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Transition-Metal-Free C−H Hydroxylation of Carbonyl Compounds

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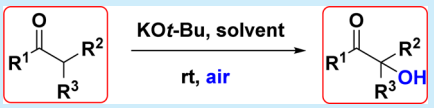
Supporting Information

ABSTRACT: Transition metal and reductant free α-C(sp3)−H hydroxylation of carbonyl compounds are reported. This method is promoted by commercially available inexpensive KO-*t*-Bu and atmospheric air as an oxidant at room temperature. This unified strategy is also very facile for hydroxylation of various carbonyl compound derivatives to obtain quaternary hydroxyl compounds in excellent yield. A preliminary mechanistic investigation, supported by isotope labeling and computational studies, suggests the formation of a peroxide bond and its cleavage by in situ generated enolate.



The oxidation reaction is a fundamentally important transformation in organic synthesis by which hydrocarbons are converted into valuable oxygenated products as feedstocks for chemical and pharmaceutical industries.[1] Of these reactions, α C−H hydroxylation of α-substituted carbonyl compounds to obtain quaternary α-hydroxyl carbonyl compounds obtains more attention in synthetic community since such a quaternary α-hydroxyl functionality is a central motif in all facets of chemistry ranging from several natural products (Figure 1) to synthetic drugs such as tephrosin,[2a] doxycycline,[2b] bicalutamide,[2c] aryloxindole,[2d] and donaxaridine.[2e] Furthermore, this type of quaternary α-hydroxyl carbonyl compounds serves as an efficient photoinitiator in the coating industry.[3a,b] Similarly, the hydroxyl derivatives of barbituric acid are responsible for improving the durability of a polarizing plate.[3c] While significant progress has been documented for the oxidation of the C−H bond by catalytic/noncatalytic approaches in the presence of various oxidant sources, there is an increasing demand for more environmentally benign approaches avoiding the use of expensive metal catalysts, hazardous stoichiometric oxidants, and reductants. Recently, the direct hydroxylation of C(sp^3)−H bond with a stoichiometric amount of oxidants such as oxaziridine, cumene hydroperoxide (CHP), PIDA, PIFA, TBHP, Oxone, and H_2O_2, etc. was reported, which suffer from the ease of handling and other hazards (Scheme 1).[4] The consumption of molecular oxygen as an oxidant accessible from air and utilization for oxygen incorporation in organic synthesis has attracted substantial attention.[5,6]

Remarkable progress has been made using transition-metal catalysis with molecular O_2 for selective C−H hydroxylation of carbonyl compounds.[7] The use of O_2 for the synthesis of quaternary α-hydroxyl carbonyl compounds was first described by Ritter and co-workers using dinuclear palladium complex with a special base hppH.[8] Interestingly, to minimize the use of metal, Jiao and co-workers developed an elegant method for C−H hydroxylation catalyzed by Cs_2CO_3, required a phosphine reductant.[9] Zhao's group reported an enantioselective C−H hydroxylation by using dimeric cinchona alkaloid-derivative in the presence of aqueous alkali and phosphine reductant.[10] Very recently, Schoenebeck et al. developed and elucidated the use of metal oxide (Cu_2O) along with special base (hppH) for C−H hydroxylation and C−C cleavage using experimental and computational studies.[11] In general, the key methodologies to achieve the synthesis of such compounds involve either hazardous oxidants or transition metals or metal oxide and additive (phosphine as a reductant) which were the drawback for above

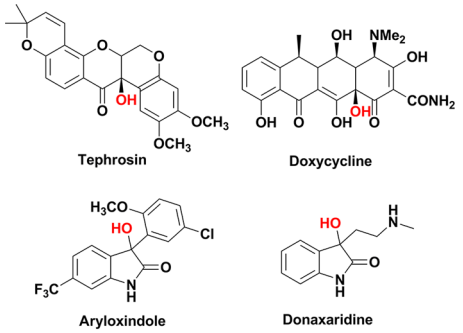


Figure 1. Quaternary hydroxyl biologically active molecules.

