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Palladium-catalyzed direct C—H arylation of 2-hydroxybenzaldehydes with organic halides in neat water

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ABSTRACT

The palladium-catalyzed cross-coupling of 2-hydroxybenzaldehydes with organic halides proceeds in the presence of *n*-Bu_4NBr in H_2O producing the corresponding 2-hydroxybenzophenones in high yields.

1. Introduction

Diaryl ketones have received much attention because of their importance in pharmaceutical industries [1], natural products [2] and also in the construction of organic molecules. Therefore, many synthetic methods for the formation of aryl aryl, alkyl aryl, and alkyl alkyl ketones have been developed. The classical method for the synthesis of these compounds is based on the Friedel–Crafts acylation in the presence of Lewis acids. Recently, catalytic systems have been reported for the synthesis of ketones by transition-metal catalyzed coupling reactions of carboxylic acid derivatives with various transmetalating reagents [3]. For example, the formation of ketones through rhodium-catalyzed C—O bond activation of unactivated esters using a range of organoborons has been reported by Tian et al. [4]. Also, organometallic acyl compounds like the other kinds of transmetalating reagents, including acylstannanes, -silanes, and -zirconocenes with organic halides offer the synthesis of ketones [5]. Carbonylative coupling of aryl halides, triflates, and aryldiazonium salts with an organometallic species of borane, silane, and tin in the presence of gaseous carbon monoxide [6] or metal carbonyls as a source of carbon monoxide [7] is another method that is commonly used for building ketone molecules. Transition metal-catalyzed aromatic C—H bond functionalization for the C—C bond formation has been considered as an atom economy and an environment-friendly approach to build complex molecules in organic chemistry [8].

Among arene C—H bonds, the selective activation of aldehyde C—H bonds and coupling with aryl halides, and alkenes forming C—C bonds has been recognized as a major area of interest for access to the array of ketone derivatives through oxidative addition of transition-metal complexes to aldehyde C—H bonds.

As an example, rhodium-catalyzed activation of aldehydes leading to the addition of the aldehyde C—H bond to alkenes has been a useful route to ketones [9]. Another approach to access ketones from aldehydes would consist of Rh-catalyzed Heck-type reaction of potassium trifluoro(organo)borates with aldehydes, which was reported as the first catalytic cross-coupling reaction of organometallic reagents with aryl aldehydes to afford diaryl ketones [10]. The first palladium-catalyzed reaction of 2-hydroxybenzaldehyde and its derivatives with aryl halides *via* cleavage of the aldehyde C—H bond to obtain the corresponding ketones has been reported by Miura [11]. However, this interesting protocol considerably suffers from the limitation of applying to only aryl iodides. After this report, effort has been made for the preparation of 2-aroylphenols using iodonium salts as analogues of aryl halides. These salts were used into the reaction with salicylaldehyde in the presence of $PdCl_2$ and LiCl as a co-catalyst to achieve corresponding ketones [12]. Generally, reports on the C—H arylation of 2-hydroxybenzaldehyde are very rare in the literature. Herein, we report catalytic cross-coupling reaction of

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2-hydroxybenzaldehydes with aryl iodides and bromides to afford diaryl ketones in water as a green solvent; while DMF was applied as a solvent in both previous reports [11,12]. This reaction type is of interest due to the use of water as a solvent, thus minimizing the cost, the operational hazards, and environmental pollution.

2. Experimental

IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Avance DPX-250 MHz spectrometer using tetramethylsilane as internal standard.

2.1. General procedure for the preparation of 2-hydroxyarylketones from the reaction of 2-hydroxybenzaldehydes with aryl halides

In a 50 mL round bottom flask equipped with a magnetic stirring bar, tetrabutylammonium bromide (0.5 mmol, 0.16 g) was added and heated at 100 °C to be melted. Then a mixture of $PdCl_2$ (3 mol%, 0.0053 g), aqueous NaOH (2.0 mmol, 0.08 g of NaOH dissolved in 2 mL H_2O), hydroxybenzaldehyde (1.0 mmol), and aryl halide (2.0 mmol) were added to molten tetrabutylammonium bromide. 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 × 5 mL). The organic layer was isolated and dried over anhydrous Na_2SO_4 and purified by column chromatography over silica gel using *n*-hexane/ethyl acetate as eluent to afford the highly pure desired products (Table 2).

