

## C–H Activation

Palladium-Catalyzed Aerobic Oxidative Carbonylation of C–H Bonds in Phenols for the Synthesis of *p*-HydroxybenzoatesVinayak V. Gaikwad<sup>[a]</sup> and Bhalchandra M. Bhanage<sup>\*[a]</sup>

**Abstract:** This work reports the synthesis of *p*-hydroxybenzoates directly from phenols by oxidative carbonylation of phenolic C–H bonds, proceeding through oxidative iodination. The developed methodology is efficient and economically attractive because phenols are cheap and easily available starting materials. This one-pot strategy was expediently applied to the

synthesis of a variety of *p*-hydroxybenzoates by utilizing simple primary and secondary alcohols with different phenols under mild reaction conditions. Advantageously, the procedure has no need for co-catalysts, co-solvents or external ligands. The utilization of molecular oxygen as a terminal oxidant for C–H bond oxidation represents an additional benefit.

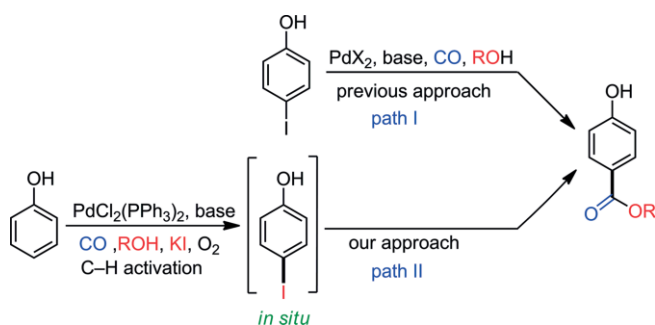
## Introduction

Transition-metal-catalyzed carbonylation of aryl halides or pseudohalides, established in 1974 by Heck and co-workers,<sup>[1–8]</sup> has served as a most potent methodology for the synthesis of carboxylic acids and their derivatives. On the other hand, activation of inert C–H bonds is a very attractive but difficult goal in synthetic chemistry; however, with the correct selection of catalyst and substrate it can be achieved.<sup>[9–12]</sup> Even so, carbonylation of C–H bonds presents a great challenge and is an attractive field.

The synthesis of benzoic acids through aryl C–H bond carbonylation was pioneered by Fujiwara and co-workers in 1980.<sup>[13]</sup> In the past two decades, significant efforts have been made towards broadening the scope of carbonylation through C–H bond activation. These reactions are environmentally benign and greener, because they avoid the need for multiple steps for functionalization of such substrates. Palladium-catalyzed carbonylation through C–H functionalization in arenes and heteroarenes for the synthesis of carboxylic acids and their derivatives has been demonstrated.<sup>[14–19]</sup> Nowadays, directing-group-assisted carbonylation of simple C–H bonds has emerged as an ideal strategy, through the introduction of carbon monoxide, to construct a variety of carbonyl compounds. Numerous directing groups such as amides, amines, heteroatoms and hydroxy groups have been used for C–H bond carbonylation.<sup>[20–27]</sup> However, most progress has been achieved with compounds containing directing groups and with the use of hazardous metals and oxidants such as copper, silver salts or peroxides, which are undesirable from a green chemistry point

of view. Molecular oxygen is an ideal and readily available, non-hazardous oxidant for oxidative carbonylation.<sup>[28–30]</sup>

*p*-Hydroxybenzoates are major chemical feedstock in the research fields of natural products, pharmaceuticals, agrochemicals and functional materials.<sup>[31–36]</sup> In the past decade, significant attention has been paid to the carbonylative synthesis of these compounds by traditional approaches.<sup>[37–41]</sup> Among these, palladium-catalyzed carbonylation of *p*-iodophenol followed by nucleophilic attack of alcohols leading to the synthesis of *p*-hydroxybenzoates is a dominant route used in the laboratory as well as on an industrial scale (Scheme 1, **Path I**).<sup>[42–45]</sup> Recently, Elango and co-workers successfully synthesized *p*-hydroxybenzoates by activation of bromophenol by use of a carbonylation method.<sup>[46]</sup> However, those methodologies have some limitations such as the need for expensive starting materials, longer reaction times, harsh reaction conditions and the use of traditional solvents, co-catalysts and Lewis acids.



Scheme 1. Synthesis of *p*-hydroxybenzoates by carbonylation.

To overcome these limitations, here we report the efficient synthesis of *p*-hydroxybenzoates directly from phenols, through palladium-catalyzed carbonylation of phenolic aryl C–H bonds (**path II**). Carbonylation occurs selectively at the *para* position of the phenol through activation of the corresponding aryl

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C–H bond through oxidative iodination. Additionally, other advantages of this methodology are that it is a single-step process and utilizes molecular oxygen as an ideal and environmentally benign oxidant (Scheme 1).

