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Palladium-Catalyzed Benzylation of Carboxylic Acids with Toluene via Benzylic C–H Activation

Hongqiang Liu, Guangfa Shi, Shulei Pan, Yuyu Jiang, and Yanghui Zhang*

Department of Chemistry, Tongji University, 1239 Siping Road, Shanghai, 200092,
P. R. China, and Key Laboratory of Yangtze River Water Environment,
Ministry of Education, Siping Road 1239, P. R. China

zhangyanghui@tongji.edu.cn

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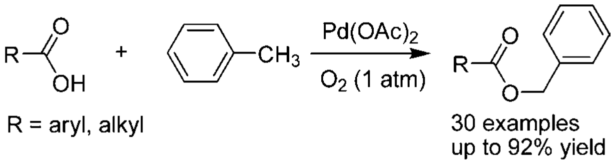
ABSTRACT



Direct benzylation of carboxylic acids with toluene has been developed via palladium-catalyzed C–H acyloxylation under 1 atm of oxygen. This reaction demonstrates good functional group tolerance and high yields, providing a facile, atom-economic, and efficient method for the synthesis of benzyl esters.

Direct C–H functionalization has gained considerable interest and has made noticeable progress in recent decades. A great number of novel organic reactions via C–H cleavage have been developed,[1] and a variety of chemical bonds can be formed through this efficient manner, including carbon–carbon[2] and carbon–heteroatom[3] bond formation. In this context, C–H acyloxylation has been investigated extensively. Since the discovery of Pd(II)-catalyzed acetoxylation of arenes with iodosyl acetate reported by Crabtree and co-workers,[4] iodosyl acetate has become an attractive acetoxylation reagent and a variety of C–H acetoxylation reactions with iodosyl acetate have been developed.[5] Concurrently, peroxide has also proven to be an effective promoter in Pd(II)-catalyzed C–H acetoxylation.[6] While these reactions are limited to acetoxylation, it is noted that direct acyloxylation of C–H bonds was realized with the assistance of directing groups recently.[7]

The benzyl group is a widely used protecting group for a range of functionalities including carboxyl groups. On the other hand, the benzyl ester is a very important functional group and ubiquitous in medicinal and natural organic molecules.[8] Although a variety of methods are available

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for the preparation of benzyl ester,[9] the most common way to introduce a benzyl group to a carboxyl group is the nucleophilic displacement of a carboxylate on benzyl bromide.[10] This reaction requires the use of toxic benzyl bromide and produces a stoicheometric amount of bromides as chemical waste. As such, it is attractive to develop more efficient and atom-economic benzylation methods. With the great advantages of C−H activation taken into consideration, direct C−H acyloxylation should be an intriguing solution to remedy the drawbacks of the traditional benzylation method. As early as the 1960s, $Pd(OAc)_2$-mediated benzylic acetoxylation of toluene in acetic acid was reported,[11] and the catalytic reaction was achieved in 1968.[12] Recently, the Jiang group described α-C−H acetoxylation of 2-alkylpyridines and 2-alkylpyrazines.[13] These reactions required the use of an excessive amount of acetic acid (normally as a solvent), which hampered the development of acyloxylation with nonvolatile carboxylic aicds. Intriguingly, the Khan group reported $NaBrO_3/NaHSO_3$-enabled benzylation of aromatic carboxylic acids with toluene.[14] Subsequently, the Yu group disclosed an efficient oxidative esterification of benzylic C−H bonds using tetrabutylammonium iodide as the catalyst and *tert*-butyl hydroperoxide as the co-oxidant.[15] For both of these two methods, the use of a stoichiometric amount of inorganic reagents is required. Herein, we describe a facile Pd(II)-catalyzed benzylation of carboxylic acids with toluene under 1 atm of oxygen (Figure 1).

