ORIGINAL PAPER



# PdCl<sub>2</sub>/DABCO-catalyzed direct arylation of 2-hydroxybenzaldehydes in H<sub>2</sub>O

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**Abstract** In this paper the successful application of DABCO both as base and as ligand for efficient coupling reactions of aryl iodides and bromides with 2-hydroxyben-zaldehydes in the presence of catalytic amounts of  $PdCl_2$  in water as solvent was introduced.

**Keywords**  $PdCl_2 \cdot DABCO \cdot Arylation \cdot 2-Hydroxybenzaldehydes$ 

### Introduction

The direct activation of the aldehydic C-H bond by transition metal complexes is a major goal in modern synthetic chemistry because of its relevance to organic synthesis through conversion of aldehyde into ketone [1-4]. Aryl ketones are important basic building blocks in chemistry and biology that have been widely used in the pharmaceutical, fragrance, dye, agrochemical, and functional material industries as well as in organic synthesis [5, 6]. For these reasons, considerable effort has been made on the development of efficient methods for aryl ketone synthesis. Generally, aryl ketones can be synthesized by Fries rearrangement [7] and Friedel–Crafts reaction [8]. As for Fries rearrangement in which aryl esters are rearranged by treatment with aluminium chloride and Friedel-Crafts reaction in which aromatic rings are condensed with acid chlorides or acid anhydrides in the presence of aluminium chloride, mixture of o- and p-isomers is often inevitable. In

Najmeh Nowrouzi nowrouzi@pgu.ac.ir many cases of the both reactions, the total yields are not good under mild conditions and the trouble of isolation of isomers leads to complicated operation. The oxidation of the corresponding secondary alcohols using more than stoichiometric amount of chromium reagents as the oxidizing agent [9, 10] and addition of organometallic reagents to acyl chlorides under anhydrous conditions are another synthetic approaches to aryl ketones [11–13]. Generally, reports on the C–H arylation of 2-hydroxybenzaldehyde are very rare in the literature [14–17].

The past decade has seen the development of a wide range of metal-catalyzed reactions that allow for the direct arylation of aldehydic C–H bonds [18]. The majority of these works have been done in organic solvents, often under relatively harsh conditions. However, cross-coupling reactions are usually carried out in polar organic solvent under inert and anhydrous conditions; recent research has shown that it is possible to perform C–H activation in water that water can allow the reactions to be carried out under milder conditions than traditional organic solvents [19]. Greaney was the first to report the direct arylation of heteroaromatic compounds in water [20]. Arylation of 2-arylthiazoles in the 5 position catalyzed by Pd(DPPF)Cl<sub>2</sub> at 60 °C occurred in good yields after 24 h in water. The reaction requires 72 h when performed in acetonitrile.

Phosphine ligands are generally used to complex and activate the palladium species, and excellent results have been reported for the palladium-catalyzed coupling reactions in the presence of phosphines [21–24]. However, phosphine ligands are sensitive to air and moisture, which places significant limits on their synthetic applications [23, 25]. Therefore, the development of phosphine-free palladium catalysts to overcome these difficulties, is considered to be one of the most challenging fields in organic chemistry [26–34].

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**Table 1** Effect of different reaction parameters on the reaction of iodobenzene and 2-hydroxybenzaldehyde (1.0 mmol) in the presence of DABCO (3.0 mmol) in  $H_2O$ 

Entry	Catalyst (mol%)	<i>T</i> (°C)	mmole of ArX	Time (h)	Yield (%) <sup>a</sup>
1	5	100	1	11	75
2	5	100	2	5	93
3	5	80	2	24	68
4	5	50	2	24	45
5	3	100	2	5	93
6	1	100	2	24	30
7	10	100	2	5	92
8 <sup>b</sup>	3	100	2	5	92

<sup>a</sup> Isolated yield

 $^{\rm b}\,$  0.5 mmol of tetrabutylammonium bromide was added to the reaction mixture

#### **Results and discussion**

Here, we report that  $PdCl_2$  combined with DABCO (1,4-diaza-bicyclo[2,2,2]octane) represents an inexpensive, phosphorus free, air and moisture stable catalytic system to successfully achieve Pd-catalyzed couplings of 2-hydroxy-benzaldehydes with aryl halides. Moreover, this methodology is of interest due to the use of water as solvent, thus minimizing the cost, the operational hazards and environmental pollution. Here, we wish to report the results of this methodology in detail.

