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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Palladium-Catalyzed Oxidative Carbonylation of Benzylic C−H Bonds via Nondirected C(sp^3)−H Activation

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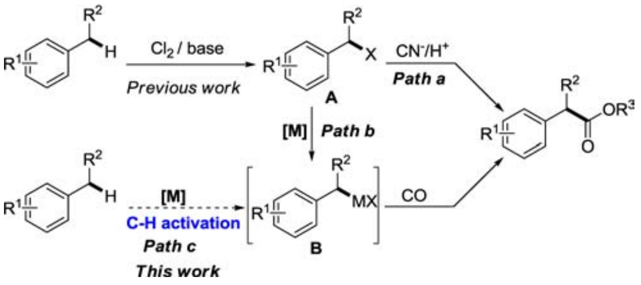
Ⓢ *Supporting Information*

ABSTRACT: A new strategy for generating benzylpalladium reactive species from toluenes via nondirected C(sp^3)−H activation has been developed. This led to construction of an efficient Pd-catalyzed reaction protocol for the oxidative carboxylation of benzylic C−H bonds to form substituted 2-phenylacetic acid esters and derivatives from inexpensive, commercially available starting materials.

Transition-metal-catalyzed carbonylation of organic halides or organic pseudohalides has long been recognized as a powerful approach to carboxylic acids and their derivatives.[1] Considerable effort has been devoted to broadening the scope of carbonylation precursors by the development of methods for direct carbonylation of other common functional groups. In this context, carbonylation of simple C−H bonds, a strategy involving transition-metal-catalyzed C−H bond activation[2] followed by carbonylation with CO, has received a lot of attention as a highly desirable and attractive approach for installing carbonyl functional groups on account of its high atom and step economy.[3] Although great progress has been made based on the directing-group-oriented carbonylation of C(sp^2)−H bonds pioneered by Fujiwara, Chatani, Orito, Yu, and others,[4] to the best of our knowledge only isolated examples have been demonstrated on the transition-metal-catalyzed activation of C(sp^3)−H bonds followed by carbonylation with CO.[5] As such, the direct activation of a simple C(sp^3)−H bond followed by carbonylation is still a great challenge.

Substituted 2-phenylacetic acids and their derivatives are important commodity chemicals, valuable synthetic building blocks for agrochemicals, and active pharmaceutical ingredients.[6] Traditional synthetic methods for those compounds mainly relied on the transformation of ArCHXR (**A**; X = halides, pseudohalides, or OH) through transition-metal-catalyzed carbonylation with CO or noncatalytic nucleophilic substitution with toxic NaCN, followed by hydrolysis with strong acids (Scheme 1, paths a and b); ArCHXR is usually prepared from the corresponding ArCH$_2$R, and harsh reaction conditions and stoichiometric amounts of bases are required.[7] In contrast, directed transformation of the simple ArCH$_2$R into the corresponding carboxylic acids or esters via transition-metal-catalyzed C−H carbonylation with CO is arguably a highly efficient and atom-economic method toward these compounds that would be highly desirable.

Scheme 1. Strategies toward Synthesis of 2-Phenylacetic Acid Derivatives



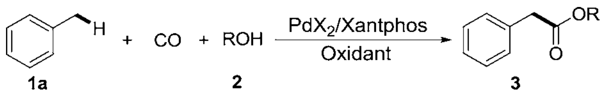
As a key intermediate for the traditional Pd-catalyzed carbonylation of ArCHXR, the benzylpalladium complex **B** is generally generated by the oxidative addition of ArCHXR to a Pd(0) complex, which is then reacted further with CO and other nucleophiles to complete the desired carbonylation process. Recent progress on transition-metal-catalyzed and radical-involved benzylic C−H functionalization[8] has prompted us to envision that such as an active species (**B**) might be generated via a single-electron-transfer (SET) process triggered by a free radical, since the oxidative addition can proceed via a radical mechanism.[9] Herein, we describe a novel Pd-catalyzed carbonylation of benzylic C−H bonds via nondirected C−H activation, providing an efficient approach to a series of 2-phenylacetic acid esters and their derivatives (Scheme 1, path c).