2.1.1. 2-Hydroxybenzophenone (Table 2, entry 1) [117–99–7]

IR (KBr): 3500, 1728 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.96 (s, 1*H*, OH), 7.62–7.40 (m, 7*H*, Ar), 7.02–6.98 (m, 1*H*, Ar), 6.83–6.77 (m, 2*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) 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). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.37; H, 4.96.

2.1.2. (2-Hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 2) [19434–30–1]

IR (KBr): 3434, 1650 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.97 (s, 1*H*, OH), 7.52–7.37 (m, 4*H*, Ar), 7.21 (d, 2*H*, *J* = 8.0 Hz, Ar), 6.97 (t, 1*H*, *J* = 8.5 Hz, Ar), 6.80–6.74 (m, 1*H*, Ar), 2.35 (s, 3*H*, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (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. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.98; H, 5.83.

2.1.3. (2-Hydroxyphenyl)(4-nitrophenyl)methanone (Table 2, entry 3) [68223–20–1]

IR (KBr): 3400, 1659 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.76 (s, 1*H*, OH), 8.34–7.83 (m, 6*H*, Ar), 7.71–7.65 (m, 2*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 137.34, 133.03, 132.61 (overlap, two peaks), 129.97, 129.87, 124.99, 123.63, 119.13, 118.83. Anal. Calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.00; H, 3.82; N, 5.70.

2.1.4. (2-Hydroxyphenyl)(o-tolyl)methanone (Table 2, entry 4) [51974–19–7]

IR (KBr): 3400, 1670 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.82 (s, 1*H*, OH), 7.54–7.10 (m, 5*H*, Ar), 6.98–6.70 (m, 3*H*, Ar), 2.36 (s, 3*H*, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (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. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.09; H, 5.63.

2.1.5. (5-Bromo-2-hydroxyphenyl)(phenyl)methanone (Table 2, entry 5) [55082–33–2]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.77 (s, 1*H*, OH), 7.49 (d, 1*H*, *J* = 8.5 Hz, Ar), 7.24 (m, 1*H*, Ar), 7.07 (d, 1*H*, *J* = 8.4 Hz, Ar), 6.97 (m, 2*H*, Ar), 6.85 (s, 1*H*, Ar), 6.56 (m, 2*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 200.05, 158.11, 147.94, 140.55, 133.85, 133.46, 132.95, 131.25, 127.96, 127.58, 119.46.

2.1.6. (5-Bromo-2-hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 6) [215380–62–4]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.63 (s, 1*H*, OH), 7.99 (m, 2*H*, Ar), 7.89 (m, 1*H*, Ar), 7.83 (m, 2*H*, Ar), 7.62 (s, 1*H*, Ar), 7.52 (m, 1*H*, Ar), 2.76 (s, 3*H*, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 200.93, 160.88, 149.20, 141.59 (overlap, two peaks), 136.29, 132.26, 126.47, 124.16 (overlap, two peaks), 118.85, 29.16.

2.1.7. 2-Hydroxybenzophenone (Table 2, entry 7) [117–99–7]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.98 (s, 1*H*, OH), 7.56–7.48 (m, 7*H*, Ar), 6.96–6.92 (m, 1*H*, Ar), 6.77–6.71 (m, 1*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 197.03, 139.70, 137.26, 134.33, 129.67, 129.20, 119.61 (overlap, two peaks), 119.29 (overlap, two peaks).

2.1.8. 4-(2-Hydroxybenzoyl)benzonitrile (Table 2, entry 8) [131117–91–4]

IR (KBr): 3500, 2200, 1650 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 12.00 (s, 1*H*, OH), 8.23–7.80 (m, 1*H*, Ar), 7.68–7.62 (m, 3*H*, Ar), 7.59–7.52 (m, 4*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) 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. Anal. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.24; H, 4.10; N, 6.18.

