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# Metal-Free Aerobic Oxidative C–O Coupling of C(*sp*<sup>3</sup>)–H with Carboxylic Acids Catalyzed by DDQ/*tert*-Butyl nitrite

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**Abstract:** The formation of C–O bond is one of the hot topics in the area of  $C(sp^3)$ –H bond functionalization. A metal-free oxidative cross-coupling between benzylic  $C(sp^3)$ –H bond and carboxylic acids has been developed. The reactions were performed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the catalyst, *tert*-butyl nitrite (TBN) as the co-catalyst, and molecular oxygen as the terminal oxidant. A variety of diarylmethanes could successfully couple with various carboxylic acids to obtain diarylmethanol esters in good to excellent yields. In addition, 2-benzylbenzoic acids could be converted into phthalides in moderate yields via intramolecular oxidative cyclization.

#### Introduction

Direct C-H bond functionalization is a powerful and robust strategy in organic synthesis. Simple raw materials with C-H bond can be directly converted into more valuable products through carbon-carbon (C-C) bond or carbon-heteroatom (C-X) bond formations.<sup>[1]</sup> During the past several years, the C-H bond functionalization has made great progress through the way of oxidative cross-coupling.<sup>[2]</sup> While most of the C-H bond functionalization reactions are catalyzed by the transition metals,<sup>[3]</sup> such as Cu, Ni, Fe, Ru, Pd, etc. Unfortunately, these methods are always unable to avoid metal residue, especially in the pharmaceutical industry. With the merits of metal-free and mild reaction conditions, organocatalysis has become a new strategy for the formation of C-C/C-X bonds.<sup>[4]</sup>

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) <sup>[5]</sup> is a powerful oxidant which has been successfully employed in many C-H bond functionalizations including  $C(sp^3)$ -H oxidation to form C=O bond <sup>[6]</sup>, and oxidative coupling of  $C(sp^3)$ -H to form C-C,<sup>[7]</sup> C-N,<sup>[8]</sup> C-O,<sup>[9]</sup> C-P<sup>[10]</sup> bonds and et al. This is mainly attributed to its single electron transfer (SET) ability and hydrogen abstraction capacity.<sup>[11]</sup> Most of these reactions require stoichiometric DDQ or a combination of catalytic amount of DDQ and a stoichiometric metal oxidant (MnO<sub>2</sub>).<sup>[7d,9d]</sup> As we known, molecular oxygen (O<sub>2</sub> or air) is considered as an ideal oxidant due to its economic and green characteristics with the sole by-product H<sub>2</sub>O after oxidation. However, it is difficult for triplet

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molecular oxygen to oxidize common singlet organic compounds directly.<sup>[12]</sup> To clear up the high energy barrier between molecular oxygen and organic substrates, a practical way is to construct an aerobic oxidation system with a catalyst combination of DDQ and a co-catalyst. Prabhu *et al* reported the aerobic oxidation system DDQ/AIBN/O<sub>2</sub>, which was applied to oxidative C-C coupling.<sup>[13]</sup> Our group has also developed an efficient oxidation system DDQ/*tert*-butylnitrite (TBN)/O<sub>2</sub>,<sup>[14]</sup> and this oxidation system has been successfully used for oxidation of C(*sp*<sup>3</sup>)–H bond <sup>[15]</sup> and oxidative C-N coupling.<sup>[16]</sup> These strategies have significant economic and environmental benefits due to the use of catalytic amount of DDQ and the natural abundance of molecular oxygen.



Scheme 1. Aerobic oxidative C–O coupling of benzylic  $C(\mathit{sp}^3)\text{-}H$  bonds with carboxylic acids.

Diarylmethanol esters are an important class of organic molecules which can be served as pharmaceutical precursors and functional molecules,<sup>[17]</sup> and they could be hydrolyzed into diarylmethanols which are also important pharmaceutical substructures.<sup>[18]</sup> Although some examples of oxidative C–O coupling reactions with benzylic  $C(sp^3)$ –H bond have been reported for synthesis of diarylmethanol esters and other compounds,<sup>[9,19]</sup> to the best of our knowledge, there is no report of metal-free oxidative C–O coupling with molecular oxygen as the terminal oxidant.

Inspired by the aforementioned works and our previous works, herein we report a DDQ/TBN-catalyzed aerobic oxidative C–O coupling of  $C(sp^3)$ –H with carboxylic acids (Scheme 1).

