Catalysis Letters
https://doi.org/10.1007/s10562-020-03108-z

Powerful and Phosphine-Free Palladium-Catalyzed Selective Formylation of Aryl Halides with Formic Acid as CO Source

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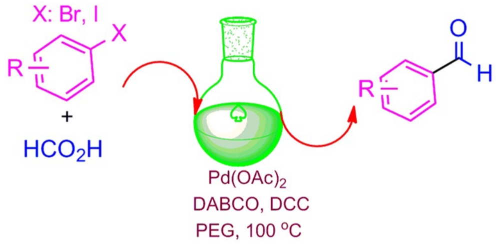
Received: 10 November 2019 / Accepted: 9 January 2020

Abstract

The phosphine-free palladium-based catalytic system Pd(OAC)$_2$/DABCO has been developed for the carbonylative transformations of aryl halides with formic acid. The DABCO acts as a base as well as *N*-donor ligand to coordinate with metal ions and stabilize Pd-catalytic sites during the reaction process. Using DCC as the activator of formic acid and PEG as the reaction media. The aryl halides have been conveniently transformed into the corresponding aldehydes in moderate to excellent yields.

Graphic Abstract

An efficient catalytic system Pd(OAc)2/ DABCO/ DCC for selective carbonylation of aryl halides with formic acid is described.



Keywords Carbonylation · Formic acid · Aldehyde · Catalyst · Palladium

1 Introduction

The value of carbonyl-containing chemicals in chemistry and biology as critical structural units and important intermediates in chemical transformations for a variety of natural and pharmaceutical products has inspired the development of various synthetic methods for their preparation [1, 2]. Aromatic aldehydes play an important role in this class of organic compounds and are one of the key synthetic blocks in formation of various C−C and C−X bonds, many natural products and pharmaceutical compounds [3, 4].

Recently, carbonylative transformations have already become one of the most powerful methodologies for the synthesis of carbonyl-containing compounds, and many related research efforts have been conducted toward this objective [5, 6]. The terms 'carbonylation' and 'carbonylative' are used specially for a large number of transformations that introduce carbon monoxide into organic and inorganic substrates. Although, CO gas has been recognized as one of the carbonyl sources and has an acceptable position in industry [6], the high toxicity and gaseous nature, prevent the applications of CO gas-based methodologies. Therefore, many synthetic studies have conducted

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10562-020-03108-z) contains supplementary material, which is available to authorized users.

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toward the developing new CO-free carbonylation methods [7–9]. Among the various carbonyl sources, formic acid (HCOOH) has attracted much attention because it can produce one molecule of CO during the reaction process [10].

Palladium-catalyzed carbonylation of aryl halides by various carbonyl sources such as CO [11–13], CO_2 [7], $Mo(CO)_6$ [14], Oxalic acid [8], *N*-formylsaccharin [15] and Formic acid [16, 17] is efficient and straightforward alternative methodology for preparing carbonyl compounds. In these reactions, generally, the use of phosphine ligands to activate and stabilize the palladium species results in high efficiency of catalyst. However, most phosphine ligands are air-sensitive, not environmentally-friendly and require a high palladium loading in carrying out the reaction, significantly limiting their applications. Therefore, there is a great interest in making new and phosphine-free ligands, and development of economic benign synthetic protocols as an important and challenging goal in organic chemistry.