2.1.9. (2-Hydroxyphenyl)(4-nitrophenyl)methanone (Table 2, entry 9) [68223–20–1]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.78 (s, 1*H*, OH), 8.35–8.17 (m, 3*H*, Ar), 7.73–7.67 (m, 3*H*, Ar), 7.49–7.25 (m, 2*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) 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.

2.1.10. (2-Hydroxyphenyl)-naphthalen-1-yl-methanone (Table 2, entry 10) [93327–63–0]

IR (KBr): 3500, 1628 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 12.21 (s, 1*H*, OH), 7.94–7.83 (m, 3*H*, Ar), 7.46–7.17 (m, 7*H*, Ar), 7.04–6.67 (m, 1*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (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. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.02; H, 4.61.

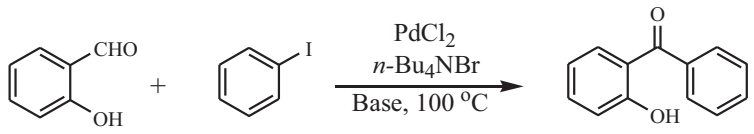
2.1.11. (2-Hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 11) [19434–30–1]

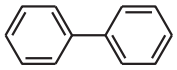
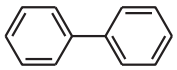
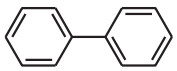
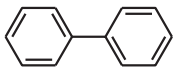
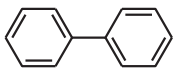
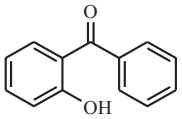
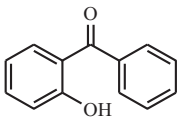
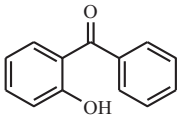
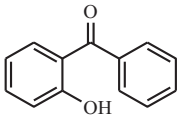
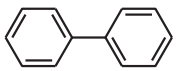
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.88 (s, 1*H*, OH), 7.54–7.37 (m, 4*H*, Ar), 7.10 (d, 2*H*, *J* = 8.0 Hz, Ar), 6.96 (t, 1*H*, *J* = 7.8 Hz, Ar), 6.88–6.84 (m, 1*H*, Ar), 2.44 (s, 3*H*, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 201.72, 163.10, 142.83, 136.07 (overlap, two peaks), 133.51, 129.46, 129.00 (overlap, two peaks), 119.03, 119.02, 30.27.

2.1.12. (2-Hydroxyphenyl)(p-tolyl)methanone (Table 2, entry 12) [19434–30–1]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.87 (s, 1*H*, OH), 7.55–7.42 (m, 4*H*, Ar), 7.11 (d, 2*H*, *J* = 8.0 Hz, Ar), 6.92 (t, 1*H*, *J* = 7.9 Hz, Ar), 6.87–6.84 (m, 1*H*, Ar), 2.45 (s, 3*H*, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 201.32, 163.11, 142.73, 136.07 (overlap, two peaks), 133.51, 129.46, 129.00 (overlap, two peaks), 119.03, 119.02, 30.18.

Table 1
Effect of different reaction parameters on the reaction of iodobenzene and salicylaldehyde[a].



Entry	Ph-I (mmol)	Base (2.0 mmol)	Time (min)	Product	Yield (%)[b]
1	2.0	NaOH	90		96
2	1.0	NaOH	30		93
3	1.0	Na_2CO_3	30		93
4	1.0	Bu_3N	30		95
5[c]	1.0	NaOH	30		96
6[d]	1.0	NaOH	24 h		40
7[d]	2.0	NaOH	35		97
8[d,e]	2.0	NaOH	45		95
9[d,f]	2.0	NaOH	24 h		60
10[g]	2.0	NaOH	45		93

[a] Reaction conditions: salicylaldehyde (1.0 mmol), base (2.0 mmol), *n*-Bu_4NBr (0.5 mmol), $PdCl_2$ (5 mol%) in 2 mL H_2O under reflux.
[b] Isolated yield.
[c] LiCl (0.2 mmol) as a co-catalyst was added to the reaction mixture.
[d] H_2O (2 mL) was selected as a solvent.
[e] The amount of $PdCl_2$ is 3 mol%.
[f] The amount of $PdCl_2$ is 1 mol%.
[g] The reaction was carried out in toluene as a solvent.