#### **Results and Discussion**

We set out to evaluate reaction parameters with the coupling of diphenylmethane (1a) and AcOH (2a) to form benzhydryl acetate (3aa) as the model reaction (Table 1). Diphenylmethanone is the

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Table 1. Optimization of the Reaction Conditions.         [a]									
	Ph	<sup>_</sup> ₽b + HO4	DDQ/TE	BN	OAc (				
	F 11		O <sub>2</sub> (0.1MPa)	, HEAT Ph	Ph Ph	`Ph			
	1	a 2a		3	aa by-pr	oduct			
Entry	Solvent	T (°C)	DDQ (mol%)	TBN (mol%)	AcOH (equiv)	Conv. <sup>[b]</sup> (%)	Yield <sup>[c]</sup> (%)		
1	Toluene	100	20	20	5	8	5		
2	EtOH	100	20	20	5	N.R.	-		
3	THF	100	20	20	5	N.R.	-		
4	AcOH	100	20	20		72	70 (67)		
5	PhCl	100	20	20	5	96	84 (81)		
6	DCE	100	20	20	5	98	96 (92)		
7	DCE	80	20	20	5	69	65		
8	DCE	60	20	20	5	3	3		
9	DCE	100	10	20	5	71	61		
10	DCE	100	-	20	5	7	0		
11	DCE	100	20	10	5	70	66		
12	DCE	100	20	-	5	13	13		
13	DCE	100		-	5	N.R.	-		
14	DCE	100	20	20	3	97	82 (77)		
15	DCE	100	20	20	1	90	70 (64)		
16 <sup>[d]</sup>	DCE	rt 🔶	20	20	5	92	78		

[a] Reaction conditions: **1a** (0.5 mmol), **2a**, DDQ, TBN, solvent (4.0 mL), O<sub>2</sub> (0.1 Mpa),36 h. [b] Determined by GC with area normalization method. [c] GC yields (the data in the parenthesis are isolated yields). [d] Photooxygenation conditions: **1a** (0.5 mmol), **2a** (2.5 mmol), DDQ and TBN, DCE (4.0 mL), 18 W blue LED, O<sub>2</sub> (0.1 Mpa), rt, reaction time 36 h.

sole by-product in this oxidative cross-coupling reaction. The reaction of **1a** and **2a** (5 equiv) was performed with DDQ (20 mol%) and TBN (20 mol%) in the solution of toluene under 0.1 MPa of oxygen at 100 °C. After 36 h, the conversion of **1a** was only 8% and the GC yield of **3aa** was only 5% (Table 1, entry 1). In polar solvent EtOH and THF, the oxidative C-O coupling reaction was obviously inhibited (Table 1, entries 2 and 3). When acetic acid was used as both solvent and reactant, 72% conversion of **1a** and 67% isolated yield of **3aa** could be obtained (Table 1, entry 4). To our delight, when the reaction was performed in chlorobenzene and 1,2-dichloroethane (DCE), the conversion of **1a** was higher than 95% (Table 1, entries 5 and 6). Especially in DCE, 92% isolated yield of **3aa** could be achieved.

Then the reaction temperature was tested. Decreasing the reaction temperature from 100  $^{\circ}$ C to 60  $^{\circ}$ C led to lower conversions (Table 1, entries 7 and 8). Later on, the loadings of

DDQ, TBN and AcOH were further examined. When the loading of DDQ was reduced to 10 mol%, the conversion of 1a was decreased to 71% (Table 1, entry 9). When DDQ was completely removed, the conversion of 1a is only 7% and no 3aa was detected (Table 1, entry 10). Similarly, decreasing the loading of TBN to 10 mol% led to 70% conversion of 1a; and when TBN was completely removed, 3aa could be obtained in 13% GC yield (Table1, entries 11 and 12). Then the oxidative coupling reaction was performed in the absence of DDQ and TBN, as we expected, no reaction took place (Table 1, entry 13). Notably, reducing the loading of AcOH from 5 equiv led to a lower yield of 3aa although the conversion of 1a was still relatively high (Table 1, entries 14 and 15). It could be found that as the amount of AcOH decreased, the by-product benzophenone increased. At last, we tried the photocatalytic strategy, but the selectivity to 3aa was not as good as that of thermal method (Table 1, entry 16).