Initially, we explored the viability of the process with toluene (**1a**) and *n*-BuOH as substrates in the presence of 10 atm of CO. Several commercially available oxidants, such as di-*tert*-butyl peroxide (TBP), *tert*-butyl hydroperoxide (TBHP), $K_2S_2O_8$, and dicumyl peroxide (DCP), were screened as terminal oxidants. Pd complexes were screened as catalysts because of their excellent performance in traditional carbonylation reactions.[1] The carbonylation reaction of toluene, *n*-BuOH, TBP, and CO (10 atm) was carried out in the presence of Pd(Xantphos)Cl$_2$ (5 mol%, based on TBP; Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) at 120 °C for 16 h. As a result, the desired product **3aa**, together with a small amount of *tert*-butyl 2-phenylacetate, was obtained in 70% yield.[10] The product resulting from carbonylation of the C(sp^2)−H bond on the phenyl ring was not observed. This result indicated that the proposed oxidative C−H carbonylation

Received: April 16, 2012
Published: June 4, 2012

proceeded exclusively at the C(sp^3)−H bond. Encouraged by this result, we surveyed other oxidants, such as $K_2S_2O_8$, TBHP, *N*-fluorobenzenesulfonimide (NFSI), and DCP, and the results demonstrated that this reaction proceeded most efficiently when TBP served as the oxidant (Table 1, entry 1). With Xantphos as ligand, other Pd species, including $Pd(OAc)_2$, $Pd(dba)_2$, and $Pd(OTf)_2$, were then screened (Table 1, entries 5−7), with $PdCl_2$ being the most effective. Other commonly used metal salts, such as $Co_2(CO)_8$, Ni(II) salts, and Cu(II) salts, were ineffective as catalysts. Furthermore, in the absence of a Pd catalyst or in oxidant-free conditions, no carbonylation product was observed under otherwise identical conditions. Screening of other phosphine ligands revealed that Xantphos was the most effective ligand for delivering the desired product (see Supporting Information). The effects of temperature and pressure of CO on the carbonylation reaction were also investigated, and the best yield could be obtained when the reaction performed in the presence of 10 atm of CO at 120 °C. Further optimization of the reaction conditions demonstrated that the choice of alcohol is crucial for the success of the present catalytic reaction, and EtOH was identified as the optimum coupling partner (Table 1, entry 13).[11] To our satisfaction, when the catalyst loading was lowered from 5 to 2 mol%, the reaction still worked well and gave the same yield of the carbonylation product (Table 1, entry 13 vs 18).

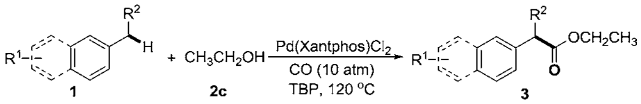
Table 1. Screening of Reaction Conditions[a]



entry	Pd species	oxidant	ROH	product, yield (%)[b]
1	$PdCl_2$	TBP	*n*-BuOH	**3aa**, 70
2	$PdCl_2$	$K_2S_2O_8$	*n*-BuOH	**3aa**, 8
3	$PdCl_2$	NFSI	*n*-BuOH	**3aa**, 20
4	$PdCl_2$	Ag_2O	*n*-BuOH	**3aa**, NR
5	$Pd(OAc)_2$	TBP	*n*-BuOH	**3aa**, 9
6	$Pd(dba)_2$	TBP	*n*-BuOH	**3aa**, 30
7	$Pd(OTf)_2$	TBP	*n*-BuOH	**3aa**, 39
8[c]	$PdCl_2$	TBP	*n*-BuOH	**3aa**, 54
9[d]	$PdCl_2$	TBP	*n*-BuOH	**3aa**, 64
10[e]	$PdCl_2$	TBP	*n*-BuOH	**3aa**, 47
11[f]	$PdCl_2$	TBP	*n*-BuOH	**3aa**, 46
12	$PdCl_2$	TBP	MeOH	**3ab**, 69 (66)
13	$PdCl_2$	TBP	EtOH	**3ac**, 81 (76)
14	$PdCl_2$	TBP	*n*-PrOH	**3ad**, 70 (63)
15	$PdCl_2$	TBP	*i*-PrOH	**3ae**, 54
16	$PdCl_2$	TBP	*i*-BuOH	**3af**, 55
17	$PdCl_2$	TBP	*t*-BuOH	**3ag**, 36
18[g]	$PdCl_2$	TBP	EtOH	**3ac**, 80 (74)
19[h]	$PdCl_2$	TBP	EtOH	**3ac**, 62

[a] Reaction conditions: **1a** (15 mmol), **2** (1 mmol), oxidant (0.5 mmol), PdX_2 (5 mol% based on oxidant), Xantphos (5 mol% based on oxidant), 16 h. [b] Yields were determined by GC analysis relative to the oxidant, with *n*-dodecane as internal standard (isolated yield in parentheses). [c] CO (5 atm). [d] CO (20 atm). [e] 100 °C instead of 120 °C. [f] 140 °C instead of 120 °C. [g] $Pd(Xantphos)Cl_2$ (2 mol%). [h] $Pd(Xantphos)Cl_2$ (1 mol%).