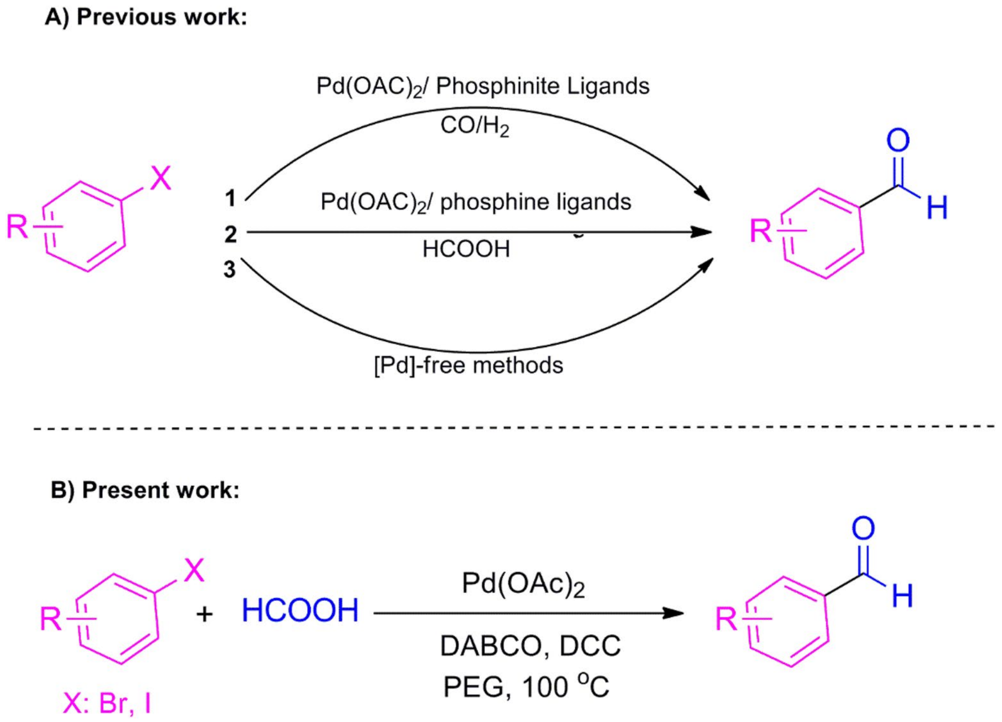
In continuation of our studies on the synthesis and development of new and efficient catalytic systems, herein we introduce a phosphine-free Pd-based catalytic system incorporating 1,4 diazabicyclo[2.2.2]octane (DABCO) for the formic acid carbonylation of aryl halides, in which DABCO acts as an inexpensive and stable base as well as an excellent ligand to stabilize Pd species in the reaction media (Scheme 1). In this reaction system, aromatic aldehydes could be synthesized via carbonylative reaction of aryl halides with the in-situ generation of CO from formic acid using DCC as the activator.

2 Results and Discussion

Our carbonylation approach was initiated using iodobenzene **1a** as the aryl halide. We examined the effect of various reaction parameters such as solvent, temperature and catalyst loading on the yields of a series of screening experiments (Table 1). The solvent effect was studied and the results suggested that the solvent system plays a crucial role in this reaction system. Among the several tested solvents such as H_2O, EtOH, MeCN, polyethylene glycol (PEG) and mixed solvents EtOH/H_2O (1:1); PEG gave the best result (Table 1, entries 1–5). Further examination of different bases proved DABCO was the best option in terms of efficiency (Table 1, entries 5–8).

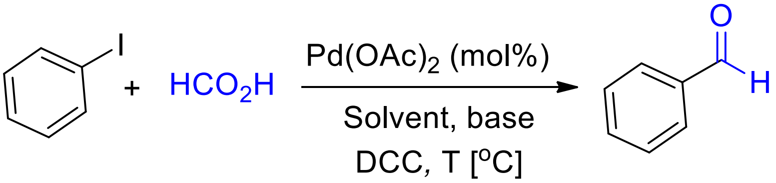
The concentration of DABCO and DCC was also examined in this reaction system, and these parameters were found to be important in the reaction progress. As shown in Table 1 (entries 9–11), the use of lower concentrations of DABCO and DCC gave a relatively lower yield.

The reaction temperature and the catalyst loadings were also studied in this reaction system. The yield of



Scheme 1 Different formylation methods. 1 [20], 2 [16, 19], 3 [21]