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Upon exploring the general applicability of this protocol, the oxidative C-O coupling of a number of diarylmethanes 1 with 2a were investigated under the optimal reaction conditions (Scheme 2). The results in Scheme 2 demonstrated the yields of desired diarylmethyl acetates to be good to excellent. This C-O bond coupling reaction was compatible with different functional groups including electron-donating groups and electrowithdrawing groups. Substrate 1b containing o-methyl reacted smoothly with 2a to give the corresponding phenyl(o-tolyl)methyl acetate (3ba) in 91% isolated yield. It is clear that the reactivities of diphenylmethanes bearing an electro-donating group (mmethyl, p-methyl, m-methoxy, p-methoxy or p-tert-butyl) were improved. The required reaction time was shortened to less than 15 h, and the isolated yields of 3ca-3ga were 88-94%. When diphenylmethanes with an electron-withdrawing group (p-F and p- CI) were used as the substrates, higher loadings of catalysts

(30 mol% DDQ and 30 mol% TBN) were required, also a longer reaction time (48 h) was needed. Nevertheless, the isolated yields of the corresponding esters 3ha and 3ia were still excellent (90% and 87%). The C-O bond coupling reaction of 2a with multi-substituted diphenylmethane 1j containing methyl and methoxy should performed at room temperature with 2a as the solvent, and 86% isolated yield of 3ja could be obtained. Moreover, diphenylmethanes bearing both electron-donating and electron-withdrawing substituents could react efficiently with 2a, and afforded their corresponding esters 3ka-3ma in 85-88% isolated yields. Polycyclic aromatic substrates 1n-1r could also be converted into their corresponding products 3na-3ra in 84-95% isolated yields. Lower temperature (80 °C) and less amounts of DDQ (10 mol%) and TBN (10 mol%) were needed in the coupling of 1-(4-methoxybenzyl)naphthalene (10) with 2a. Substrate 1s containing a heterocyclic thiophene was also explored, the product **3sa** could be obtained in 81% isolated yield. However, the presence of strong electron-withdrawing group (4-CN and 4-NO<sub>2</sub>) on diphenylmethane would hinder the reaction. The isolated yield of (4-cyanophenyl)(phenyl)methyl acetate (3ta) was only 20%, and (4-nitrophenyl)(phenyl)methyl acetate (3ua) could not be obtained in the reaction.





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Next, we tried to investigated DDQ/TBN-catalyzed aerobic oxidative C-O coupling of diphenylmethanes with various carboxylic acids (Scheme 3). Initially, some common carboxylic acids, including isobutyric acid (2b), benzoic acid (2c), cyclohexanecarboxylic acid (2d), and *p*-tolylacetic acid (2e), successfully coupled with diphenylmethanes (1a and 1d) in 61-91% isolated yields (3ab-3de). It is obvious that the yields of diphenylmethanes and the acidity of carboxylic acids. When the low-activity 1a coupled with 2c, it was difficult to achieve high yield of 3ac. Then heteroaromatic acid (thiophene-3-carboxylic acid 2f) and cinnamic acid (2g) were submitted to couple with 1d, the isolated yields of 83% (3df) and 82% (3dg) were also satisfactory.



In order to examine the practicability of this aerobic oxidative C-O coupling reaction, gram-scale reaction was performed under the optimized conditions (6 mmol of 1-benzyl-4-methoxybenzene (1f)). The corresponding product 3fa could be isolated in 90% yield [Eq. (1)].



According to above results, the metal-free DDQ/TBN catalytic system exhibited a strong catalytic ability in intermolecular oxidative cross-coupling between benzylic  $C(sp^3)$ -H bond and carboxylic acid. We turned our attention to intramolecular oxidative cyclization of 2-benzylbenzoic acids (Scheme 4). Phthalides have great potential in pharmaceutical and biological application, and have been used from academic to industry.<sup>[20]</sup> Varieties synthetic methods of phthalides have been reported, such as reduction of phthalic anhydrides or phthalaldehydic acids, coupling of phthalaldehyde and arylboronic acids, and photocyclization.<sup>[21]</sup> When we explore this DDQ/TBN catalytic

system for the intramolecular oxidative cyclization of 2benzylbenzoic acids, 40-51% isolated yields of phthalides (**5a-5d**) were obtained. According to our previous research work and the experimental results, we believed that H<sub>2</sub>O produced in the reaction could react with the intermediates (diphenylmethyliums) to form by-products. Hence, stoichiometric DDQ was used in order to reduce the effect of H<sub>2</sub>O. The results in Scheme 5 demonstrated that the isolated yields of the oxidative cyclization products have been significantly improved (66-76%). Although only moderate yields of phthalides can be obtained, this DDQmediated oxidative lactonization of 2-benzylbenzoic acids strategy still has application value in the synthesis of pharmaceutical intermediates.



