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A metal-free method for direct $C(sp^3)$ -H bond functionalization of simple ethers with α, α -diaryl allylic alcohols is described. The established protocol provides facile access to α -aryl- β -oxyalkylated carbonyl ketones *via* radical addition and a 1,2-aryl migration cascade process. An application of the product has been demonstrated in the synthesis of a serotonin antagonist.

Direct C-H functionalization has emerged as an attractive protocol to construct C-C and C-X bonds, as it reduces prefunctionalization while improving atom-economy and environmental sustainability.¹⁻⁴ In the past decades, remarkable advances have been achieved on the activation of an inert C(sp³)-H bond.^{3,4} Recently, much attention has been paid to the free-radical-initiated direct α -C(sp³)-H bond functionalization of ethers.⁵⁻¹⁴ In particular, substituted ether derivatives are featured in the synthesis of various pharmaceuticals and biologically active molecules.¹⁵ However, the cleavage of these stable bonds is still a challenging task for chemists. Several groups have disclosed a variety of novel C-C,⁶ C-O,⁷ C-N,⁸ C-S⁹ bond formations of ethers with different nucleophiles via Cross-Dehydrogenative-Coupling (CDC) reactions. Zhang et al.¹⁰ and Wang et al.¹¹ reported oxyalkylation reactions of vinylarenes with cyclic ethers under homogeneous and heterogeneous systems, respectively (Scheme 1, eqn (1)). Recently, Li and coworkers investigated iron-catalyzed 1,2-alkylarylation of activated alkenes via a tandem radical addition/homolytic aromatic substitution process (Scheme 1, eqn (2)).¹² Later, Lei's group developed copper-catalyzed oxidative C-H/C-H coupling between olefins and simple ethers (Scheme 1, eqn (3)).¹³ Similarly, we also described an efficient pathway leading to 6-alkyl phenanthridine, involving C(sp³)-H/ $C(sp^2)$ -H bond cleavage (Scheme 1, eqn (4)).¹⁴

Metal-free oxidative direct $C(sp^3)$ –H bond functionalization of ethers with α, α -diaryl allylic alcohols[†]

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Although these type of reactions, using ethers as reactants, have considerably improved, more versatile C–C formation for the synthesis of pharmaceuticals and biologically active molecules is still highly desirable. To the best of our knowledge, a neophyl-type rearrangement^{16,17e} driven by an α -carbon-centered radical adjacent to a heteroatom addition to allylic alcohols **1**, leading to a variety of α -aryl- β -oxyalkylated carbonyl ketones, has never been previously reported (Scheme **1**, eqn (5)). As a continuation of our interest in the radical pathway transformations,¹⁷ herein, we developed a novel reaction of α , α -diaryl allylic alcohols with ethers under mild metal-free conditions.

Previous studies^{5–14} revealed that the α -H of an ether can be oxidized with peroxide for the generation of radicals. Based on this assumption, initial studies were focused on the model reaction of allylic alcohol **1a** and **1**,4-dioxane **2a** in the presence of various catalysts and oxidants under air (Table 1, entries 1–9). It was found that direct alkylation with concomitant 1,2-migration of a phenyl group was achieved with catalytic amounts of Cu₂O, TBAI or AgNO₃, and the targeted carbonyl compound **3aa** was obtained in 71–83% GC-yield after 24 h (Table 1, entries 1–3). To our delight, the GC-yield of **3aa** could be increased to 91%, when 3 equiv. of di-*tert*-butyl



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Table 1 Optimization of the reaction conditions^a