2.1.13. (5-Bromo-2-hydroxyphenyl)(phenyl)methanone (Table 2, entry 13) [55082–33–2]

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.80 (s, 1*H*, OH), 7.45 (d, 1*H*, *J* = 8.4 Hz, Ar), 7.19 (m, 1*H*, Ar), 7.06 (d, 1*H*, *J* = 8.4 Hz, Ar), 6.90 (m, 2*H*, Ar), 6.79 (s, 1*H*, Ar), 6.63 (m, 2*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 200.00, 158.02, 147.77, 140.86, 133.85, 133.46, 132.95, 132.04, 127.96, 127.58, 120.01.

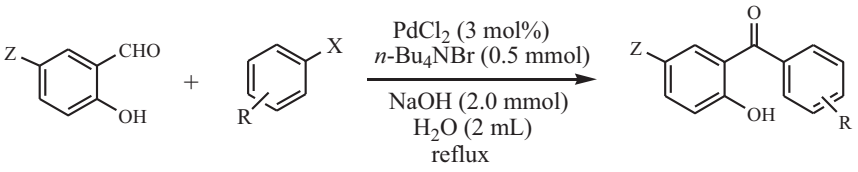
2.1.14. (5-Bromo-2-hydroxyphenyl)(4-nitrophenyl)methanone (Table 2, entry 14)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.95 (s, 1*H*, OH), 8.16 (m, 1*H*, Ar), 7.98 (m, 2*H*, Ar), 7.89 (d, 1*H*, *J* = 8.4 Hz, Ar), 7.83 (m, 2*H*, Ar), 7.63 (s, 1*H*, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 205.65, 159.12, 147.81, 144.05, 134.36, 133.26, 133.00, 132.89, 129.96, 127.77, 121.38.

2.1.15. 1-(2-Hydroxyphenyl)-2-phenyl ethanone (Table 2, entry 15) [2491–31–8]

IR (KBr): 3433, 1633 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 10.40 (s, 1*H*, OH), 7.71–7.67 (m, 1*H*, Ar), 7.25–7.19 (m, 6*H*, Ar), 6.86 (d, 2*H*, *J* = 8.5 Hz, Ar), 4.97 (s, 2*H*, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 189.60, 161.06, 135.98, 128.74, 128.37, 128.27, 127.32, 125.50, 121.00 (overlap, two peaks), 113.10, 70.39. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.90; H, 5.63.