Scheme 1. State of the Art on C−H Hydroxylation

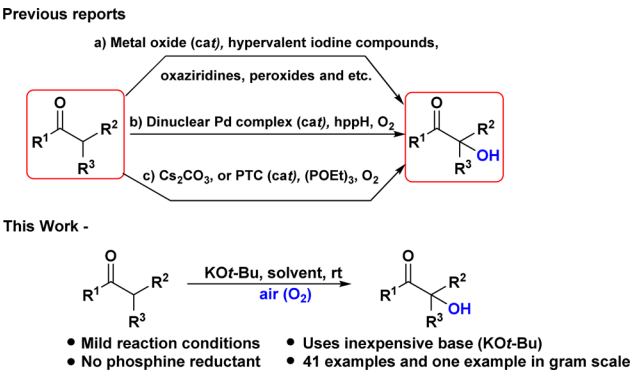


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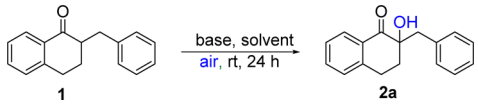
Table 1. Optimization for α-C−H Hydroxylation Reaction[a]



entry	base	solvent	yield (%)
1		DMSO	no reaction
2	KO-*t*-Bu (0.1 equiv)	DMSO	31
3	KO-*t*-Bu (0.3 equiv)	DMSO	45
4	KO-*t*-Bu (0.5 equiv)	DMSO	56
5	KO-*t*-Bu	DMSO	90
6	KO-*t*-Bu	toluene	40
7	KO-*t*-Bu	THF	52
8	KO-*t*-Bu	1,4-dioxane	56
9[b]	KO-*t*-Bu	DMSO	no reaction
10	Cs_2CO_3 (0.1 equiv)	DMSO	traces
11	Cs_2CO_3 (1 equiv)	DMSO	traces
12	NaO-*t*-Bu	DMSO	67
13	LiO-*t*-Bu	DMSO	88

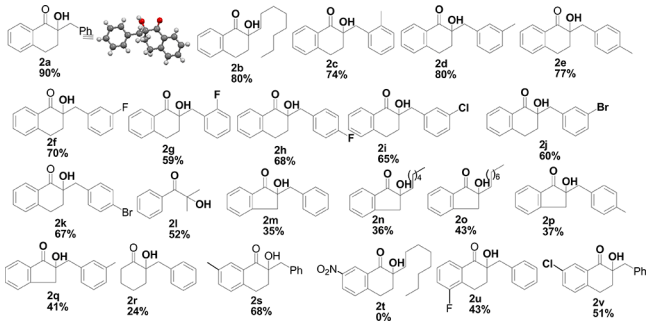
[a]Reaction conditions: base (0.25 mmol), ketone (0.25 mmol), and solvent (1 mL) were stirred at room temperature for 24 h under open air conditions. [b]The reaction was carried out under Ar atmosphere.

protocols. Despite their success for transition-metal-catalyzed α-hydroxylation of carbonyl compounds, transition-metal-free methods for α-hydroxylation are required in the pharmaceutical industry that can eliminate the heavy metal contamination in the final products. Hence, there is a demand to develop a variant protocol which enables the C−H hydroxylation with easy operation for the synthesis of quaternary α-hydroxyl carbonyl compounds and avoids the use of an expensive metal catalyst, special bases, hazardous phosphine-based additives, longer reaction time, cryogenic conditions, and protecting groups.

Herein, we report KO-*t*-Bu, as a base, mediated aerobic C−H hydroxylation of various carbonyl compounds under simple reaction conditions without using any additives and reductants. The present finding comprises the following: (i) air as a source of hydroxyl functionality, which makes this protocol environmentally benign; (ii) readily available, inexpensive base KO-*t*-Bu rather than expensive metal catalyst; (iii) avoids the use of stoichiometry amount of hazardous phosphine compounds as a additive and reductant.