	HO Ph Ph + 1a	2a Cat./Oxidant 120 °C 120 °C under air	h Ph O 3aa	
Entry	Catalyst (mol%)	Oxidant (equiv.)	Time (h)	GC yield ^{b} (%)
1	$Cu_2O(5)$	DTBP (3)	24	83
2	TBAI(5)	DTBP(3)	24	71
3	$AgNO_3(5)$	DTBP(3)	24	82
1	_	DTBP(3)	24	91
5	_	TBHP(3)	24	51
5	_	TBPB(3)	24	92
7	_	CHP(3)	24	48
8	_	$PhI(OAc)_2(3)$	24	64
9	_	$K_2S_2O_8(3)$	24	0
10	_	_	24	Trace
11	_	TBPB(2)	24	92
12	_	TBPB(2)	12	95(95 [°])
13	_	TBPB(2)	12	47 ^d
14	_	TBPB(2)	3	64
15	_	TBPB(1)	2.4	72

0

^{*a*} Reaction conditions: **1a** (0.3 mmol), **2a** (1 mL), catalyst (5 mol%) and oxidant (1–3 equiv.) (DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide (70% in aqueous solution), TBPB = *tert*-butylperoxybenzoate, CHP = cumyl hydroperoxide) at 120 °C under air. ^{*b*} Yields were determined by GC with an internal standard. ^{*c*} Isolated yields. ^{*d*} At 100 °C.

peroxide (DTBP) was used without any catalysts (Table 1, entry 4). Furthermore, other radical initiators besides DTBP were examined, and *tert*-butylperoxybenzoate was demonstrated to be the best one (Table 1, entries 5–9). In the absence of an oxidant, no reaction took place, which suggested the crucial importance of peroxide in this transformation (Table 1, entry 10). Further screening of the amount of TBPB, the reaction temperature and reaction time established the optimized conditions as follows: α , α -diphenyl allylic alcohol **1a** and 1,4-dioxane **2a** in the presence of 2.0 equiv. TBPB at 120 °C for 12 h. The desired **3aa** could be obtained in 95% GC-yield, along with an isolated yield of 95% (Table 1, entry 12).

With the optimal conditions in hand, the generality and substrate scope of this radical rearrangement reaction were investigated using various readily available ether derivatives and symmetrical a,a-diaryl allylic alcohols (Table 2). Tetrahydro-2H-pyran was first employed to react with α, α -diphenyl allylic alcohol **1a**, smoothly rendering the target alkylation product in 63% yield (Table 2, 3ab). The fivemembered cyclic ethers, such as THF, 2-ethyl-2-methyl-1,3-dioxolane and 1,3-dioxolane, were also suitable under the optimal conditions (Table 2, 3ac-3ae). It was noted that the cleavage of the C-H bond at the 2-position of 1,3-dioxolane was preferential and the α -aryl- β oxyalkylated ketone 3ae was isolated as the major product. Open-chain diethyl ethers were also good candidates, affording 4-ethoxy-1,2-diphenylpentan-1-one 3af in 45% yield. The regioselectivity of direct oxidative functionalization of glycol dimethyl ether 2g was observed. The reaction was more prone to occur at the $C(sp^3)$ -H bond of the internal methylene moiety than at the terminal methyl group, and two isomers 3ag and 3ag' were obtained with a ratio of 2:1. Unfortunately, when oxybis(methylene)dibenzene was used, only a trace amount of the product was detected (Table 2, 3ah). When the current typical method was applied to symmetrical compounds 1 bearing methoxyl (1b) and methyl (1c) groups on the aromatic ring, the desired ketones 3ba and 3ca were obtained in

 Table 2
 Reaction of 1 with ethers^a



 a All reactions are carried out under the optimal conditions; yields of isolated products. b Determined by $^1\rm H$ NMR of the isolated product. c At 150 °C for 11 h.

80% and 89% yields, respectively. Although the electronic effect on the aryl ring reduced the yields to some extent, good yields of **3da**, **3ea** and **3fa** were still obtained. Meanwhile, a *meta*-substituted aryl group also worked well as a migrating group and the product **3ga** was isolated in 76% yield. In addition, benzo[*d*][1,3]dioxole could be tolerated (Table 2, **3ci**).

