligands were found to be less effective, byproducts **3r** and **4r** increased slightly when PCy_3, TFP or JohnPhos were employed (Table 1, entries 9, 10 and 12).

The effects of different hydride sources were investigated using dppe as the ligand. Sodium formate reacted with a higher chemoselectivity than lithium formate in the formylation pathway, giving no byproducts **3r** or **4r** (Table 1, entry 14 and 24). Potassium formate was less reactive than the former two formate salts under comparable condition, resulting 81 % of aldehyde **2r** along with 6 % of ethyl benzoate **3r** and 7 % of amide **4r** (Table 1, entry 25). Calcium formate was apparently much inferior to HCO_2Na with only 9 % of desired product **2r** obtained (Table 1, entry 26). It was worth noting that, in addition to ethyl 4-iodobenzoate (**1ra**), ethyl 4-bromobenzoate (**1rb**) afforded **2r** in good yields when changing HCO_2Na with HCO_2K (Table 2, entry 3). Ethyl 4-chlorobenzoate (**1rc**) also reacted, although the yield was quite low (Table 2, entry 4). The outcome was really interesting and reasonable, because in various transition metal-catalyzed cross- coupling reactions, the order of the leaving reactivities of halide atoms are as follow: I> Br> Cl. As a result, hydrogen iodide (of **1ra**) could be extruded out under the assistance of a relative weaker base

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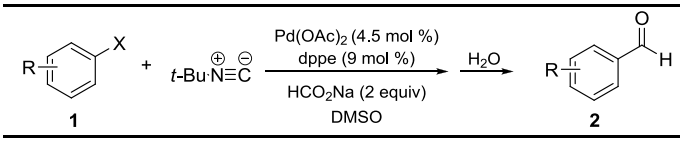
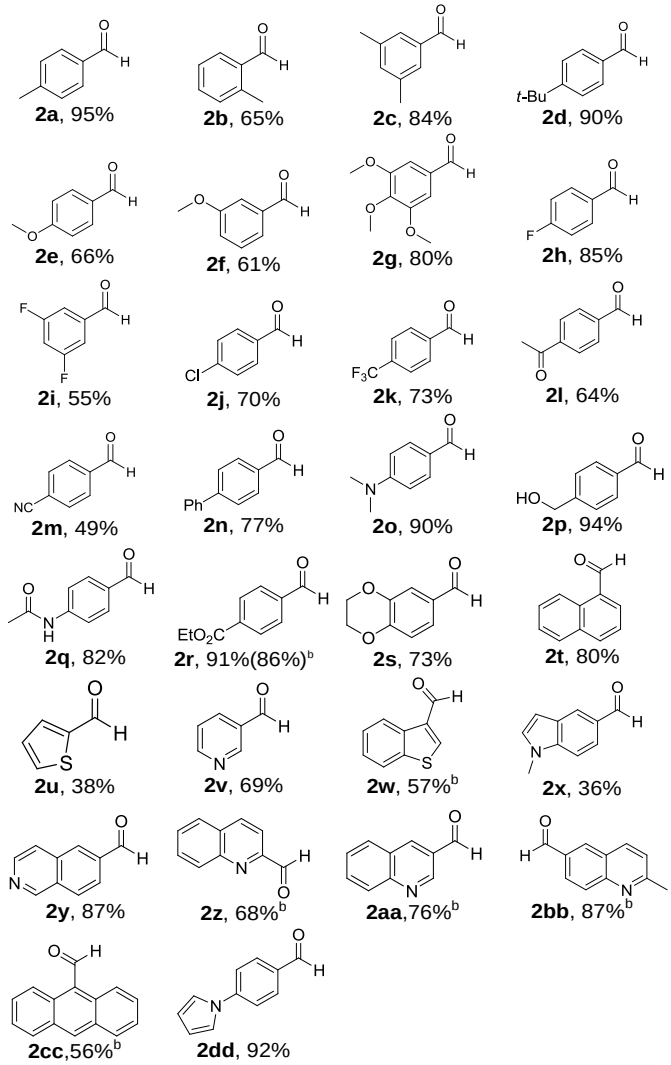
Table 3 Palladium-catalyzed hydroformylation of aryl halides.

