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Palladium Catalysed C–O Bond Formation: Synthesis of Aryl Benzoates

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Abstract

A [Pd]-catalysed intermolecular C–O bond formation strategy is established towards the formation of aryl benzoates. The coupling between carboxylic acids and iodoarenes was feasible in the presence of a palladium catalyst and oxidant. Interestingly, water in TBHP served as the reaction medium. This process was found to be suitable for various functional groups.

Keywords: Palladium catalysis, Aryl ester, Carboxylic acids, Oxidative coupling, Esterification

1. Introduction

Aryl benzoates are significant and abundant functional compounds. They are usually found in pharmaceuticals, agrochemicals, polymers,[1]and natural products,[2] and are occasionally employed as arylating agents in transition metal cataylsis[3] (Figure 1). Hence, the synthesis of aryl ester[4] has caught a lot of attention within organic chemists and interesting reports have been presented on their synthesis. Nevertheless, a traditional approach to the synthesis of ester even now requires the straight forward esterification of carboxylic acids involving alcohol, through highly acidic or basic conditions.[5]

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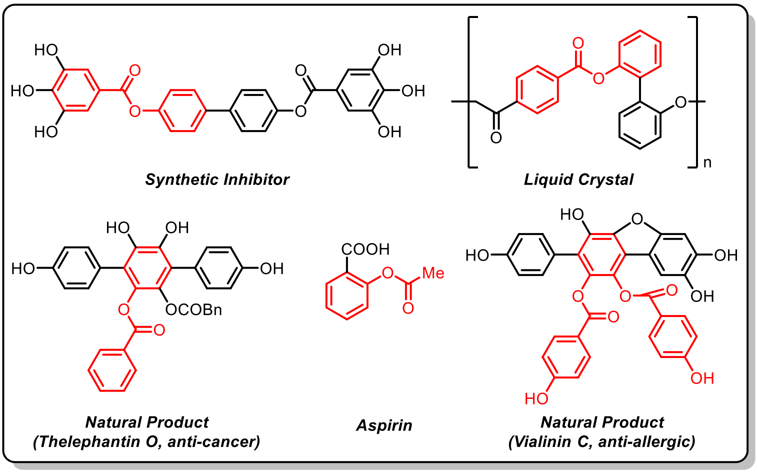
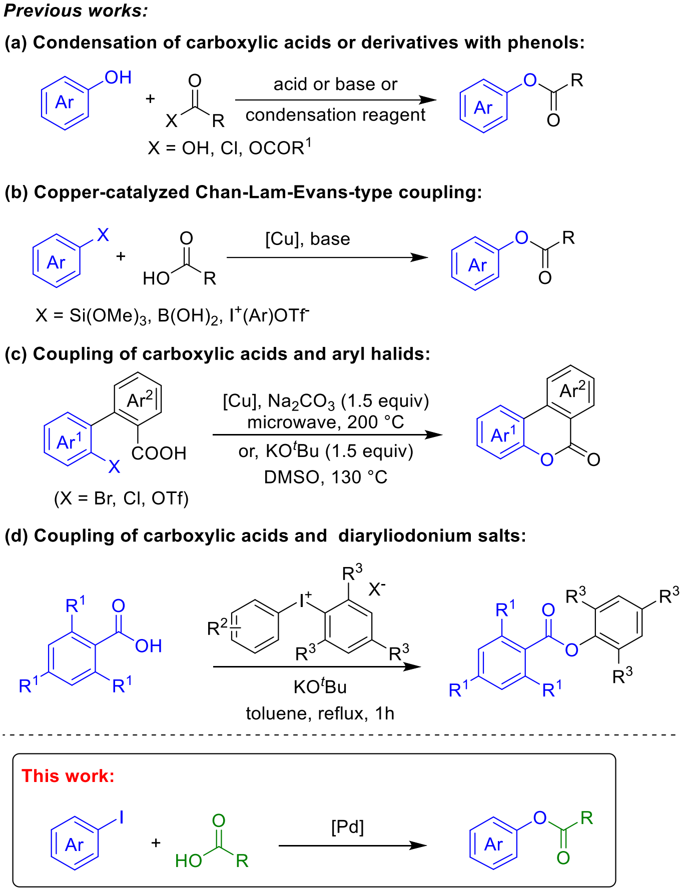