## Results and Discussion

Carbonylative coupling between phenol and methanol for the synthesis of methyl 4-hydroxybenzoate was selected as a model reaction. Various reactions parameters were screened (Table 1). Initially, we investigated various palladium precursors for the carbonylative coupling in the presence of a CO/O<sub>2</sub> (7+1 = 8 bar) mixture. We used molecular oxygen as a terminal oxidant along with KI for 18 h at 100 °C. We first used Pd(OAc)<sub>2</sub> as a catalyst precursor and observed the carbonylative products methyl 4-hydroxybenzoate (**p**) and methyl 2-hydroxybenzoate (**o**) with 80 % conversion of **1** and 85:15 % selectivity. (Table 1, Entry 1). However, the **p/o** selectivity was decreased to 80:20 % and 68:32 % at 80 % conversion with use of PdCl<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub>, respectively, as catalysts (Table 1, Entries 2 and 3). Next, we obtained 93:7 % **p/o** selectivity and 98 % conversion with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as an effective catalyst. Because this catalyst fur-

nished higher conversion, we used it for further studies (Table 1, Entry 4).

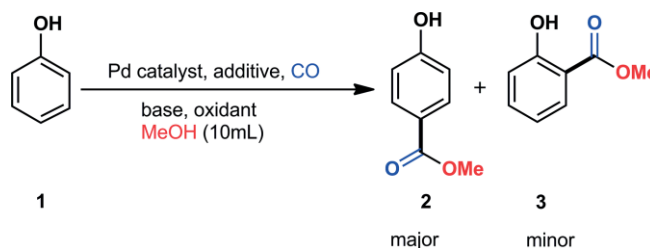
Further, we screened various commercial oxidants such as Ag<sub>2</sub>O, Cu(OAc)<sub>2</sub>, Oxone and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> to see the effects on conversion and selectivity. Molecular oxygen was the only oxidant that gave better conversion of **1** (Table 1, Entries 5–8), and this was used for the next optimization study.

We also investigated the PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyst along with different additives to increase the selectivity in favour of the desired ester of **2**. We carried out the reaction in the presence of various additives such as TBAI, NaI, NH<sub>4</sub>I and I<sub>2</sub>, observing **p/o** selectivity of 85:15 %, 65:35 %, 60:40 % and 63:37 %, respectively (Table 1, Entries 9–12). The highest conversion, as well as selectivity, was obtained with use of KI as an additive, and further reactions were carried out with this.

Subsequently, the effects of various solvents were investigated. We observed 98 % conversion of **1** with methanol as a solvent (Table 1, Entry 4). Methanol is a good solvent and it also acts as an effective nucleophile and was hence considered for the next optimization studies (cf. Table 1, Entries 13–16).

The degree of conversion of **1** was significantly increased by use of K<sub>2</sub>CO<sub>3</sub> as a base and it furnished a good **p/o** selectivity

Table 1. Screening of optimal reaction condition.<sup>[a]</sup>



Entry	Pd precursor	Oxidant	Additive	Base	Solvent	Conversion <sup>[b]</sup> [%]	Selectivity <sup>[b]</sup> <b>p/o</b> [%]
1	Pd(OAc) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	80	85:15
2	PdCl <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	79	80:20
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	80	68:32
4	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	98	93:7
5	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	Ag <sub>2</sub> O	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	–	–
6	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	Cu(OAc) <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	–	–
7	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	oxone	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	–	–
8	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	–	–
9	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	TBAI	K <sub>2</sub> CO <sub>3</sub>	MeOH	80	85:15
10	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	NaI	K <sub>2</sub> CO <sub>3</sub>	MeOH	70	65:35
11	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	NH <sub>4</sub> I	K <sub>2</sub> CO <sub>3</sub>	MeOH	55	60:40
12	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	I <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	MeOH	30	63:37
13 <sup>[c]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	30	70:30
14 <sup>[c]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	DMF	25	65:35
15 <sup>[c]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	THF	17	60:40
16 <sup>[c]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	toluene	–	–
17	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	Na <sub>2</sub> CO <sub>3</sub>	MeOH	78	80:20
18	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	Cs <sub>2</sub> CO <sub>3</sub>	MeOH	80	83:17
19	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	NaOH	MeOH	75	65:35
20	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	KOH	MeOH	72	62:37
21	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	NEt <sub>3</sub>	MeOH	60	60:40
22	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	DBU	MeOH	50	55:45
23 <sup>[d]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	60	75:25
24 <sup>[e]</sup>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	O <sub>2</sub>	KI	K <sub>2</sub> CO <sub>3</sub>	MeOH	55	69:31

[a] Reaction conditions: phenol (1 mmol), base (1.5 mmol), MeOH (10 mL), additive (1.5 mmol), catalyst (2 mol-%), CO/O<sub>2</sub> (7:1), 8 bar, 100 °C, 18 h. [b] Conversion and selectivity determined by GC and GC–MS. [c] MeOH (5 mL) and solvent (5 mL). [d] PPh<sub>3</sub> (5 mol-%). [e] Xantphos (5 mol-%).

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