To achieve this reaction, 2-hydroxybenzaldehyde and iodobenzene were initially used as cross-coupling partners to optimize the reaction conditions. First, a mixture of 2-hydroxybenzaldehyde (1.0 mmol) and iodobenzene (1.0 mmol) was heated in the presence of 5 mol% of PdCl<sub>2</sub> and DABCO (3.0 mmol) as base in H<sub>2</sub>O (2 mL) at 100 °C (Table 1, entry 1). Surprisingly, we discovered that even without any reducing agent and ligand, the reaction proceeds and afforded the coupling product in 75 % yield after 11 h (Table 1, entry 1). This indicated that Pd(II) could be reduced to a Pd(0) species to initiate the coupling process in this reaction system. This promising result encouraged us to do further optimization to improve the reaction time. Increasing the amount of iodobenzene from one equimolar to two improved the yield to 93 % and decreased the reaction time (Table 1, entry 2). Therefore, the amount of aryl halide is very effective in these reactions. A temperature of 100 °C is the optimal temperature for this reaction (Table 1, entry 2). When the reaction temperature was lowered to 80 and 50 °C, the yield also decreased (Table 1, entry 3, 4). Next, the reaction was carried out with different amounts of PdCl<sub>2</sub> (10, 3, 1 mol%). As it was shown in entries 5-7 of Table 1, at 100 °C, 3 mol% of the catalyst was sufficient to catalyze the reaction efficiently; in this case, the corresponding product was obtained in 93 % yield within 5 h (Table 1, entry 5). Finally, 0.5 mmol of tetrabutylammonium bromide (TBAB) as phase transfer catalyst was added to the reaction mixture which did not improve the catalytic activity of the system (Table 1, entry 8).

After optimizing the reaction conditions, the reactions of 2-hydroxybenzaldehydes with various aryl halides containing electron-donating or electron-withdrawing groups were explored using similar reaction conditions, the results of which are shown in Table 2. Under the above optimized reaction conditions, a wide range of aryl iodides, whether electron-rich or electron-deficient, all worked well with 2-hydroxybenzaldehydes. Both 4-methyl- and 2-methyliodobenzene exhibited excellent reactivity under similar reaction conditions and gave the desired products in 88 and 86 % yields, respectively, indicating that these reactions are not considerably inhibited by the steric hindrance of aryl halides (Table 2, entries 2, 3). However, with electron-releasing halides, elongations of the reaction times were observed. Then, the applicability of this reaction was extended to aryl bromides. We were happy to discover that the scope of the protocol could be extended to aryl bromides. Also, the reaction of 1-bromonaphthalene, a more sterically hindered substrate, afforded good yields of the corresponding coupled product (Table 2, entry 10). Unfortunately, an attempt to coupling the 4-chlorobenzonitrile with 2-hydroxybenzaldehyde was unsuccessful (Table 2, entry 12). We also screened the reaction between aryl iodide and benzaldehyde or *p*-hydroxybenzaldehyde, but no target product was obtained (Table 2, entries 13, 14). It is worthy to mention that in neither of these reactions external ligand was needed and the nitrogen atoms in the molecule of the base (DABCO) can effectively act as the required ligand to complete the reaction with excellent vields.

According to the above presented results, DABCO is playing important role both in the formation of Pd(0) catalyst and also stabilization of Pd(0) species preventing their aggregation and deactivation. In order to have more information about the reducing property of DABCO, we probed the ultraviolet (UV) spectrum of Pd(II) in aqueous solution of DABCO. The UV spectrum of palladium chloride solution is shown in curve A of Fig. 1. The peak at around 450 nm shows the presence of Pd(II). Curve B belongs to the aqueous solution of DABCO including PdCl<sub>2</sub>. The disappearance of the peak around 450 nm confirms that Pd(II) has been reduced to the Pd(0) species in the presence of DABCO (Fig. 1).

A possible mechanism as outlined in Scheme 1 was proposed on the basis of the present results. Step 1 involves the oxidative addition of aryl halide to palladium (0) species. The formed Pd(II) species subsequently reacts with salicylaldehyde to form intermediate  $\mathbf{I}$  with liberation of

hydrogen halide under the act of DABCO as base. Insertion of the aryl to the carbonyl group gives intermediate **II**, which then affords intermediate **III** via a  $\beta$ -hydride elimination process. Finally, the subsequent reductive elimination from **III**, yields 2-hydroxybenzophenone and also regenerates the Pd(0) catalyst.