Evidence for a radical pathway was obtained by performing the aerobic oxidative C-O coupling of **1a** with **2a** in the presence of excess TEMPO (2 equiv.) as a radical scavenger [E1. (2)]. In this case, no reaction was observed, suggesting that a radical mechanism was plausible (Scheme 5). In the DDQ/TBN/O<sub>2</sub> system, DDQ is employed as the main catalyst, oxygen as the terminal oxidant, and TBN as the co-catalyst which serves as an equivalent of nitric oxide.<sup>[22]</sup> The reaction of **1a** and DDQ generates alkyl radical (I) and DDQH<sup>-</sup> via hydrogen atom transfer (HAT). Subsequent single electron transfer (SET) led to diphenylmethylium (II) and DDQH<sup>-</sup>.<sup>[9a]</sup> The cation II can react with AcOH (**2a**) to give the corresponding product **3aa**. Meanwhile, DDQH<sup>-</sup> is protonated to the hydroquinone DDQH<sub>2</sub>, which could be re-oxidized to DDQ by NO<sub>2</sub>.



Scheme 5. Plausible reaction mechanism.

#### Conclusions

In summary, we have developed a metal-free aerobic oxidative cross-coupling between benzylic  $C(sp^3)$ -H bond and carboxylic acids catalyzed by DDQ/TBN. A range of diarylmethanes could successfully couple with various carboxylic acids, and diarylmethanol esters could be obtained in good to excellent

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yields. The presence of electron-withdrawing groups will strongly reduce the reactivity of diphenylmethanes. This strategy realizes C-H functionalization of diarylmethanes by oxidative crosscoupling to construct C-O bond. The highlight of the research is that it successfully diminishes the usage of transition-metal catalysts and harmful stoichiometric terminal oxidants, and can be regarded as a typical example of green chemistry in oxidative C-O coupling reaction. Furthermore, phthalides could also be synthesized via intramolecular oxidative cyclization mediated by DDQ.

#### **Experimental Section**

**General experimental procedure (3):** A 25-mL tube equipped with a magnetic stirrer bar was added diphenylmethanes **1** (0.5 mmol), dry carboxylic acid **2** (2.5 mmol), DDQ (22.7 mg, 20 mol%) and 4.0 mL of dry DCE. After the air in the tube was replaced with O<sub>2</sub>, TBN (12  $\mu$ L, 20 mol%) was added and the tube was sealed. The sealed tube was placed in an oil-bath and heated at 100 °C until the reaction was completed. Then the mixture was concentrated on a rotary evaporator. The obtained residue was dissolved in 2 mL of ethanol, and hydroxylamine hydrochloride (14 mg, 0.2 mmol) and pyridine (16  $\mu$ L, 0.2 mmol) were added. The mixture was completely converted into oxime. Then the mixture was concentrated and the residue was purified by column chromatography (silica gel, PE-EtOAc) to afford the title compound.

General experimental procedure (5): Method (1): A 25-mL tube equipped with a magnetic stirrer bar was charged with 2-benzylbenzoic acid 5 (0.5 mmol), DDQ (34.0 mg, 30 mol%) and dry DCE (4.0 mL). After the air in the tube was replaced with  $O_2$ , TBN (18 µL, 30 mol%) was added and the tube was sealed. The sealed tube was placed in an oilbath and heated at 100 °C until the reaction was completed. The mixture was then concentrated on a rotary evaporator, and the residue was purified by column chromatography (silica gel, PE-EtOAc) to afford the title compound. Method (2): A 25-mL tube equipped with a magnetic stirrer bar was charged with 2-benzylbenzoic acid 5 (0.5 mmol), DDQ (136.2 mg, 1.2 equiv) and dry DCE (4.0 mL). The tube was sealed after the air in it was replaced with N2. The sealed tube was placed in an oilbath and heated at 100 °C until the reaction was completed. The mixture was then concentrated on a rotary evaporator, and the residue was purified by column chromatography (silica gel, PE-EtOAc) to afford the title compound.

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**Aerobic C–O coupling:** A metal-free aerobic oxidative cross-coupling between benzylic  $C(sp^3)$ –H bond and carboxylic acids catalyzed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone / *tert*-butyl nitrite has been developed. This protocol provides a mild and efficient route to obtain diarylmethanol esters and phthalides. It can be regarded as a typical example of green chemistry in oxidative C–O coupling.

Decheng Pan, Zilong Pan, Zhiming Hu, Meichao Li,\* Xinquan Hu, Liqun Jin, Nan Sun, Baoxiang Hu, Zhenlu Shen\*

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Metal-Free Aerobic Oxidative C–O Coupling of  $C(sp^3)$ –H with Carboxylic Acids Catalyzed by DDQ/*tert*-Butyl nitrite