To further expand the scope of this particular metal-free oxidative alkylation reaction and to obtain information on the selectivity of the aryl migration, we turned our attention to allylic alcohols bearing two different aryl groups (Table 3). To our delight, 1h ran smoothly to afford ketone 3hi and its isomer in an inseparable mixture of 49% yield, and the ratio was determined by ¹H NMR (4:1). Although the procedure was not sensitive to the nature of the substituted group, the electronic properties of the aryl ring affect the migration rate. For substrates 1i-k and heterocyclic 1m, preferential migration of the more electron-poor aryl groups was detected. This chemoselective manner suggested that the reaction might involve a radical ("neophyl") rearrangement process.¹⁶ The structure of 3mi was confirmed by X-ray single crystal diffraction.¹⁸ On the other hand, ortho-substituted aryl rings (11) migrated less effectively, indicating that steric hindrance had a detrimental effect on the rearrangement. However, pentafluorophenyl 1n was almost inert under our conditions.

During the course of our studies, other types of allylic alcohol substrates were chosen as the reactants (Scheme 2). However, ring expansion did not happened when 9-vinyl-9*H*-fluoren-9-ol **10** was introduced to the reaction with **2a**. Notably, the mono-aryl-type allylic alcohol **1p** was almost inert under our conditions. It was demonstrated that the two aryl groups in the starting material were necessary for the addition–rearrangement reaction.



^{*a*} All reactions were carried at 150 °C under air for 12 h. ^{*b*} Yields of 3 and its isomer. Only major products were shown. ^{*c*} Determined by ¹H NMR of the isolated products. ^{*d*} Major product yields. ^{*e*} Determined by ¹H NMR of the crude products.

To gain further insight into the possible radical mechanism, a control experiment of **1a** and **2a** in the presence of 2 equiv. TEMPO was carried out (Scheme 3). As expected, the formation of the desired product **3aa** was suppressed, and only the TEMPO-1,4-dioxane adduct **4** was observed (determined by LC-MS analysis). This result indicated that TBPB mediated reaction of α, α -phenyl allylic alcohol **1a** with 1,4-dioxane might be a radical-initiated route¹⁷ to the target product.

On the basis of recent publications^{16,17e} and the results above, we proposed a plausible reaction mechanism in Scheme 4. First, high temperature results in the homolysis of TBPB, which is decomposed to the *tert*-butoxyl radical and the benzoate radical. Then, the C–H bond adjacent to the oxygen atom of 1,4-dioxane is activated by the *tert*-butoxyl radical, providing the active intermediate I, which could be trapped by TEMPO to give 4. The resulting α -carbon-centered radical I adds to allylic alcohol and produces an alkyl intermediate II. Subsequently, an intramolecular radical addition to generate the spiro[2,5]octadienyl radical III, followed by the migration of the electron-deficient aryl group preferentially releases IV.^{16d,17e} Note that *ortho*-substituted groups are reluctant to migrate owing to a sterically congested radical III might be not favorable. Finally, the desired product 3 and benzoate are delivered after further oxidation and deprotonation.



Scheme 2 The reaction of 10-p with 2a.



Scheme 3 Radical-trapping experiment.



Scheme 4 A plausible reaction mechanism.



4-(4-(2-Methoxyphenyl)piperazin-1-yl)-1,2-diphenylbutan-1-one belongs to a family of arylpiperazines that are well known serotonin antagonists for the treatment of depression and related disorders.^{15/;19} Finally, we demonstrated a representative synthesis of a known serotonin antagonist **5** starting from ketone **3ae** in an efficient manner (Scheme 5).

In conclusion, we have developed a novel TBPB-promoted radical alkylation reaction of α, α -diaryl allylic alcohols with ethers (cyclic and open-chain ethers) that provides straightforward access to α -aryl- β -akylated carbonyl ketones. Two new C–C bonds were formed in this reaction *via* C(sp³)–H bond functionalization and a 1,2-aryl migration process under metal-free conditions. The application of product **3ae** has been demonstrated in the synthesis of a serotonin antagonist **5**.

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