It should be noted that treatment of benzaldehyde or p-hydroxybenzaldehyde, in place of 2-hydroxybenzaldehyde, with iodobenzene never underwent the palladiumcatalyzed arylation of aldehyde C–H bond (Table 2, entries 13 and 14). This fact could confirm the mechanism that the phenolic function at the ortho-position of the formyl group is necessary for successful performance of the reaction.

#### Conclusion

In conclusion, we have described a new, simple and highly efficient protocol for the synthesis of aryl ketones by palladium-catalyzed C–H activation and arylation of 2-hydroxybenzaldehydes with aryl iodides and aryl bromides in  $H_2O$ . This transformation is very practical; it does not require the use of strong bases or expensive ligands and is conducted in the presence of ambient air/moisture. DABCO is considerably inexpensive and readily available, which emerged as an attractive alternative to the phosphine ligands. Importantly, this method used  $H_2O$  as solvent, which makes it more attractive for organic synthesis and industry.

#### **Experimental**

### General procedure for arylation of 2-hydroxybenzaldehydes with aryl halides

In a 50 mL round bottom flask containing H<sub>2</sub>O (2 mL) at 100 °C, PdCl<sub>2</sub> (3 mol%, 0.0053 g), DABCO (3.0 mmol, 0.34 g), 2-hydroxybenzaldehyde (1.0 mmol), and halobenzene (2.0 mmol) were added. The mixture was stirred with a mechanical stirrer. The progress of the reaction was monitored by TLC. After the appropriate reaction time, the mixture was cooled to room temperature and extracted with diethyl ether (3 × 3 mL). The organic layer was isolated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and purified by column chromatography over silica gel using *n*-hexane/ethyl acetate (5:1) as eluent to afford 2-hydroxybenzophenones in good to excellent yields (Table 2).

#### 2-Hydroxybenzophenone (Table 2, entry 1)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 11.96 (s, 1H), 7.62– 7.40 (m, 7H), 7.02–6.98 (m, 1H), 6.83–6.77 (m, 2H); Table 2 PdCl<sub>2</sub>-catalyzed arylation of 2-hydroxybenzaldehyde in H<sub>2</sub>O

Z	CHO + K	PdCl <sub>2</sub> (3 mol%) DABCO (3.0 mmol) ► H <sub>2</sub> O (2 mL) reflux	Z OH	R
	Z=H, Br X=I, Br			
Entry	ArX	Product	Time (h)	Yield (%)
1		OH OH	5	93
2	H <sub>3</sub> C	OH CH3	14	88
3	CH <sub>3</sub>	O CH <sub>3</sub>	16	86
4	O <sub>2</sub> N	OH NO2	4.5	90
5		Br	5	89
6	Br	O OH	29	85
7	NC Br		18	75
8	O <sub>2</sub> N Br		16.5	77
9	H <sub>3</sub> C Br	ОНССН3	40	66
10	Br		24	75
11	Br	Br OH	24	85
12	NC	-	48	-
13 <sup>b</sup>		-	24	-
14 <sup>c</sup>		-	24	-

Reaction conditions: Aryl halide (2.0 mmol), 2-Hydroxybenzaldehyde (1.0 mmol),  $PdCl_2$  (3 mol%), DABCO (3.0 mmol),  $H_2O$  (2 mL), 100 °C

<sup>a</sup> Isolated yield

<sup>b</sup> The reaction was carried out with benzaldehyde

<sup>c</sup> The reaction was carried out with *p*-hydroxybenzaldehyde



Fig. 1 UV spectra of the palladium catalyst. a  $PdCl_2$ , b DABCO +  $PdCl_2$ 

<sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>) δ ppm: 200.01, 158.02, 140.77, 133.85, 133.76, 132.95, 132.04, 127.96, 127.46, 120.01 (overlap, two peaks).

# (2-Hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 2)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 11.97 (s, 1H), 7.52–7.37 (m, 4H), 7.21 (d, 2H, J = 8.0 Hz), 6.97 (t, 1H, J = 8.5 Hz), 6.80–6.74 (m, 1H), 2.35 (s, 3H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 201.31, 163.11, 142.73, 136.07 (overlap, two peaks), 133.51, 129.46 (overlap, two peaks), 129.00, 118.53, 118.33, 30.18.