Figure 1: Representative example of esters

This conventional method leads to a few side reactions and restricted substrate scopes.[6] Usually, esterification reactions rely on pre-activation of carboxylic acids by transforming it into acyl chloride or mixed anhydride with the help of a stoichiometric amount of coupling reagents that make the process more expensive yet wasteful.[7] For a couple of years, metal-catalyst mediated, aryl coupling reaction utilising carboxylic acids as the *O*-nucleophiles has gained more importance as an alternative route.[8] In this context, the Chan–Lam–Evans-type reaction was employed using copper as a catalyst, for example, carboxylic acids have been coupled with different coupling partners such as aryl-substituted trimethoxysilanes,[9] aryl boronic acids[10] and diaryliodonium salts.[11] Notably, metal-free strategies have also been reported in affording aryl benzoates.[12] Little attention was paid to haloarenes as arylating agents[13] in constructing C_{aryl}–O_{acyl} bond to access aryl esters (Scheme 1). More attention is now being put towards developing such C–O bond formation which makes the method economical and environment friendly. An achievable solution involves a metal catalytic method using coupling between haloarenes and carboxylic acids. Considering the exceptional practicality, stability, and easy accessibility of aryliodides, they have been thoroughly examined as electrophilic arylation reagents in the construction of C–O bond.



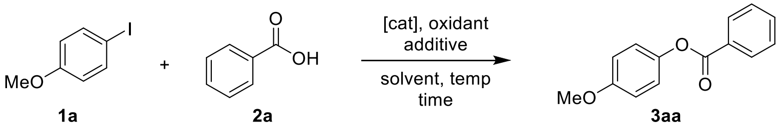
Scheme 1: Previous reports *vs*presentstrategy on the synthesis of aryl esters.

In regards to the focus on arylation Chemistry, particularly, using various haloarene precursors,[14] the scope for constructing the C–O bond of ester *via* a coupling reaction between carboxylic acids and aryl iodides (Scheme 1) was explored. Hence, in an attempt to establish a relatively green protocol, we examined the creation of a bond between carbon and oxygen (i.e. C_{aryl}–O_{acyl} bond) *via* coupling of iodoarenes with acids intermolecularly, under palladium catalysis. This concept was based on the grounds of established reports on the synthesis of ketones catalysed by palladium,[15] with the help of peroxide as an oxidant and a co-catalyst. Herein, the [Pd]-catalysed C–O bond formation between iodoarenes and benzoic acids has been described.

2. Result and Discussion

The screening investigation was initiated from benzoic acid **2a** and aryl iodide **1a** using palladium catalysis. A range of reaction conditions utilising palladium catalysis was examined and the out comes are depicted in Table 1. Thus, the reaction between aryl iodide **1a** and acid **2a,** with the help of $Pd(OAc)_2$ (5 mol%), Ag_2O (2 equiv), in aqueous TBHP (5 equiv) in DCE at 120 °C for 12 h. As predicted, the product **3aa** was isolated although in poor yield (Table 1, entry 1). However, other solvents such as toluene and DMSO could not help obtain the expected yield of **3aa** (Table 1, entries 2 & 3).