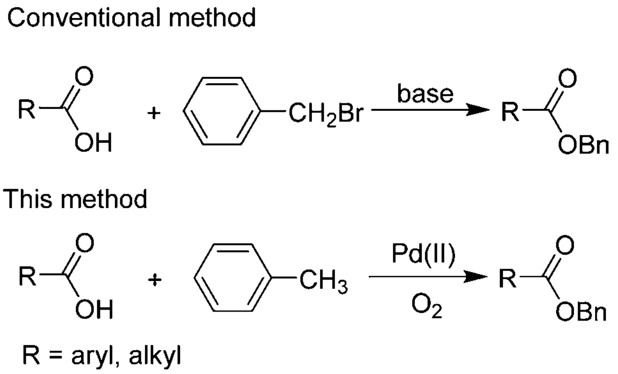
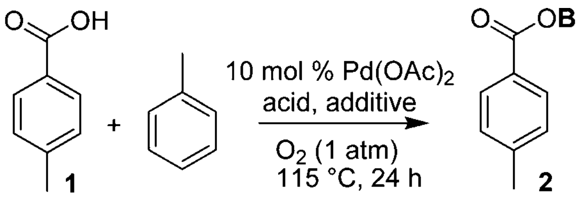


Figure 1. A new strategy for the benzylation of carboxylic acids.

Table 1. Survey of Reaction Conditions



entry	toluene (mL)	acid (0.1 equiv)	additive (1.0 equiv)	yield (%)[a]
1	1.5	none	none	25
2	1.5	none	DMF	24
3	1.5	none	DMSO	0
4	1.5	CF_3SO_3H	None	0
5	1.5	CF_3SO_3H	DMF	50
6	0.5	CF_3SO_3H	DMF	78
7	**0.5**	**CF_3SO_3H**	**DMA**	**88 (82[b])**
8	0.5	CF_3SO_3H	DMA	0[c]
9	0.5	CF_3SO_3H	DMA	0[d]

[a] The yields were determined by ^1H NMR analysis of crude products using $CHCl_2CHCl_2$ as the internal standard. [b] Isolated yield. [c] No $Pd(OAc)_2$. [d] $PdCl_2$ was used. DMF: *N*,*N*-dimethylformamide. DMA: *N*, *N*-dimethylacetamide.

The research was initiated by investigating the benzylation of *p*-toluic acid. As shown in Table 1, when 0.5 mmol of *p*-toluic acid was stirred with 10 mol % $Pd(OAc)_2$ in 1.5 mL of toluene under 1 atm of O_2 at 115 °C for 24 h, benzyl 4-methylbenzoate was observed, albeit in a low yield (25%). The addition of DMF failed to improve the yield, and the use of DMSO or trifluoromethanesulfonic acid suppressed the formation of the benzylation product. Gratefully, when a combination of DMF (1.0 equiv) and trifluoromethanesulfonic acid (10 mol %) was used, the yield increased to 50%. The yield was further improved to 78% when the amount of toluene was reduced to 0.5 mL. Finally, a good yield was obtained when DMA was used in place of DMF. In the absence of $Pd(OAc)_2$ or in the presence of $PdCl_2$ instead of $Pd(OAc)_2$, no benzylation products were observed.

The optimal conditions (0.5 mmol of carboxylic acid and 10 mol % $Pd(OAc)_2$ in the presence of 1.0 equiv of DMA and 10 mol % trifluoromethanesulfonic acid under 1 atm of O_2 in 0.5 mL of toluene at 115 °C for 24 h) proved to be compatible with a wide array of benzoic acids. While

