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## Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

# Pd/C-Catalyzed methoxycarbonylation of aryl chlorides

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ARTICLE INFO	A B S T R A C T
Keywords: Carbonylation Aryl chlorides Methoxycarbonylation Esters Palladium catalyst	A new protocol for the methoxycarbonylation of aryl chlorides has been developed. Various methyl benzoates were produced in good to excellent yields. Several parameters are crucial for the success of this procedure: 1) the usage of LiOMe as the base or co-nucleophile which facilitate the carbonylative transformation; 2) employing Pd/C as the catalyst to prevent the palladium reduced by MeOH and subsequent agglomerate; 3) CO concentration, excessive CO concentration will directly lead to the termination of the reaction.

Since the seminal report from Heck and co-workers in 1974, palladium-catalyzed carbonylation has emerged as one of the most powerful methods for the synthesis of carbonyl-containing compounds [1,2]. For these carbonylative transformations of aryl halides, aryl chlorides are particularly attractive starting materials as they are nonexpensive and widely available [3]. However, relatively high dissociation energy of the C (sp<sup>2</sup>)-Cl bond (402, 339, and 272 kJ mol<sup>-1</sup> for PhCl, PhBr, and PhI, respectively, at 298 K) lead aryl chlorides more challenging substrates [4]. In addition, the coordination of CO to the metal center significantly reduced the electron density of the palladium complex which is one of the key factors for the oxidative addition step [5]. These reasons cause limited methods on aryl chloride carbonylation were developed compared with the other more expensive aryl halides (aryl iodides and aryl bromides).

In particular, there are even less procedures for the preparation of methyl benzoates from aryl chlorides been reported. In 1989, Osborn and co-workers reported their studies on the carbonylation of chlorobenzene and dichloromethane [6]. Palladium complexes were prepared by reacting [Pd(PCy<sub>3</sub>)<sub>2</sub>(dba)] with chlorobenzene or dichloromethane, and then carbonylated. The complex was also applied as catalyst in the presence of additional PCy<sub>3</sub> under 15 bar of CO at 180 °C, methyl benzoate was produced from chlorobenzene. In the same year, Milstein and co-workers developed a bulky and electron-rich bidentate phosphine ligand 1,3-bis(diisopropylphosphanyl)propane (dippp; air sensitive oil) and applied in carbonylative conversion of aryl chlorides [7]. Good yields of the desired esters, acids, and amides were produced at 150 °C. The corresponding Pd(dippp)<sub>2</sub> complex was prepared and applied as well. In 2001, Beller and co-workers reported an efficient catalytic system for the carbonylation of chloroarenes [8]. By employing ferrocene-based electron-rich bidentate bisphosphine ligand 1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane, chlorobenzenes were efficiently converted into esters, acids, or amides. Later on, they applied their *n*-butylbis(1-adamantyl)-phosphine (cata*CX*ium\* A) ligand in palladium-catalyzed alkoxycarbonylations of aryl chlorides with alkyl formats as well [9]. Recently, Jun and co-workers demonstrated a novel procedure on carbonylation of aryl chlorides. Interestingly, primary alcohols serve as both carbonyl source and nucleophiles in this protocol. In the case of methanol, three examples of methyl benzoates were produced in 22–37 % yields [10]. From our understanding, besides the challenges above discussed, the main reason for the limited reports on carbonylative synthesis of methyl benzoates from aryl chlorides might due to the fact that methanol can reduce palladium(II) precursors to Pd(0) easily which may agglomerate and become palladium black precipitates.

Herein, we report a new method for the methoxycarbonylation of aryl chlorides. In this procedure, the usage of LiOMe is important for the success of this transformation; and employing Pd/C as the catalyst to minimize the palladium catalyst been reduced by MeOH and agglomerate into inactively clusters (palladium black). Various aryl chlorides were effectively carbonylated under standard conditions.

Initially, the catalytic performance for the methoxycarbonylation of chlorobenzene was assessed by using several metal-based catalysts. To our delight, in the presence of DPPF (1,1'-bis(diphenylphosphino)ferrocene), NaF and LiOMe, a commercially available Pd/C catalyst afforded methoxycarbonylated product **2a** in excellent yield (Table 1, entry 1). Homogeneous palladium salts could only provide very low conversions, most likely because they were readily reduced and agglomerated into inactively clusters (palladium black was observed) in

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https://doi.org/10.1016/j.mcat.2020.111043

Received 20 April 2020; Received in revised form 22 May 2020; Accepted 25 May 2020 2468-8231/ © 2020 Elsevier B.V. All rights reserved.