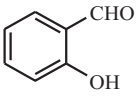
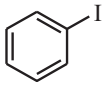
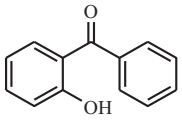
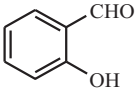
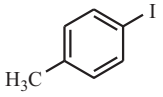
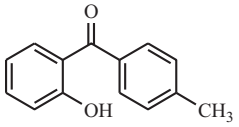
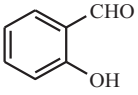
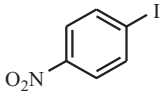
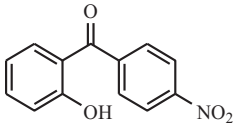
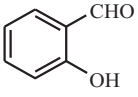
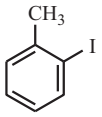
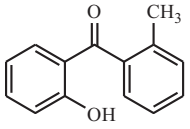
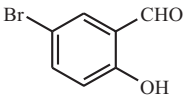
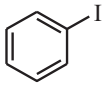
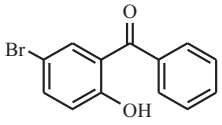
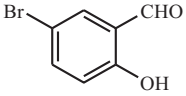
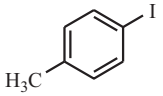
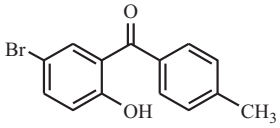
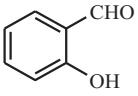
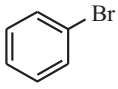
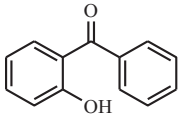
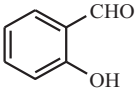
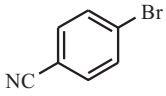
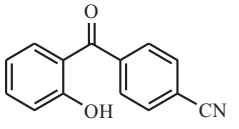
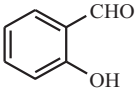
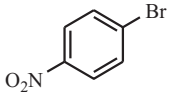
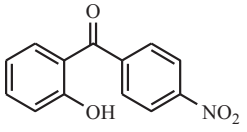
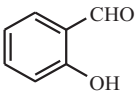
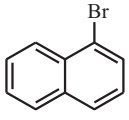
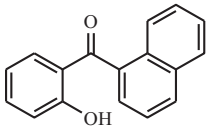
Table 2
Cross coupling of salicylaldehyde with organic helides[a].



Z= H, Br

X= I, Br, CH_2Br

R= H, CH_3, NO_2, CN

Entry	Aldehyde	ArX	Time (h)	Product	Yield[b] (%)[ref]
1			45 min		95 [12]
2			4		90[12]
3			2		95[13]
4			13		88[13]
5			40 min		89[14]
6			3.5		85[15]
7			6		81[12]
8			20		60[13]
9			18		75[13]
10			19		74[11]

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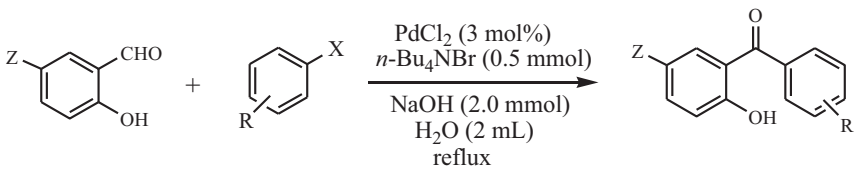
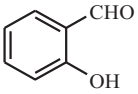
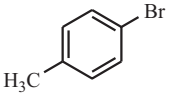
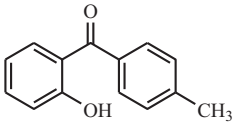
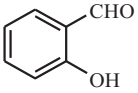
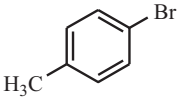
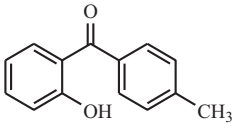
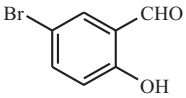
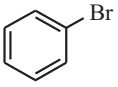
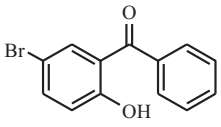
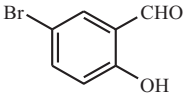
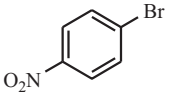
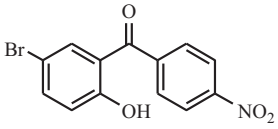
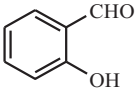
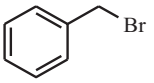
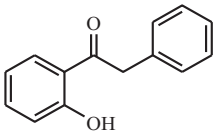
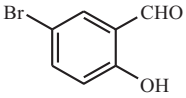
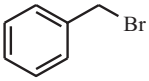
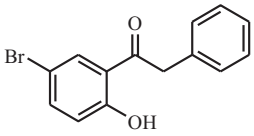
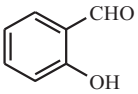
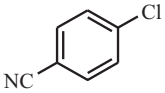
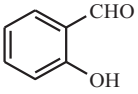
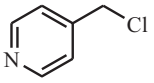
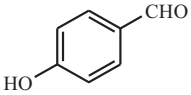
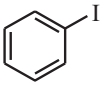
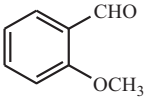
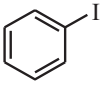