### (2-Hydroxyphenyl)(o-tolyl)methanone (Table 2, entry 3)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 11.82 (s, 1H), 7.54– 7.10 (m, 5H), 6.98–6.70 (m, 3H), 2.36 (s, 3H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 202.56, 157.09, 150.93, 145.57, 145.11, 130.02, 129.94 (overlap, two peaks), 125.29, 122.66 (overlap, two peaks), 119.08, 119.03, 28.17.

# (2-Hydroxyphenyl)(4-nitrophenyl)methanone (Table 2, entry 4)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 11.76 (s, 1H), 8.34–7.83 (m, 6H), 7.71–7.65 (m, 2H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 137.34, 133.03, 132.61 (overlap, two peaks), 129.97, 129.87, 124.99, 123.63, 119.13, 118.83.

### (5-Bromo-2-hydroxyphenyl)(phenyl)methanone (Table 2, entry 5)

<sup>1</sup>H-NMR (250 MHz,  $CDCl_3$ )  $\delta$  ppm: 11.77 (s, 1H, OH), 7.49 (d, 1H, J = 8.5 Hz, Ar), 7.24 (m, 1H, Ar), 7.07 (d, 1H, J = 8.4 Hz, Ar), 6.97 (m, 2H, Ar), 6.85 (s, 1H, Ar), 6.56 (m, 2H, Ar); <sup>13</sup>C-NMR (62.9 MHz,  $CDCl_3$ )  $\delta$  ppm: 200.05, 158.11, 147.94, 140.55, 133.85, 133.46, 132.95, 131.25, 127.96, 127.58, 119.46.





### 2-Hydroxybenzophenone (Table 2, entry 6)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 11.98 (s, 1H), 7.56– 7.48 (m, 7H), 6.96–6.92 (m, 1H), 6.77–6.71 (m, 1H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>) δ ppm: 197.03, 139.70, 137.26, 134.33, 129.67, 129.20, 119.61 (overlap, two peaks), 119.29 (overlap, two peaks).

### 4-(2-Hydroxybenzoyl)benzonitrile (Table 2, entry 7)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 12.00 (s, 1H), 8.23– 7.80 (m, 1H), 7.68–7.62 (m, 3H), 7.59–7.52 (m, 4H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>) δ ppm: 202.85, 138.83, 132.77, 132.61 (overlap, two peaks), 124.99, 124.04 (overlap, two peaks), 119.37, 116.69 (overlap, two peaks), 116.09.

# (2-Hydroxyphenyl)(4-nitrophenyl)methanone (Table 2, entry 8)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 11.78 (s, 1H), 8.35– 8.17 (m, 3H), 7.73–7.67 (m, 3H), 7.49–7.25 (m, 2H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>) δ ppm: 204.77, 136.88, 132.97, 132.62, 129.99, 129.97, 124.99, 123.84 (overlap, two peaks), 118.76, 118.10.

## (2-Hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 9)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 11.88 (s, 1H), 7.54–7.37 (m, 4H), 7.10 (d, 2H, J = 8.0 Hz), 6.96 (t, 1H, J = 7.8 Hz), 6.88–6.84 (m, 1H), 2.44 (s, 3H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 201.72, 163.10, 142.83, 136.07 (overlap, two peaks), 133.51, 129.46, 129.00 (overlap, two peaks), 119.03, 119.02, 30.27.

### (2-Hydroxyphenyl)-naphthalen-1-yl-methanone (Table 2, entry 10)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 12.21 (s, 1H), 7.94– 7.83 (m, 3H), 7.46–7.17 (m, 7H), 7.04–6.67 (m, 1H); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 192.79, 153.44, 135.86 (overlap, two peaks), 133.00, 131.69, 131.49, 130.75, 128.95, 128.61, 128.21, 127.03, 126.21, 125.96, 123.04 (overlap, two peaks), 119.50.

### (5-Bromo-2-hydroxyphenyl)(phenyl)methanone (Table 2, entry 11)

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>) δ ppm: 11.80 (s, 1H, OH), 7.45 (d, 1H, J = 8.4 Hz, Ar), 7.19 (m, 1H, Ar), 7.06 (d, 1H, J = 8.4 Hz, Ar), 6.90 (m, 2H, Ar), 6.79 (s, 1H, Ar), 6.63 (m, 2H, Ar); <sup>13</sup>C-NMR (62.9 MHz, CDCl<sub>3</sub>) δ ppm: 200.00, 158.02, 147.77, 140.86, 133.85, 133.46, 132.95, 132.04, 127.96, 127.58, 120.01.

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