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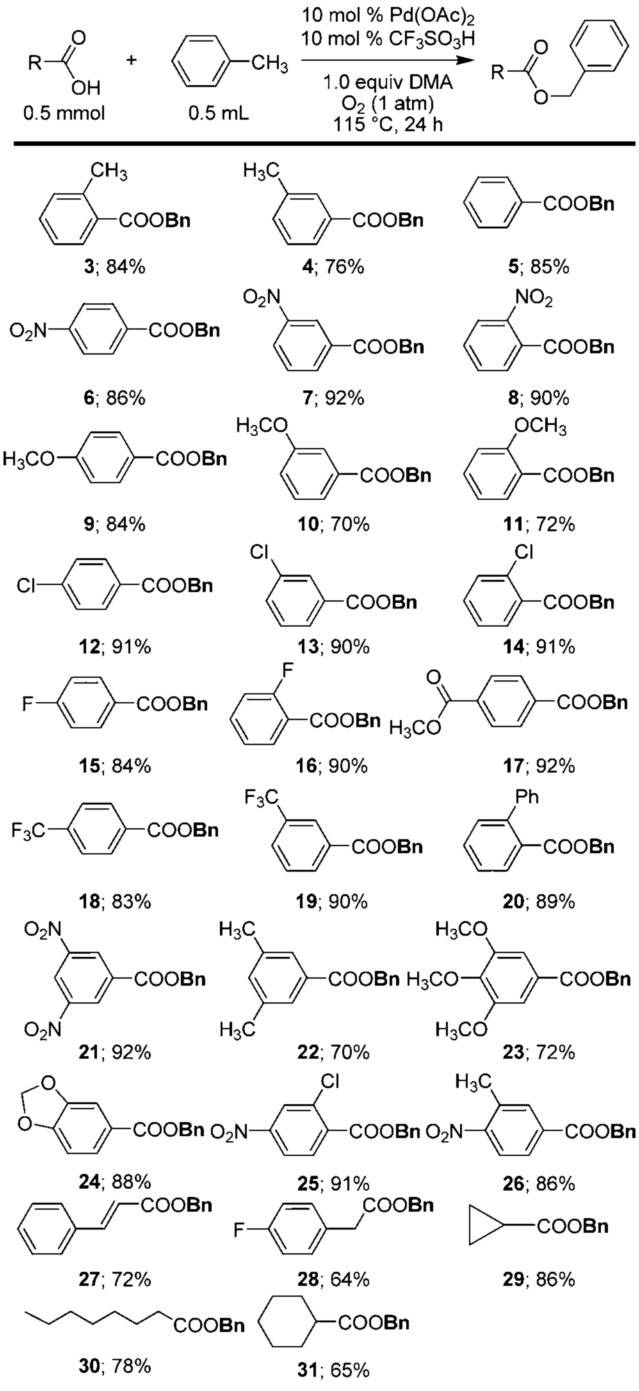
Scheme 1. Substrate Scope of Benzylation of Carboxylic Acids[a]



[a] Isolated yield.

o-toluic acid afforded the benzylation product in a similar yield to *p*-toluic acid, the yield decreased to 76% for *m*-toluic aicd. Both electron-withdrawing (**6** nitro and **18** trifluoromethyl) and electron-donating (**9**, methoxy) functionalities were tolerated, and *o*-, *p*-, and *m*-isomers were all compatible with the benzylation protocol. Chloro and fluoro groups were also well-tolerated, and the reactions furnished benzylation products in good yields. The reactions of benzoic acids with multiple substituents were also investigated. A variety of disubstituted benzoic acids proved to be reactive under the reaction conditions in good to excellent yields. Generally speaking, benzoic acids with electron-withdrawing groups were benzylated in higher yields than those with electron-donating groups.

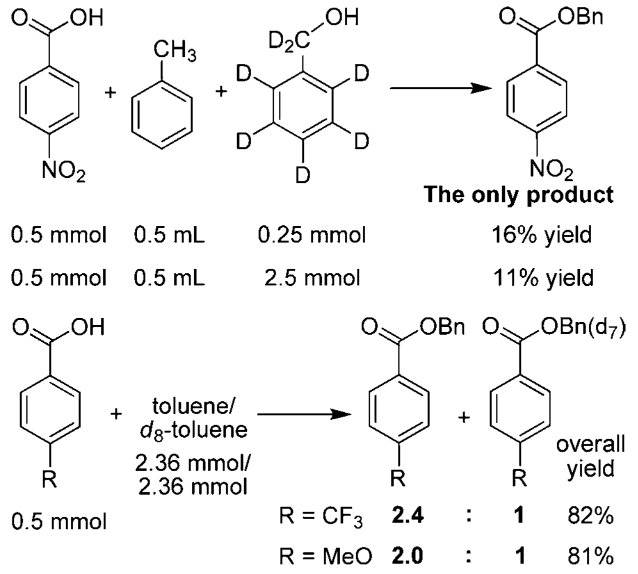


Figure 2. Preliminary mechanistic studies. Conditions: 10 mol % $Pd(OAc)_2$, 10 mol % CF_3SO_3H, 1.0 equiv of DMA, O_2 (1 atm), 115 °C, 24 h.

In addition to benzoic acids, other carboxylic acids are also found to be compatible with this benzylation protocol. As shown in Scheme 1, both cinnamic acid (**27**) and 2-(4-fluorophenyl)acetic acid (**28**) formed benzylation prodcuts in moderate yields. It is noted that aliphatic acids can be also benzylated under the conditions (**29**–**31**). While cyclopropanecarboxylic acid furnished the benzylation product in high yield, the yield for cyclohexanecarboxylic acid decreased to 65%.