Z= H, Br

X= I, Br, CH_2Br

R= H, CH_3, NO_2, CN

Entry	Aldehyde	ArX	Time (h)	Product	Yield[b] (%)[ref]
11			48		55[12]
12[c]			22		85[12]
13			6		85[14]
14			16.5		72[12]
15[d]			2:20		70[13]
16[d]			2		76[16]
17			20	–	Trace
18			24	–	–
19			24	–	–
20			24	–	–

[a] Reaction conditions: organic halide (2.0 mmol), salicylaldehyde (1.0 mmol), *n*-Bu_4NBr (0.5 mmol), $PdCl_2$ (3 mol%), NaOH (2.0 mmol), H_2O (2 mL), reflux.
[b] Isolated yield.
[c] PPh_3 (0.12 mmol) was added to the reaction mixture.
[d] 15% Of ether product was detected.

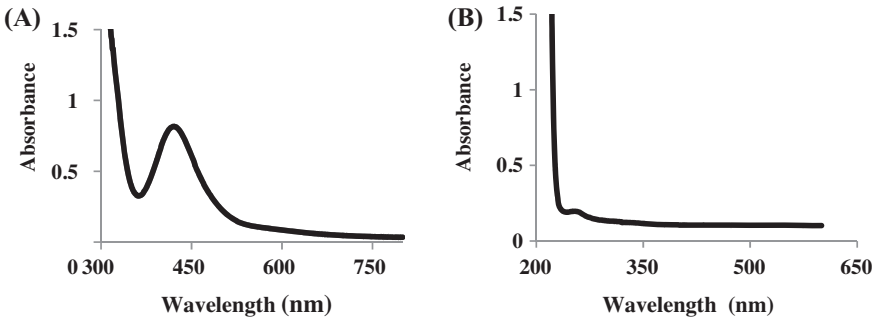


Fig. 1. UV spectra of the palladium catalyst: (A) $PdCl_2$, (B) *n*-Bu_4NBr + $PdCl_2$.

2.1.16. 1-(5-Bromo-2-hydroxyphenyl)-2-phenyl ethanone (Table 2, entry 16) [54981–34–9]

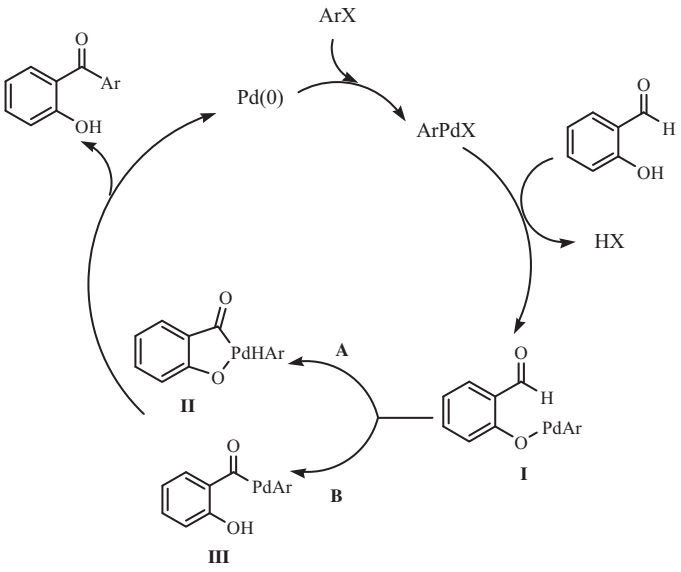
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 11.06 (s, 1*H*, OH), 7.30–7.27 (m, 2*H*, Ar), 7.15 (d, 1*H*, *J* = 8.0 Hz, Ar), 7.11 (s, 1*H*, Ar), 7.08–6.87 (m, 4*H*, Ar), 4.96 (s, 2*H*, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 200.01, 160.69, 146.91, 137.06, 134.45, 132.07, 129.76, 123.06, 121.95, 118.16 (overlap, two peaks), 67.80.