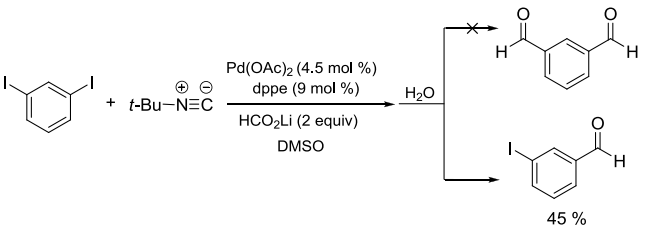




[a] Reaction conditions: aryl iodides (0.7 mmol), *tert*-butyl isocyanide (0.84 mmol), HCO_2Na (1.4 mmol), $Pd(OAc)_2$ (0.032 mmol), dppe (0.063 mmol), and 3.0 mL of anhydrous DMSO under a nitrogen atmosphere in a sealed tube; isolated yields. [b] aryl bromides (0.7 mmol), *tert*-butyl isocyanide (0.84 mmol), HCO_2K (1.4 mmol), $Pd(OAc)_2$ (0.032 mmol), dppe (0.063 mmol), and 3.0 mL of anhydrous DMSO under a nitrogen atmosphere in a sealed tube.

HCO_2Na whereas hydrogen bromide (of **1rb**) and chloride (of **1rc**) need a stronger base HCO_2K. Thus, the optimal condition is aryl halides with 1.2 equivalents of *tert*-butyl isocyanide, 4.5 mol % of $Pd(OAc)_2$, 9 mol % of dppe, 2 equivalents of HCO_2Na/HCO_2K in anhydrous DMSO under a nitrogen atmosphere at 120 °C.

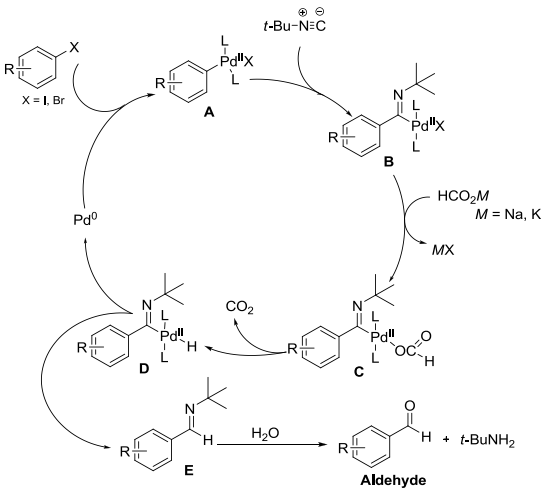
With the best conditions in hand (Table 1, entry 14), we explored the scope and limitations of this method. A variety of functional groups (ether, ketone, cyano, alcohol, amide, ester



Scheme 2. Palladium-catalyzed hydroformylation of 1,3-diiodobenzene.

and dioxane groups) were tolerated under the optimized conditions (Table 3, **1e-1g**, **1l-1m**, **1p-1s**), affording corresponding products in mild to excellent yields. In general, there was no significant difference between electron-donating groups and electron-withdrawing substituents. Gratifyingly, the methodology was found to work well with aryl bromides (Table 3, **1w**, **1z-1cc**). The formylation of 1,3-diiodobenzene also took place, giving monoformylated 3-iodobenzaldehyde in 45 % yield (Scheme 2).

From the above experimental results and the previous corresponding reports,[8b,15] a possible reaction mechanism was proposed in Scheme 3. Rapid oxidative addition of Pd(0) into the carbon-halogen of aryl halide in the first step to generate **A**, followed by *tert*-butyl isocyanide insertion to afford intermediate **B**. Formate salt has dual roles: serving both as a base and as a hydride donor. Ligand exchange with HCO_2Na/HCO_2K leads to **C** and extrusion of CO_2 delivers palladium(II) hydride **D**. The targeted aldehyde is achieved via sequent reductive elimination of Pd(II) as well as loss of *tert*-butylamine.



Scheme 3. Proposed mechanism

In conclusion, a practical method for Palladium-catalyzed direct formylation of aryl halides into aromatic aldehydes using *tert*-butyl isocyanide as a C_1 source and formate salts as a hydride donor was generally observed. Characterized with wide substrate scope, synthetic simplicity, and economy, the

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methodology may encourage a much deeper examination of isocyanides application in our future experiments. Further mechanism studies are underway in our laboratory.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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