To gain insight into the catalytic pathway of the benzylation reaction, we conducted some mechanistic experiments. It has been reported that toluene can be oxidized to benzyl alcohol,[16] which might react with carboxylic acids to form benzyl esters. To rule out this possibility, 0.5 or 5 equiv of deuterated benzyl alcohol was added to the reaction mixture of *p*-nitrobenzoic acid. For both of the reactions, the benzyl ester derived from deuterated benzyl alcohol was not observed and the yields decreased to 16% and 11% respectively, which provided evidence that the benzylation reaction does not proceed via a benzyl alcohol intermediate (Figure 2). Furthermore, isotope effect experiments were also conducted. Therefore, the reactions were run in a mixture of toluene and d_8-toluene of the same amount. The kinetic isotope effects were determined as 2.0 and 2.4 for 4-methoxybenzoic acid and

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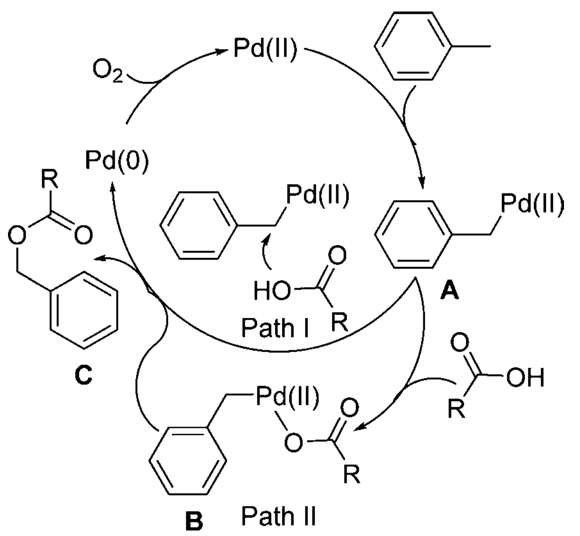

Figure 3. Proposed mechanism for the Pd-catalyzed benzylation of carboxylic acids.

4-trifluoromethylbenzoic acid respectively, which implies that C−H bond breaking was involved in the rate-determining step in this benzylation reaction (Figure 2). It has been reported that 1,2-diphenylethane may be formed in the reactions involving benzyl radicals.[17] In our reactions, 1,2-diphenylethane was not observed, which is against a benzyl radical mechanism. On the basis of these observations, a plausible mechanism was proposed as shown in Figure 3. Therefore, the catalytic cycle starts with Pd(II)-mediated C−H cleavage to form benzyl Pd(II) species **A**. The benzylation products may result from nucleophilic attack on the benzylic carbon by benzoate (Path I). Alternatively, **A** may undergo ligand exchange to afford benzyl Pd(II)carboxylate **B**, and subsequent reductive elimination yields benzylation product **C** (Path II). It should be noted that the carboxylate may coordinate with Pd(II) first, and the resulting Pd(II) carboxylate functions as the actual catalyst for C−H cleavage. In both Path I and II, a Pd(0) species is generated and is oxidized to Pd(II) by O_2 to continue the catalytic cycle. While the precise roles of DMA and CF_3SO_3H remain unclear, DMA may promote the reoxidation of Pd(0) by O_2 and may suppress Pd(0) aggregation,[18] and CF_3SO_3H might facilitate C−H bond cleavage by assisiting the formation of a cationic Pd(II) species.[19]

In summary, the current transition-metal-catalyzed C−H acyloxylation reactions either are restricted to acetoxylation or have to rely on the use of directing groups, so they are not applicable to the benzylation of regular carboxylic acid. To solve this problem, we developed a facile and efficient protocol for the benzylation of carboxylic acids via Pd-catalyzed C−H functionalization. The major advantages of this method include the use of toluene as the benzylation reagent and 1 atm of oxygen as the oxidant, which avoids the use of benzyl halides and reduces the production of chemical wastes. This Pd-catalyzed reaction demonstrates good functional group tolerance and high yields. Preliminary mechanistic studies suggest that this reaction proceeds via direct C−H acyloxylation. Further studies of this type of reaction and exploration of further applications are underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.