3. Results and discussion

Initially, we selected the reaction of salicylaldehyede with iodobenzene as a model reaction and studied the effects of different parameters on the progress of reaction (Table 1). When a mixture of salicylaldehyde (1.0 mmol) and iodobenzene (2.0 mmol) was heated in the presence of 5 mol% of $PdCl_2$ and NaOH (2.0 mmol) in *n*-Bu_4NBr (0.5 mmol) at 100 °C, the only obtained product was biphenyl and salicylaldehyde remained intact (Table 1, entry 1). Decreasing the amount of iodobenzene from two equimolar to one, the desired ketone was not observed (Table 1, entry 2). The use of the other bases such as Na_2CO_3 as an inorganic base and *n*-Bu_3N as an organic base also resulted in the formation of biphenyl (Table 1, entries 3 and 4). According to the literature [12], LiCl as a co-catalyst with $PdCl_2$ forms the complex Li_4PdCl_6, which is more reactive and efficient. Therefore, we decided to add this co-catalyst to the reaction mixture, but the reaction failed to give ketone (Table 1, entry 5). The reaction was then conducted in water as a solvent. Surprisingly, the most crucial component for the success of the reaction was found to be water; a synergic effect was observed in water which produced 2-hydroxybenzophenone under the initial condition with 100% conversion of salicylaldehyde to product (Table 1, entry 7). The amount of iodobenzene is very effective in these reactions. By decreasing the amount of iodobenzene, lower yield of the ketone product and longer reaction time was observed (Table 1, entry 6). Next, the reaction was carried out with different amounts of $PdCl_2$ (5, 3, 1 mol%). As was shown in entries 7–9 of Table 1, 3 mol% of the catalyst was sufficient to catalyze the reaction efficiently at 100 °C; in this case; the corresponding product was obtained in 95% yield within 45 min (Table 1, entry 8). When the cross-coupling reaction was performed in toluene as an organic solvent, the only product was biphenyl (Table 1, entry 10). According to the obtained results in water, the probable reason refers to intra- and inter-H-bonding of 2-hydroxybenzaldehyde. The intramolecular hydrogen bonds are present in the case of 2-hydroxybenzaldehyde in toluene. In this case, the interactions within individual molecules are greater, and there is less attraction between molecules. This causes less reactivity because the molecules are not really attracted to each other much. On the other hand, intramolecular interactions are much stronger since the two atoms forming the hydrogen bond remain in each other proximity due to structure of the molecule. H_2O molecules are able to form intermolecular H-bonding with phenolic function of 2-hydroxybenzaldehyde. This type of H-bonding only takes place for a short time when two molecules are in each other vicinity. Shortly after, the molecules separate and the interaction do no longer exist. As a result, the phenolic function is available to perform the reaction with other molecules in water.