Table 1 Optimization of the reaction conditions for the carbonylation coupling



Entry	Solvent	Base (2 equiv.)	DCC	Catalyst (mol%)	T [°C]	Yield [%][a]
1	H_2O	DABCO	2 equiv	2.7	100	–
2	EtOH	DABCO	2 equiv	2.7	Reflux	10
3	H_2O/EtOH (1:1)	DABCO	2 equiv	2.7	Reflux	15
4	CH_3CN	DABCO	2 equiv	2.7	Reflux	50
5	**PEG-200**	**DABCO**	**2 equiv**	**2.7**	**100**	**90**
6	PEG-200	–	2 equiv	2.7	100	20
7	PEG-200	Et_3N	2 equiv	2.7	100	75
8	PEG-200	K_2CO_3	2 equiv	2.7	100	70
9[b]	PEG-200	DABCO	2 equiv	2.7	100	75
10	PEG-200	DABCO	–	2.7	100	50
11	PEG-200	DABCO	1 equiv	2.7	100	70
12	PEG-200	DABCO	2 equiv	2.7	60	40
13	PEG-200	DABCO	2 equiv	1.7	100	75
14	PEG-200	DABCO	2 equiv	0.9	100	50
15	PEG-200	DABCO	2 equiv	–	100	–
16	PEG-200	DABCO	2 equiv	2.7	rt	Trace

Reaction conditions: iodobenzene (0.5 mmol), HCOOH (3.5 mmol), DCC, $Pd(OAc)_2$, base, solvent (3 mL), 3 h

[a] GC yield

[b] DABCO (1 equiv.)

the model reaction decreased when the reaction temperature was changed from 100 to 60 °C (Table 1, entry 12). The optimal catalyst loading was found to be as low as 2.7 mol% (Table 1, entries 5, 13–15).

According to the extensive experimental results, the optimized conditions were established as $Pd(OAc)_2$ (2.7 mol%), DABCO (2 equiv), DCC (2 equiv), HCOOH (7 equiv) in PEG at 100 °C.

We next explored the scope and limitations of this transformation (Scheme 2). Various aryl iodides and bromides reacted successfully under the optimal conditions to give the corresponding aldehydes in moderate to excellent yields.

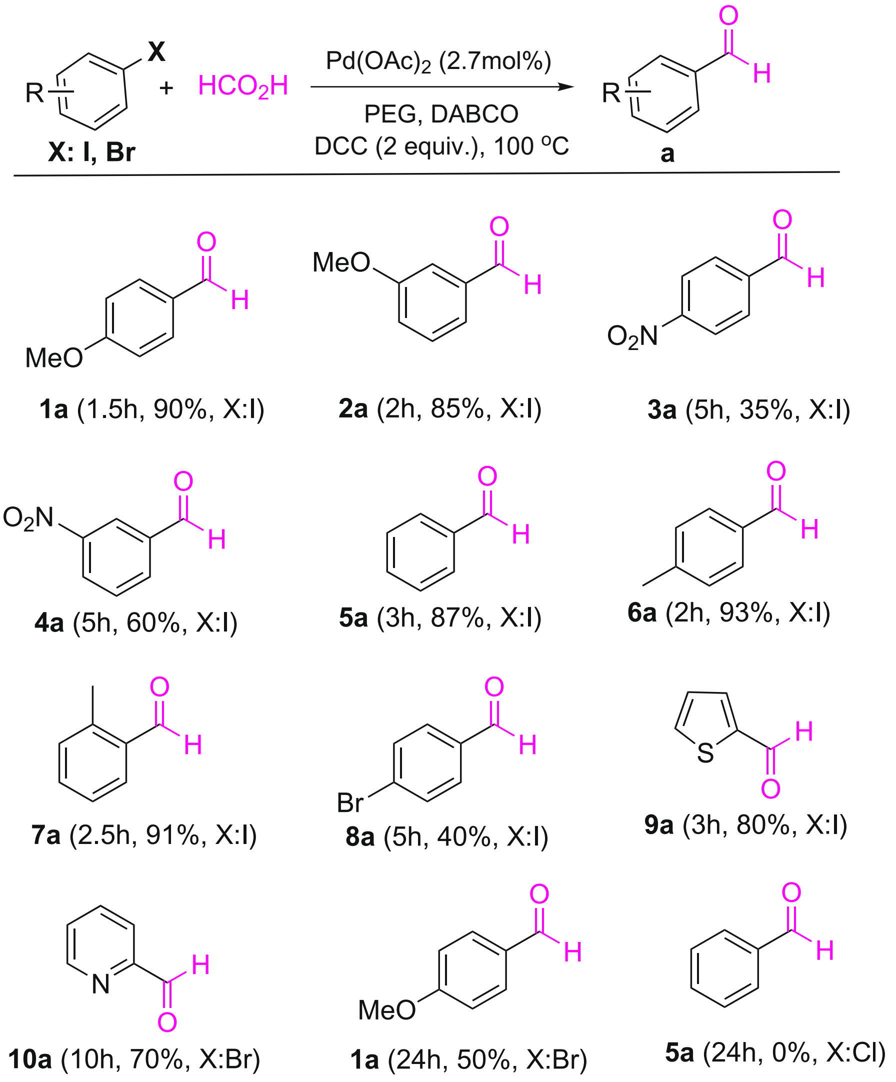
As shown in Scheme 2, the most of aryl iodides were successfully converted to the corresponding aldehyde products with excellent yields. Aryl bromides also reacted in this system to afford the corresponding aromatic aldehydes (Scheme 2. **10a** and **1a**). However, the reactivity of aryl bromides was lower than aryl iodides. Aryl bromides required longer reaction times and gave lower yields. Aryl chlorides were inactive in this reaction system.