Table 2. Scope of Pd-Catalyzed Oxidative Benzylic Carbonylation[a]



entry	R^1, R^2	product, yield (%)[a,c]	TON[b]
1	H, H	**3ac**, 74	288
2	2-Me, H	**3bc**, 70	275
3	3-Me, H	**3cc**, 71	232
4	4-Me, H	**3dc**, 68	280
5	3,5-diMe, H	**3ec**, 67	249
6	4-MeO, H	**3fc**, 66	250
7	4-EtO, H	**3gc**, 59	250
8	4-*n*-PrO, H	**3hc**, 65	236
9	4-*n*-BuO, H	**3ic**, 59	220
10	4-*n*-HexO, H	**3jc**, 55	190
11[d]	4-Ph, H	**3kc**, 63	220
12	4-F, H	**3lc**, 63	239
13	2-Cl, H	**3mc**, 69	230
14	3-Cl, H	**3nc**, 70	205
15	4-Cl, H	**3oc**, 68	265
16	4-Br, H	**3pc**, 50	200
17	2,6-Cl_2, H	**3qc**, 41	139
18	4-Ac, H	**3rc**, 44	145
19	1-naphthyl, H	**3sc**, 53	178
20	2-naphthyl, H	**3tc**, 46	170
21[e]	H, Me	**3uc**, 26	82

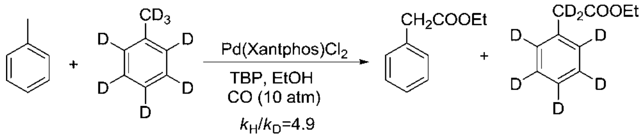
[a] Condition A: **1** (15 mmol), **2c** (1 mmol), TBP (0.5 mmol), $Pd(Xantphos)Cl_2$ (0.01 mol), CO (10 atm) at 120 °C for 16 h. [b] Condition B: **1** (15 mmol), **2c** (4 mmol), TBP (3 mmol), $Pd(Xantphos)Cl_2$ (0.005 mmol), CO (10 atm) at 120 °C for 18 h. [c] Isolated yield based on TBP; 2−5% corresponding *tert*-butyl ester was observed in all cases. [d] **1k** (10 mmol) in 1 mL of benzene. [e] CO (30 atm).

With the optimized conditions in hand, the substrate scope was explored at 120 °C under 10 atm of CO using 2 mol% of $Pd(Xantphos)Cl_2$ as the catalyst and TBP as the oxidant. As summarized in Table 2, electron-donating groups such as methyl and alkoxyl groups on any position of the phenyl ring favored the reaction, providing corresponding substituted ethyl 2-phenylacetate in moderate to good yields (Table 2, entries 2−10). Substrates **1b**−**1e**, with multiple potentially reactive benzylic methyl groups, could only produce the monocarbonylation products (Table 2, entries 2−5). With benzene as solvent, the solid substrate 4-methylbiphenyl (**1k**) could also be transformed into the corresponding product **3kc** in 63% yield (Table 2, entry 11). Furthermore, substrates with electron-withdrawing groups such as F, Cl, and acetyl group on the ortho-, meta-, and para-positions of the phenyl ring were effective under the standard conditions (Table 2, entries 12−15 and 18). The bromide-containing substrate **2p** was also suitable for this carbonylation, giving the desired ester **3pc** in 50% yield, although a small amount of methyl 4-methylbenzoate was observed. A slight steric hindrance effect on the reactivity was observed, which was demonstrated by the reactivy of 2,6-dichlorotoluene (Table 2, entry 17, 41% yield). 1- and 2-methylnaphthalene could also participate in the oxidative C−H carbonylation reaction to give the corresponding products in 53% and 46% yields, respectively (Table 2, entries 19 and 20). In addition, ethylbenzene was also successfully employed for the reaction at higher CO pressure, and the corresponding product was obtained in 26% yield (Table 2, entry 21).

