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# AIBN initiated functionalization of the benzylic sp<sup>3</sup> C—H and C—C bonds in the presence of dioxygen



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## Introduction

In the past decades, great development has been achieved in the functionalization of the inert C–H bonds [1–3], in which the reactions mediated by free radical intermediates show a huge advantage in the functionalization of sp<sup>3</sup> C–H bond due to the nature that the saturated C-H bonds are prone to undergo homolytic fission. Therefore, in recent years, radical C-H bond activation gradually become the mainstream of sp<sup>3</sup> C–H activation, and a large number of elegant transformations have been developed [3,4]. Among them, the aerobic functionalization of sp<sup>3</sup> C—H bond is particularly noticeable, for dioxygen might be one of the mildest and greenest oxidants. However, its weak oxidizability as well as low concentration in general solvents limits the application in organic synthesis, albeit some great progress has been achieved <sup>[4m-o, 5]</sup>. As part of our research interests, screen of the catalyst systems that can promote the participation of oxygen has been a focus in the study of our group [5]. Although in our previous research, the triarylamine radical cation salts and alkyl nitrites were found to be a kind of good initiator of the C-H bond oxidation, new catalyst systems are still highly desirable.

2,2'-Azobis(isobutyronitrile) (AIBN) is popularly used as a radical initiator in various radical reactions. Through pyrolysis, after extruding amolecule of N<sub>2</sub>, it can release the 2-cyanoprop-2-yl

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# ABSTRACT

A sp<sup>3</sup> C—H bond functionalization and C—C bond cleavage were realized by AIBN/O<sub>2</sub> catalyst system, providing a series of benzophenones under mild reaction conditions. The mechanistic study shows that a peroxide intermediate is involved in this transformation, and in the case of diphenylmethanes, the sp<sup>3</sup> C—C bond is cleaved through the peroxide rearrangement, which might provides a new way to cleave relatively strong C—C bond and be applied to more general C—C bond activation.

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radical to initiate radical reactions [6]. However, AIBN initiated  $sp^3$  C—H bond functionalization is still rare. It is well-known that

the considerable difference in bond dissociation energies (BDE) between the starting materials and the products is one of the most important driving forces of radical reactions. Given the BDE of the C-H bond in isobutyronitrile is comparable or even lower than most sp<sup>3</sup> C–H bonds, intermolecular hydrogen atom transfer (HAT) between the 2-cyanoprop-2-yl radical and sp<sup>3</sup> C–H bond containing substrates are generally not efficient (Scheme 1, eq 1) [7]. For the same reason, most initiators used in sp<sup>3</sup> C–H activation are peroxides (such as TBHP, DTBP), in which the O-H bonds of the corresponding alcohols are greatly stronger than most sp<sup>3</sup> C-H bonds. At the other hand, in the aerobic conditions, the generated 2-cyanoprop-2-yl radical can smoothly capture dioxygen to form 2-cyano-2-propyloxyl radical species, and this process was widely utilized to achieve various C-H bond cyanation [8]. So we questioned whether this 2-cyano-2-propyloxyl radical could initiate the functionalization of sp<sup>3</sup> C-H bond and other inert chemical bond activation (Scheme 1, eq 2). Herein, we reported an AIBN initiated aerobic oxidation of the benzylic sp<sup>3</sup> C–H bond and cleavage of sp<sup>3</sup> C–C bond.

## **Results and discussion**

To test our idea, diphenylmethane 1a was chosen as a model substrate to explore the suitable conditions for the aerobic C—H bond oxidation (Table 1). To our delight, in the presence of





Scheme 1. Cleavage of C—H and C—C bonds.

dioxygen, the desired reaction occurred smoothly, and benzophenone **2a** was isolated in 69% yield (entry 1). Increasing the amount of AIBN, higher yields were obtained (entries 1–5), and 3 equivalent of AIBN gave the best result, providing **2a** in 82% isolated yield (entry 4). When the reaction temperature was reduced to 60 °C, the reaction efficiency was lower and a large number of the starting material remained unchanged (entry 5). Then, a solvent screen was performed, and the results show that MeCN is still the best solvent (entries 6–14). It is worth noting that when toluene was employed as the solvent, benzaldehyde was detected by GC–MS, which implied that the relatively active benzylic C—H bond might disturb the desired reaction process. In the examination of the reaction scope we can see that the substrates with benzylic methyl groups generally gave lower yields of the expected products (vide post).