Table 1: Screening conditions for the synthesis of benzoate ester**3aa**.[a,b,c,d,e]



Entry[a]	Catalyst (5 mol %)	Co-catalyst (2 equiv)	Oxidant (5 equiv)	Temp (°C)	Additive (1 equiv)	Solvent (2 mL)	Time (h)	Yield **3aa**[b] (%)[c]
1	$Pd(OAc)_2$	Ag_2O	TBHP/ H_2O	120	–[e]	DCE	12	30
2	〃	〃	〃	〃	–[e]	toluene	12	25
3	〃	〃	〃	〃	–[e]	DMSO	12	32
4	〃	〃	〃	〃	–[e]	–[e]	**12**	**48**
5	〃	〃	H_2O_2 (30%)	〃	–[e]	–[e]	12	40
6	〃	〃	DTBP	〃	–[e]	–[e]	12	40
7	〃	〃	TBHP/ decane	〃	–[e]	–[e]	12	47
8	〃	〃	$(NH_4)_2S_2O_8$	〃	–[e]	DCE	12	0[d]
9	$Cu(OTf)_2$	〃	TBHP/ H_2O	〃	–[e]	–[e]	12	0[d]
10	CuI	〃	〃	〃	–[e]	DCE	12	0[d]
11	$NiBr_2$	〃	〃	〃	–[e]	–[e]	12	0[d]
12	$Pd_2(dba)_3$	〃	〃	〃	–[e]	–[e]	12	40
13	Pd(O	〃	〃	80	–[e]	–[e]	12	38

	Ac)$_2$							
14	"	$Cu(OAc)_2$	"	120	–^{e}	–^{e}	12	0^{d}
15	"	CuI	"	"	–^{e}	–^{e}	12	0^{d}
16	"	CH_3CO_2Ag	"	"	–^{e}	–^{e}	12	44
17	"	Ag_2O	"	"	–^{e}	–^{e}	24	47
18	"	"	"	"	$PhI(OA)_2$	DCE	12	0^{d}
19	"	"	"	"	^{t}BuOK	toluene	12	0^{d}
20	"	"	"	"	^{t}BuOK	DCE	12	0^{d}
21	"	"	"	"	TBAI	–^{e}	12	25
22	"	"	"	"	TBAI	DMSO	12	26
23	"	"	"	"	DMAP	–^{e}	12	15
24	"	"	"	"	$FeCl_3$	–^{e}	12	5
25	"	"	"	"	$ZnCl_2$	–^{e}	12	5
26	"	"	"	"	O_2 balloon	–^{e}	12	35
27	"	"	"	"	Et_3N	–^{e}	12	15
28	"	"	"	"	TEMPO	–^{e}	12	15
29	"	"	"	"	–^{e}	–^{e}	6	30
30	"	"	–^{e}	"	–^{e}	DCE	12	20
31	–^{e}	–^{e}	TBHP/H_2O	"	^{t}BuOK	"	12	0^{d}

[a] Reaction conditions: **1a** (100 mg, 0.43 mmol, 1 equiv), **2a** (103 mg, 0.86 mmol, 2 equiv), catalyst (5 mol%), co-catalyst (2 equiv), oxidant (5 equiv), additive (1 equiv), solvent (2 mL). [b] In**3aa** the first alphabet letter from iodoarene **1a**, second alphabet letter from benzoic acid **2a**. [c] Yields of pure products. [d] Starting material was recovered. [e] Reactions carried out without catalyst/co-catalyst/oxidant/additive/solvent.