The electronic properties of aryl halides had significant influence on the resulting yields in this procedure. Electron-rich aryl halides in comparison to electron-poor aryl halides showed better conversions in shorter reaction time. The methoxy- and methyl-aryl iodides gave excellent yields, in contrast the reaction of nitro-aryl iodides required longer reaction times and afforded lower yields.

Steric effects were also examined for this catalytic system by treating 2-iodotoluene under optimized reaction conditions. As shown in Scheme 2, the steric hindrance does not have a significant effect on the yield. The 2-iodothiophene and 2-bromopyridine were chosen as heteroaryl halides and gave the corresponding aldehyde in good yields (Scheme 2, 9a and 10a).

To date, several mechanisms for Pd-assisted formic acid-based carbonylation reactions have been described in the literatures. Wu et al. [16, 18] have reported the in-situ generation of one molecule of carbon monoxide from the reaction of formic acid with DCC as the activator, that this CO-molecule forms an acyl-palladium intermediate in the catalytic cycle. Sun et al. [19] have studied the hydrogen

Scheme 2 Scope of aryl halides in carbonylation coupling reaction with HCOOH



1a (1.5h, 90%, X:I)
2a (2h, 85%, X:I)
3a (5h, 35%, X:I)
4a (5h, 60%, X:I)
5a (3h, 87%, X:I)
6a (2h, 93%, X:I)
7a (2.5h, 91%, X:I)
8a (5h, 40%, X:I)
9a (3h, 80%, X:I)
10a (10h, 70%, X:Br)
1a (24h, 50%, X:Br)
5a (24h, 0%, X:Cl)

[a] Reaction conditions: aryl halide (0.5 mmol), HCOOH (3.5 mmol), DCC (1.0 mmol), $Pd(OAc)_2$ (2.7 mol%), DABCO (2.0 equiv.), solvent (3 mL), 100 °C.

source of the aldehyde products in the palladium-catalyzed formylation reaction of aryl iodide with isotopically labeled reagent D_2-formic acid. They found that the hydrogen source of the aldehyde group derived from formic acid.

Based on these reports and our experimental results, a possible reaction mechanism was proposed. As shown in the Scheme 3, the catalytic cycle begins with the oxidative addition of aryl halide to the Pd(0) species, in which the DABCO acted as both an efficient base and a *N*-donor excellent ligand to stabilize the Pd-catalytic sites.

The present catalytic method was compared with the some procedures previously reported by other groups, in which different catalytic systems based on palladium catalysts combined with the ligands promote the synthesis of aldehydes from aryl halides. As shown in Table 2, the most important advantages of this carbonylation method are mild and phosphine-free conditions, availability, low catalyst-loading, short reaction times and good yields. In general, reaction condition, reaction rate, selectivity and availability are important factors that must be considered in this transformations.

Due to the increasing importance of carbonyl-containing compounds in many aspects, the design of high-yielding and selective synthetic methodologies for preparation of these compounds will be interesting to follow in the near future.