We then applied our optimized reaction conditions (2.0 mmol aryl halide, 5.3 mg (3 mol%) $PdCl_2$, 1.0 mmol hydroxybenzaldehyde, 2.0 mmol NaOH, and 0.5 mmol *n*-Bu_4NBr in 2.0 mL H_2O under reflux), for the reaction of different aryl halides with salicylaldehydes and the desired products were obtained in good to excellent yields (Table 2). The cross-coupling proceeded smoothly for iodobenzene and salicylaldehyde within 45 min in excellent yield (Table 2, entry 1). The reaction of iodobenzenes bearing either an electron withdrawing or an electron donating group at the *para* position with salicylaldehyde were carried out efficiently (Table 2, entries 2 and 3). A substituent such as methyl on the *ortho* position has some steric effect and slightly decreases the yield of 2-hydroxy-2′-methylbenzophenone with elongation of reaction time (Table 2, entry 4). Then, the applicability of this reaction was extended to aryl bromides which makes this protocol very attractive. Bromobenzene reacted with salicylaldehyde after 6 h, and 2-hydroxybenzophenone was obtained in excellent yield (Table 2, entry 7). The coupling of salicylaldehyde with 4-cyano and 4-nitro substituted bromobenzene proceeded successfully (Table 2, entries 8 and 9). Also, 1-bromonaphthalene, a more sterically hindered substrate, afforded a good yield of the corresponding coupled product (Table 2, entry 10). 4-Bromotoluene as a deactivated aryl bromide produced a moderate yield of the corresponding ketone after a long time (Table 2, entry 11). We decided to add PPh_3 as a ligand to the reaction mixture of 4-bromotoluene and 2-hydroxybenzaldehyde in order to decrease the reaction time and increase the yield of product. It was observed that both yield and reaction time were improved in the presence of PPh_3 (Table 2, entry 12). The cross-coupling was also applicable to benzyl bromide, and the corresponding product was obtained in 70% yield (Table 2, entry 15). Apart from salicylaldehyde, we extended the reaction to 5-bromo-2-hydroxybenzaldehyde; the reaction could be carried out with aryl iodides and bromides smoothly to give excellent yields of the desired products under optimized reaction conditions (Table 2, entries 5, 6, 13, 14 and 16). The reaction of 4-chlorobenzonitrile and 4-(chloromethyl)pyridine with salicylaldehyde failed (Table 2, entry 17 and 18). Finally, we replaced 2-hydroxybenzaldehyde with 4-hydroxybenzaldehyde and 2-methoxybanzaldehyde, but the starting materials remained intact (Table 2, entries 19 and 20).

An important role of tetrabuthylammonium bromide was studied by UV–Vis spectra which showed conversion of Pd(II) to Pd(0) in the presence of tetrabuthylammonium bromide by the disappearance of the peaks related to Pd(II) at 450 nm (Fig. 1) [17]. Tetraalkylammonium salt additives have previously been reported by Jeffery [18], for biphasic (organic solvent/water) Heck reactions. It was believed that the salts were acting as phase-transfer catalysts



Scheme 1. A possible mechanism for the cross-coupling of salicylaldehyde with organic halides.

and increasing the solubility of the organic starting materials in the catalyst solution. Also, the ability to generate a stable form of the catalyst without the addition of stabilizing ligands is as an operating factor which suggests that tetraalkylammonium salts have been used to stabilize nanoparticles/colloids as a solute in a molecular solvent. It was reported by Reetz that this may be occurring when $R_4N^+X^-$ was being used as the ionic liquid [19].

According to this observation, a possible mechanism for the present cross-coupling of salicylaldehyde with organic halides is illustrated in Scheme 1. The first step involves the oxidative addition of aryl halide to palladium (0) species, followed by reaction with salicylaldehyde to form an aryl(aryloxy)palladium intermediate **I** with liberation of hydrogen halide under the act of added base. In the next step, there are two paths **A** and **B** to form intermediates **II** and **III**. According to the literature [11], the second oxidative addition of the aldehyde C—H bond to adduct **I** affords palladium(IV) species **II** in path **A** and the subsequent two-fold reductive elimination from it may occur to produce the corresponding ketone. In the path **B**, direct insertion of Pd–Ar into the C—H bond of aldehyde followed by reductive elimination reaction produces ketone. In our experiment, we found the isomer 4-hydroxybenzaldehyde never underwent the palladium-catalyzed arylation of aldehyde C—H bond (Table 2, entry 19), suggesting that the phenolic function in 2-hydroxybenzaldehyde acts as a good anchor for the reaction. In addition, treatment of 2-methoxybanzaldehyde, in place of 2-hydroxybenzaldehyde, with iodobenzene did not produce the corresponding coupling product. This fact further confirmed the mechanism that the formation of the intermediate **I** was the key step.

4. Conclusion

In conclusion, we have reported, for the first time, an efficient method for the cross-coupling reaction of aryl bromidesand benzyl bromide with 2-hydroxybenzaldehydes in H_2O to access 2-aroylketones without the need for any co-catalyst and ligand.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2014.10.013.

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