With the best reaction conditions established, the reactions of various substituted diphenylmethanes were performed under the standard reaction conditions (Scheme 2). At the outset,

## Table 1

Optimization of the oxidation of diphenylmethane.

monosubstituted substrates were employed to test the influence of the substituent effect. The results show that halogen atom did not affect the reaction efficiency, giving the desired products in moderate to good yields (**2b-2d**), and even iodine atom can be smoothly tolerated. When the electron-donating groups were connected on the phenyl ring, the expected products were isolated in lower yields (**2f-2 g**). The reason might lie in that in the presence of electron-rich phenyl ring, the rearrangement of the generated peroxide would be accelerated (see Scheme 5). By GC–MS, the corresponding benzoic acids were detected, which suggested that the rearrangement of the peroxide intermediate occurred. The



Scheme 2. The aerobic oxidation of diphenylmethanes.

$\begin{array}{c} H \\ \hline \\ H \\ \hline \\ \hline \\ \hline \\ 1a \end{array} \xrightarrow{AIBN (x equiv), O_2} \\ \hline \\ solvent, T \circ C \\ \hline \\ 24 h \\ 2a \end{array}$							
Entry	AIBN (x equiv)	Solvent	T (°C)	Yield (%) <sup>a</sup>			
1	1.5	CH <sub>3</sub> CN	75	69%			
2	2.0	CH <sub>3</sub> CN	75	71%			
3	2.5	CH <sub>3</sub> CN	75	72%			
4	3.0	CH <sub>3</sub> CN	75	82%			
5	4.0	CH <sub>3</sub> CN	75	81%			
6	3.0	CH <sub>3</sub> CN	60	51%			
7	3.0	1,4-Dioxane	75	30%			
8	3.0	DCE	75	61%			
9	3.0	anisole	75	22%			
10	3.0	THF	75	9%			
11	3.0	CHCl <sub>3</sub>	75	45%			
12	3.0	toluene	75	28%			
13	3.0	NO <sub>2</sub> Me	75	55%			
14	3.0	ClPh	75	48%			
15	3.0	DMF	75	15%			

Isolated yields.

#### Table 2

Optimization of the oxidation of diphenylethane.



	58		20 70	
Entry	Solvent	Time (h)	Additive (mol %)	Yield (%) <sup>a</sup>
1	MeCN	72	none	20 (44) <sup>b</sup> , <sup>c</sup>
2	ClPh	72	none	10 (34) <sup>b</sup> , <sup>c</sup>
3	DCE	72	none	15 (22) <sup>b</sup> , <sup>c</sup>
4	CHCl <sub>3</sub>	72	none	35 (<10) <sup>b</sup> , <sup>c</sup>
5	CHCl <sub>3</sub>	96	CF <sub>3</sub> CO <sub>2</sub> H (30)	20 (36) <sup>b</sup> , <sup>c</sup>
6	CHCl <sub>3</sub>	96	MeSO <sub>2</sub> OH (30)	22 (26) <sup>b</sup> , c
7	CHCl <sub>3</sub>	96	p-TsOH (30)	19 (41) <sup>b, c</sup>
8	CHCl <sub>3</sub>	96	FeBr <sub>2</sub> (30)	25 <sup>c</sup>
9	CHCl <sub>3</sub>	96	FeCl <sub>3</sub> (30)	10 <sup>c</sup>
10	CHCl <sub>3</sub>	96	FeCl <sub>2</sub> (30)	14 <sup>c</sup>
11	CHCl <sub>3</sub>	96	NiCl <sub>2</sub> (30)	39 (<10) <sup>b, c</sup>
12	CHCl <sub>3</sub>	96	$NiBr_2$ (30)	68 (<10) <sup>b, c</sup>
13	CHCl <sub>3</sub>	72	$NiBr_2$ (15)	49 (<10) <sup>b, c</sup>
14	CHCl <sub>3</sub>	72	NiBr <sub>2</sub> (15)	<b>88</b> (<10) b, <sup>d</sup>

<sup>a</sup> Isolated yields;

<sup>b</sup> The yields in the brackets are the yields of **4a**;

<sup>c</sup> 3 equivalent of AIBN added;

<sup>d</sup> 4 equivalent of AIBN added.

existence of strong electron-withdrawing CF<sub>3</sub> group would destabilize the corresponding radical intermediate, therefore, product **2 h** was obtained in reduced yield (**2 h**). As a comparison, conjugate electron-withdrawing groups, such as NO<sub>2</sub> and CN, could increase the stability of the radical intermediate, giving the desired benzophenones in higher yields (**2i-2j**). The substrates with *meta*groups could also be well tolerated in this reaction, providing the desired products in acceptable yields (**2 k-2n**). Then, various substituted diphenylmethanes were evaluated (**2o-2y**), and again, conjugate electron-withdrawing groups gave better results (**2v**-**2w**). Benzylnaphthalene **1z** was also tolerated in this C—H bond oxidation, albeit the yield was slightly lower (**2z**).