On the other hand, when tried without using solvent and atthe same conditions, **3aa** was isolated in 48% yield (Table 1, entry 4). Other attempts under a series of conditions employing various oxidising agents such as TBHP in decane, DTBP, H_2O_2 (30%) and $(NH_4)_2S_2O_8$ were not beneficial (Table 1, entries 5 to 8). Similarly, different catalysts such as $Cu(OTf)_2$, CuI, $NiBr_2$ and $Pd_2(dba)_3$ were also proved to be ineffective (Table 1, entries 9 to 12). To check the influence of temperature, sticking to same reaction conditions as entry 4 of Table 1, the reaction was conducted at a slightly lower temperature (80 °C), however, could not raise the yield of the desired product **3aa** (Table 1, entry 13). On the other hand, other co-catalysts were also not useful (Table 1, entries 14 to 16). Further,increasing the duration of reaction to 24 h was also not of any use to improve the yield (Table 1, entry 17). Moving forward, utilising base ^{t}BuOK, hypervalent reagent PhI(OAc)$_2$, and nitrogen-based agents (TBAI & DMAP) showed no improvement (Table 1, entries 18 to 23). Using different transition metal-based agents such as $FeCl_3$ and $ZnCl_2$ as additives were also not effective (Table 1, entries 24 to 25). Further, using O_2 (balloon), Et_3N, TEMPO proved to not help in this context (Table 1, entries 26 to 28). The decrease in reaction time to 6 h (Table 1, entry 29) as well as the reaction exclusively with the [Pd]-catalyst, Ag_2O as a co-catalyst by eliminating the use of oxidant (Table 1, entry 30), could not show any improvement. While without [Pd]-catalyst did not show any progress of the reaction revealing the importance of pallidum catalyst to facilitate the reaction (Table 1, entry 31). Furthermore, it was observed that altering the equivalent of both reactants also had no positive influence on the yields of **3aa** (Table 2).

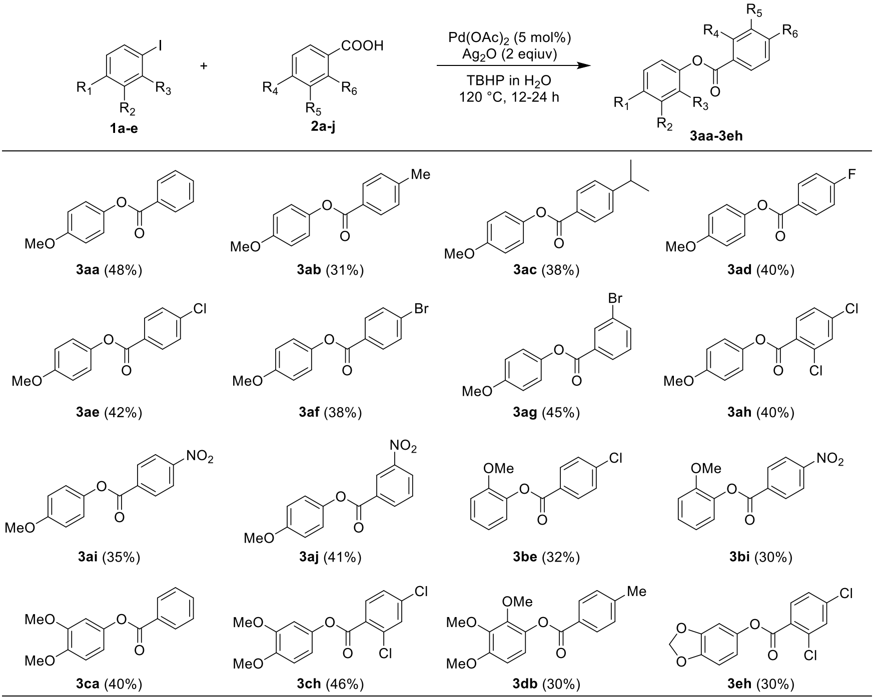
Table 2: Screening of substrates equivalents and co-catalyst.[a]

Entry	Benzoic acid **2a** (equiv)	Aryl iodide **1a** (equiv)	Ag_2O (equiv)	The yield of **3aa** (%)
1	1	3	1	40
2	3	1	1	41
3	**2**	**1**	**2**	**48**
4	1	3	2	47

[a]Remaining conditions are same as of entry 4 of Table 1.