To further demonstrate the usefulness of this transformation, a modified procedure (condition B) with lower catalyst loading was developed, which increased the practicality of the reaction process dramatically. In the modified reaction conditions, the catalyst loading was lowered from 2 to 0.167 mol% (based on the oxidant TBP, S/C = 600) and the reaction time was prolonged to 18 h; the product **3ac** was obtained in 48% yield with a turnover number (TON) of 288 (Table 2, entry 1). Other substrates were also subjected to this procedure, and high TONs were observed for almost all of the substituted toluenes (Table 2, entries 1−18). 1- and 2-methylnaphthalene also proved to be good substrates for this transformation under the same conditions, generating adducts **3sc** and **3tc** with TON = 178 and 170, respectively (Table 2, entries 19 and 20). Finally, for the substrate **1u**, TON = 82 could also be achieved when the reaction was conducted in the presence of 30 atm of CO (Table 2, entry 21). Compared to other reported Pd-catalyzed C−H carbonylation reactions (TON < 40), our catalytic system is much more efficient.[4,5]

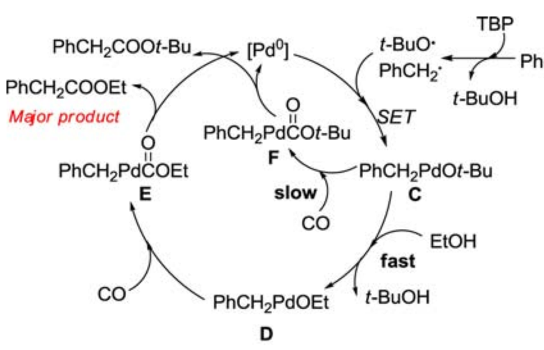
To gain some insight into the mechanism of the present C−H carbonylation reaction, some control experiments were conducted under the standard reaction conditions. Radical scavengers, such as TEMPO and 1,1-diphenylethylene, were employed in the standard reaction, and no desired carbonylation product was detected. This result suggested that a free radical process was involved in the present oxidative C−H carbonylation reaction. Moreover, kinetic isotope effect experiments were carried out under the standard conditions (Scheme 2, see Supporting Information). The observed significant isotopic effects (k_H/k_D = 4.9) indicated that the benzylic C−H bond cleavage step occurs before the rate-limiting step or might be involved in the rate-limiting step of this transformation.

Scheme 2. Kinetic Isotope Effect Experiment



Although the mechanistic details of this transformation are not clear at the moment, on the basis of the results we obtained here and previously,[1] a plausible mechanism for the present process can be proposed as shown in Scheme 3. In this scenario, homolytic cleavage of the TBP produces two alkoxyl radical intermediates, one of which abstracts a benzylic hydrogen atom from the substrate to give the benzyl radical. In the presence of ligands, sequential oxidation of Pd(0) with the two radicals step by step through the SET reaction[9] provides the benzylpalladium complex **C**.[12] Due to the steric hindrance of complex **C**, intermediate **F** is formed slowly through CO insertion,[13] which leads exclusively to the less hindered intermediate **D** through an anion-exchange process.[14] Subsequent CO insertion forms the intermediate **E**, which undergoes reductive elimination to afford the final carbonylation product along with regeneration of the active Pd species for the next catalytic cycle. The corresponding *tert*-butyl ester might also be produced as a minor product through the intermediate **F**.

Scheme 3. Proposed Reaction Mechanism



Ligand was omitted for clarity

In summary, we have succeeded in developing an efficient Pd-catalyzed carbonylation of benzylic C−H bonds with CO through nondirected C(sp^3)−H bond activation. This carbonylation process represents a practical and efficient methodology for the synthesis of substituted phenylacetic acid esters from simple toluenes. The new strategy for generation of such a benzylpalladium intermediate should pave the way to some new classes of C−H functionalization reactions, complementary to the classical synthetic methods with organic halides. Ongoing work seeks to gain a detailed mechanistic understanding of this reaction, and applications of this C−H bond activation strategy in other C−H functionalization reactions are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Chinese Academy of Sciences, the National Natural Science Foundation of China (21172226 and 21133011).

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(10) A small amount of 1,2-diphenylethane (ca. 2% yield based on TBP) resulted from oxidative homocoupling of toluene.

(11) In the absence of other alcohols, only 12% *tert*-butyl 2-phenylacetate **3ag** was obtained.

(12) ESI-MS studies indicated that the benzylpalladium complexes **C** and **D** were formed; for details, see Supporting Information.

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