Scheme 3 Proposed mechanism of formylation reaction

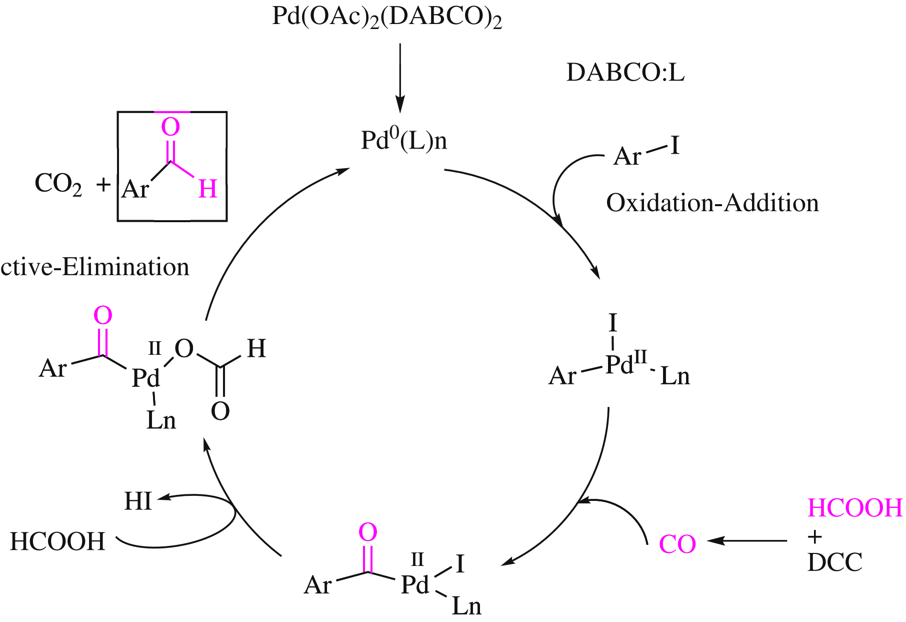
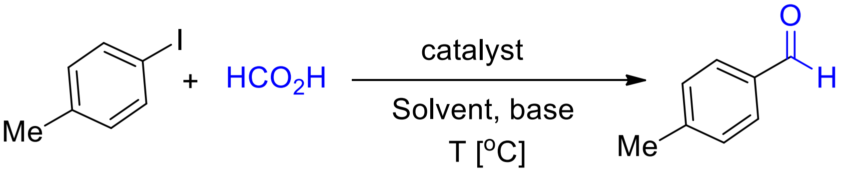


Table 2 Comparison of catalytic systems with literature examples for the formylation of 4-iodotoluene via carbonylation rection



Entry	Catalyst	Reaction conditions	Yield (%) [Refs.]
1	$Pd(OAc)_2$ (3 mol%)	PPh_3,I_2, HCOOH, Et_3N, Toluene, 80 °C, 2 h	83 [19]
2	$Pd(OAc)_2$ (3 mol%)	PCy_3, DCC, HCOOH, Et_3N, DMF, 80 °C, 10 h	76 [16]
3	$Pd_2(dba)_3$ (0.025 equiv.)	Dppe, Et_3SiH, EtN(*i*-Pr)$_2$, Acetic Formic Anhydride, 60 °C, 48 h	82 [22]
4	$PdCl_2$ (3.5 mol%)	SDPP, $Fe(CO)_5$, Et_3N, H_2O/DMF (1.3% v/v H_2O)	92 [23]
5	Present work	DABCO, DCC, HCOOH, PEG, 100 °C, 1.5 h	93

2.1 Experimental

2.1.1 General Procedure for Carbonylation Reaction

Aryl halide (0.5 mmol), $Pd(OAc)_2$ (2.7 mol%), PEG (3.0 mL) and formic acid (3.5 mmol) were transferred into a round-bottom flask. After, DABCO (1.0 mmol) and DCC (1.0 mmol) were added to the reaction flask, immediately sealed, and the mixture was stirred at 100 °C. After the reaction was completed the mixture was diluted with CH_2Cl_2 and filtered and concentrated. The crude product was purified by column chromatography on silica gel to afford the corresponding product.

Acknowledgements We are thankful to Persian Gulf University Research Council for partial support of this work.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest associated with this publication. They also confirm that the manuscript has been read and approved by all 3 authors.

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