Methoxycarbonylation of chlorobenzene under various cond	ditions <sup>a</sup> .
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$\bigcirc$	CI Catalyst + MeOH DPPF (5 m0%) base additive	O_Me			
Entry	7 Catalyst (mol% metal)	Base (equiv)	Additive	Conv. [%]	Yield [%] <sup>b</sup>
1	Pd/C (5)	LiOMe (2)	NaF	100	94
2	$PdCl_2$ (5)	LiOMe (2)	NaF	30	24
3	$Pd(OAc)_2$ (5)	LiOMe (2)	NaF	35	26
4	Pt/C (5)	LiOMe (2)	NaF	-	-
5	Rh/C (5)	LiOMe (2)	NaF	-	-
6	Pd/C (5)	NaOMe (2)	NaF	55	48
7	Pd/C (5)	NaO <sup>t</sup> Bu (2)	NaF	-	-
8	Pd/C (5)	LiO <sup>t</sup> Bu (2)	NaF	58	48
9	Pd/C (5)	LiCl (2)	NaF	-	-
10	Pd/C (5)	LiOMe (1)	NaF	89	81
11	Pd/C (5)	LiOMe (1)	$KHF_2$	76	66
12	Pd/C (5)	LiOMe (1)	KPF <sub>6</sub>	-	-
13	Pd/C (2.5)	LiOMe (2)	NaF	76	70
14	Pd/C (5)	LiOMe (2)	NaF	20	15 <sup>c</sup>

<sup>a</sup>Reaction conditions: PhCl (0.5 mmol), MeOH (5 mmol), DPPF (5 mol%), additive (1 mmol), catalyst, base, 1,4-dioxane (0.5 mL), under 1 bar CO and 5 bar N<sub>2</sub>, 150 °C, 24 h. <sup>b</sup>Yields and conversions determined by GC analysis with hexadecane as the internal standard. <sup>c</sup>The reaction was performed at 120 °C.

the presence of methanol (Table 1, entries 2-3). When applying related Pt/C or Rh/C as the catalyst, no desired product was formed under the identical reaction conditions (Table 1, entries 4-5), thus highlighting the specific high activity of Pd/C on this methoxycarbonylation reaction. The benefit of LiOMe for the methoxycarbonylation of chlorobenzene became obvious when compared with the other tested bases. When NaOMe or LiO<sup>t</sup>Bu was applied, the conversion and the yield of 2a was almost halved (Table 1, entries 6 and 8). However, changing the base to NaO<sup>t</sup>Bu or LiCl, no desired product could be detected (Table 1, entries 7 and 9). Subsequent attempts with different additives showed that NaF greatly contributed to the conversion and selectivity of the reaction (Table 1, entries 10-12). The reaction was conducted under reduced amount of palladium (2.5 mol% of catalyst) as well, and good yield of the desired product 2a can still be achieved (Table 1, entry 13). Notably, the yield of methyl benzoate decreased rapidly when we lowered the reaction temperature (Table 1, entry 14).

Next, under the optimized reaction conditions, a variety of aryl chlorides were explored for this methoxycarbonylation (Table 2). Various functional groups, such as trifluoromethyl (2b), ester (2c), cyano (2d, 2e) and acetyl (2f), can be well tolerated and gave the desired methoxycarbonylation products in good yields. Besides activated aryl chlorides, which were substituted by electron withdrawing groups, electron donating group substituted substrates can be effectively transformed as well. For example, methoxy substituted aryl chlorides could be carbonylated in good to excellent yields under identical conditions (2g, 2h and 2i). It's worth noting that, when a mixture of 1chloronaphthalene and 2-chloronaphthalene (85:15) was used, the corresponding products (2 j) were obtained in high yields with identical ratio as the substrates. Subsequently, methyl-substituted chlorobenzenes were tested (2k-2m), even ortho substituted substrate can gave the desired methoxycarbonylated product (2 m) in moderate vield. Finally, substrates containing heterocycles, including quinoline (2n), pyridines (2o-2q) and thiophene (2r) were all successfully transformed into the corresponding esters in moderate to good yields. 4-Chlorophenol and 2-chlorophenol were tested under our standard conditions as well, very low yield of the desired products was detected which might due to the consumption of LiOMe by the phenol group. Besides methanol, ethanol was tested as well. However, a mixture of methyl benzoate and ethyl benzoate was obtained with decreased overall yield.