With the success of  $sp^3 C$ —H bond oxidation, we decided to try a more difficult reaction. Since the peroxide intermediate would be generated in the reaction, we questioned whether the peroxide rearrangement could be utilized to promote the cleavage of sp<sup>3</sup> C-C bond. With this idea in mind, the reaction of 1,1-diphenylethane 3a was tested under the standard reaction conditions (Table 2). To our disappointed, benzophenone 2a was isolated in only 20%, which was disturbed by phenyl benzoate 4a in 44% yield (entry 1). Then, several solvents were screened (entries 1-4). When CHCl<sub>3</sub> was employed as the solvent, the selectivity was improved, and only trace amount of phenyl benzoate was detected (entry 4). Next, a series of Brönsteic acid were added into the reaction solution, however, the results were not satisfactory (entries 5-7). To accelerate the peroxide rearrangement, Lewis acids were tested (entries 8-14) and NiBr<sub>2</sub> exhibited good activity, providing the desired product in 68% yield (entry 12). Further optimization of the reaction condition showed that 4 equivalent of AIBN with 15 mol % NiBr<sub>2</sub> in CHCl<sub>3</sub> gave the best result and the desired sp<sup>3</sup> C–C bond cleaved product was obtained in 88% yield (entry 14).

Next, the reactions of various representative 1,1-diphenylethanes were conducted under the optimized conditions, and the results were compiled in Scheme 3. From the results we can see that no matter electron-donating or electron-withdrawing groups could be well tolerated in this reaction, generating the expected products in acceptable yields. It is worth noting that benzylic methyl group still interfere with the reaction, giving the corresponding benzophenone **2f** in poor yield.

To illuminate the reaction mechanism, several control experiments were performed (Scheme 4). In the absence of dioxygen or



Scheme 3. The aerobic oxidation of diphenylethanes.

AIBN, no reaction occurred (eq 1-2), which supported that AIBN and dioxygen cannot solely initiate the oxidation of the C–H bond. Equation 3 shows that the reaction was totally inhibited in the existence of TEMPO, implying that a radical intermediate might be involved in this C-H oxidation. Since the mechanism of the oxidation of diphenylmethane is relatively simple, the reaction of 1,1diphenylethane was focused on. First, the reaction mixture was analyzed by HRMS, and a peroxide intermediate (calcd for C<sub>18</sub>H<sub>19</sub>-NO<sub>2</sub> + Na<sup>+</sup>, 304.1308; found, 304.1299) were detected (eq 4). This intermediate suggested that the C-C bond is cleaved by the rearrangement of the corresponding peroxide. Fortunately, when the model reaction was guenched before completion, this peroxide intermediate 5 was isolated in 12% yield, which is suspected to be generated through the coupling between radical intermediate **D** and 2-cvanoprop-2-vl radical **A** (see Scheme 5). This result might explain why the transfer of methyl group is preferred rather than more nucleophilic phenyl group, for the 2-cyanopropan-2-yl group is bulky and the shift of phenyl group is inhibited by steric hindrance.

According to the results of control experiments and the literature precedents [8], a plausible mechanism was proposed (Scheme 5). By pyrolysis, 2-cyanoprop-2-yl radical **A** is generated and trapped by dioxygen, giving the 2-cyano-2-propyloxyl radical





Scheme 5. Proposed mechanism.

**B**. Then intermolecular H-abstraction occurs, followed by coupling between intermediate **C** and dioxygen, affording the peroxide radical **D**. Due to the high concentration of AIBN, the peroxide species are captured by radical **A** to deliver peroxide **5**. In the case of diphenylmethane, elimination of cyanohydrin directly provides the product **2**. If R group is methyl, NiBr<sub>2</sub> coordinates with the peroxide **5** to accelerate the extrusion of cyanohydrin, and benzophenone **2** is yielded after the peroxide rearrangement. In the absence of NiBr<sub>2</sub>, the rate of peroxide rearrangement is slow, and an alkoxy radical **E** will be generated by homolysis of the peroxide intermediate **5**. Then, the alkoxy radical undergoes radical rearrangement to provide a more stable carbon-centered radical **F**, which is captured by dioxygen, resulting in the formation of intermediate **G**. After the final β-fragmentation of intermediate **G**, phenyl benzoate **4** is afforded.

# Conclusion

In summary, a functionalization of sp<sup>3</sup> C—H and C—C bonds was developed by AIBN/O<sub>2</sub> catalyst system, synthesizing a series of benzophenones under mild reaction conditions. In particular, this reaction provides a new way to cleave relatively strong C—C bond through the rearrangement of the generated peroxide intermediate, which are potentially useful for the study of C—C bond activation. Application of this catalyst system to other reactions together with the mechanistic studies are still underway in our laboratory.

# **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Experimental details, mechanistic study and spectroscopic data to this article can be found online. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020. 152806.

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