Across the various reaction conditions examined, the one communicated in Table 1, entry 4 is the most suitable. With these conditions in hand, the scope of the method needed to be surveyed. Therefore, a range of carboxylic acids **2** was subjected to a coupling reaction with various iodoarenes **1**. As expected,the strategy enabled to deliver the desired benzoate ester products **3** (Table 3). Furthermore,the benzoic acids having *ortho*-substitution under went smoothly using the established conditions and furnished **3ah**, **3ch** & **3eh** inmoderate yields. Benzoic acids with alkyl substituents (**2b** & **2c**) were also smooth in delivering the products **3ab**, **3ac** and **3db**. Delightfully, benzoic acids with different halogens substituents (F, Cl, Br) other than iodine at different positions of the aromatic ring were also effective to generate the products (**3ad**-**3ag**) in moderate yields. Further, benzoic acids (**2i** & **2j**) bearing a strong electron-withdrawing nitro functionality were amenable and afforded the benzoate esters **3ai**, **3aj** and **3bi**. It is important to mention that the electron-rich iodoareneswere found suitable when compared to simple and electron-deficient iodoarene coupling partners (Table 3).

Table 3: Scope for the formation of various benzoate esters **3aa-eh**.[a,b]



3aa (48%) **3ab** (31%) **3ac** (38%) **3ad** (40%)

3ae (42%) **3af** (38%) **3ag** (45%) **3ah** (40%)

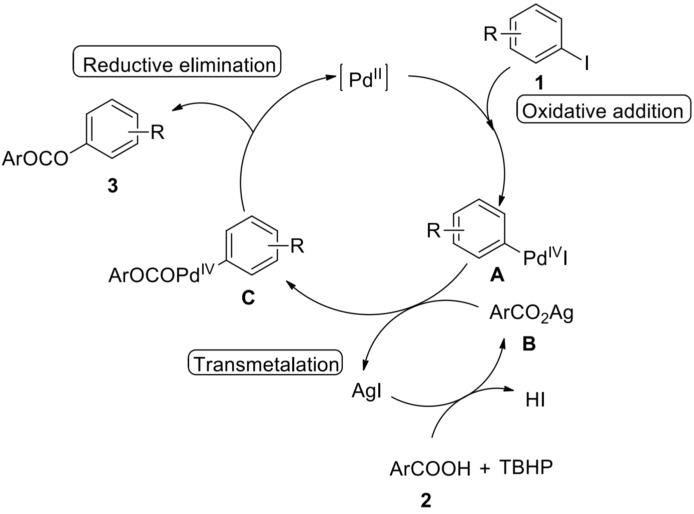
3ai (35%) **3aj** (41%) **3be** (32%) **3bi** (30%)

3ca (40%) **3ch** (46%) **3db** (30%) **3eh** (30%)

[a] All reactions conditions: **1a-e** (0.21 to 0.47 mmol, 1 equiv), **2a-j** (0.43 to 0.86 mmol, 2 equiv), $Pd(OAc)_2$ (3 to 5 mg, 5 mol%), Ag_2O (97 to 219 mg, 2 equiv), TBHP in H_2O (1 to 2.25 mL, 5 equiv), for 12 to 24 h at 120 °C. [b] Isolated yields of pure products of **3aa-3eh**.

3. Plausible mechanism

Though the exact mechanistic path is not very clear at this point of time, based on the literature background, an attempt was made to predict a plausible mechanism as depicted in Scheme 2. It was presumed that the reaction might have proceeds *via* Pd(II)/Pd(IV) species. Thus, primarily Pd(II)-catalyst could undergo oxidative addition with aryl iodide **1** and generates an aryl-Pd(IV) species **A**. on the other hand, carboxylic acid **2** would under go transmetalation with silver salt Ag_2O with the aid of the oxidant TBHP and forms **B**. Now, **B** could combine with **A** and yields the new Pd(IV) species **C**. Lastly, the palladium intermediate **C** can undergoes reductive elimination and furnishes the desired product **3** and regenerates the Pd(II) catalyst and thus concludes the catalytic cycle.



Scheme 2: A plausible mechanism for the formation of benzoate ester **3**.

4. Conclusion

In conclusion, simple palladium catalyzed protocol was established for the esterification of readily available aryl iodides with carboxylic acids. The strategy was able to deliver benzoate esters through C_{aryl}−O_{acyl} bond formation. This process was found to be effective with various functional groups to accesses various benzoate esters in moderate yields. Importantly, water in TBHP was served as the reaction medium.

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