To figure out the effect of each component and gain more insight into the reaction mechanism, control experiments were conducted

#### Table 2 Substrates soons of Pd/C astolyzed methowses



<sup>a</sup>Reactions were performed on a 0.5 mmol scale. Isolated yields. <sup>b</sup>1-Chloronaphthalene (85 %, with 15 % of 2-chloronaphthalene) was used. <sup>c</sup>The reaction was performed at 140  $^{\circ}$ C.

#### Table 3

Control	experiments	а
COLLUDI	experiments.	

CI +	Pd/C (6 mol%) DPPF (6 mol%)         Operation           MeOH         LiOMe (2 eq.)         Image: Comparison of the			
Entry	Variations from standard conditions above	Conv. [%]	Yield [%] <sup>b</sup>	
1	w/o Pd/C	-	-	
2	w/o DPPF	-	-	
3	Xantphos instead of DPPF	75	70	
4	w/o NaF	70	46	
5	w/o MeOH	80	50	
6	w/o LiOMe	30	17	
7	Anisole instead of PhCl	-	-	
8	6 bar $N_2$ instead of 1 bar CO and 5 bar $N_2$	-	-	
9	6 bar CO instead of 1 bar CO and 5 bar $\mathrm{N}_2$	-	-	

 $^{\rm a}Reactions$  were performed on a 0.5 mmol scale.  $^{\rm b}Yields$  and conversions were determined by GC analysis with hexadecane as the internal standard.

(Table 3). It's showed that Pd/C and the ligand were necessary for the reaction (Table 3, entries 1-3). In the absence of NaF, the reaction proceeds as well but with decreased efficiency (Table 3, entry 4) [10]. Subsequently, the reaction was performed in the absence of MeOH or LiOMe, respectively (Table 3, entries 5-6). The desired product can still be obtained in our cases. However, in the absence of LiOMe, the conversion and yield dropped significantly. Those results strongly suggest LiOMe acted both as a base and as a co-nucleophile, thereby facilitating an otherwise challenging transformation. Furthermore, no carbonylation product could be detected, when chlorobenzene was replaced by anisole (Table 3, entry 7). Meanwhile, CO gas atmosphere is crucial for this reaction (Table 3, entry 8). We found that the catalyst was deactivated when the CO pressure increased to 6 bar (Table 3, entry 9). This observation is consistent with the necessity of an open coordination site on the palladium center in an inner-sphere substrate activation step [5,11].

Base on the above results and previous reports [6,10,12], a plausible mechanism is proposed (Scheme 1). The reaction starts from an in situ



Scheme 1. Proposed reaction pathway.

generated palladium(0) complex A which was released from Pd/C and formed together with DPPF. After oxidative addition with aryl chlorides which might be activated by NaF [10], an organopalladium complex B will be formed which subsequently undergoes CO coordination and insertion to form complex C as the key intermediate. After attacked by MeOH or LiOMe, the final methyl benzoates will be eliminated and regenerate palladium(0) for the next catalytic cycle.

#### Conclusions

In conclusion, we have developed a new protocol for methoxycarbonylation of aryl chlorides under low pressure of CO. Electronrich, -neutral and -deficient substituted aryl chlorides were all successfully converted into the corresponding methyl benzoates in moderate to good yields. The critical innovation in this process was the use of LiOMe as the base and a co-nucleophile to facilitate the carbonylative transformation. Meanwhile, employing Pd/C as the catalyst can minimize the palladium catalyst been reduced by MeOH and agglomerated into inactively clusters. The control experiment shows the concentration of CO is critical for the reaction. Excessive CO concentration will directly lead to the termination of the reaction.

### **Declaration of Competing Interest**

We have no conflict of interest to declaration.

### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2020.111043.

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