We commenced our reaction studies using cyclic ketone **1**. The control experiment was performed by stirring ketone **1** in DMSO under air at rt for 24 h, which showed no reaction (Table 1, entry 1). To identify optimal reaction conditions for metal-free base-mediated aerobic C−H hydroxylation, various concentrations of KO-*t*-Bu (10, 30, and 50 mol %) were added to the solution of **1** in DMSO and allowed to stir at room temperature under air for 24 h. This results indicated that a gradual increase of the amount of KO-*t*-Bu considerably increased the formation of the product **2a**, leading to 31, 45, and 56% yield, respectively (Table 1, entries 2, 3, 4). This reaction was also monitored at a different course of time (8−24 h) and showed the disappearance of the starting material in 24 h. To our delight, the addition of a stoichiometric amount of KO-*t*-Bu afforded desired product **2a** in excellent yield (90%) (Table 1, entry 5). Similarly, the solvent effect on the C−H hydroxylation of compound **1** was studied. A higher yield was observed when the C−H hydroxylation reaction was performed in DMSO. Other solvents such as toluene, THF, and 1,4-dioxane were ineffective to produce the product **2a** in higher yield (Table 1, entries 6−8). Further, this reaction did not proceed to form the

Scheme 2. Substrate Scope of Ketone C−H Hydroxylation



product **2a** under Ar atmosphere, which ruled out DMSO acting as an oxidant source (Table 1, entry 9). Additionally, we performed C−H hydroxylation using Cs_2CO_3 (Table 1, entries 10 and 11), as developed by Jiao and co-workers,[9] without the addition of any phosphine reductant, which showed only a trace amount of C−H hydroxylated product (Table 1, entries 10 and 11). This proved that changing the base from Cs_2CO_3 to KO-*t*-Bu allows the reaction to occur without the need for phosphine reductant. Other strong bases such as NaO-*t*-Bu and LiO-*t*-Bu also afforded the product **2a** in 67 and 88% yield, respectively (Table 1, entries 12 and 13) suggesting an important role of the strength of the base. Notably, the developed reaction is promoted by the less expensive base and avoided the use of hazardous oxidizing agents and reductant. To eliminate the possibility of trace metal involvement, we analyzed KO-*t*-Bu using MP-AES analysis and found negligible quantities of such contaminants (section 5 of the Supporting Information (SI). Using the optimized conditions, the scope of the reaction was investigated with a variety of substrates. Thus, the reaction of 2-benzyl-3,4-dihydronaphthalen-1(2*H*)-one with optimized conditions gave **2a** (2-benzyl-2-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one) in 90% yield. The reaction product was characterized by spectroscopic techniques and X-ray analysis. In the case of 2-octyl-3,4-dihydronaphthalen-1(2*H*)-one, this reaction proceeded smoothly to afford the product **2b** in 84% yield (Scheme 2). Electron-donating or electron-withdrawing group substitutions on the phenyl ring decreased the yield of the products. This aerobic α-hydroxylation reaction with 2-(2-, 3-, or 4-methylbenzyl)-3,4-dihydronaphthalen-1(2*H*)-one furnished the corresponding products **2c−e** in 74, 80, and 77% yield, respectively (Scheme 2). These reaction conditions were also compatible with the halogenated substrate; in particular, with the fluorine substituent the reaction worked well and provided a moderate yield of **2f−k** (Scheme 2). Interestingly, all of the above reactions did not afford the product derived from α-cleavage of the intermediate. Encouraged by the results obtained with cyclic ketones, we followed the same methodology to acyclic ketone **2l**, which serves as UV curing agent,[3] and achieved a moderate yield of 52%. This α-hydroxylation was also generalized with various α-substituted 1-indanones to give the quaternary hydroxyl-functionalized products **2m−q** (Scheme 2). In the case of benzylcyclohexanone (tertiary nonaromatic ketone), we obtained a 24% isolated yield of **2r**. The reaction worked well with an electron-donating as well as an electron-withdrawing tetralone skeleton, which afforded a moderate yield of **2s**, **2u**, and **2v**. Unfortunately, no desired product was observed with 2-benzyl-7-nitro-3,4-dihydronaphthalen-1(2*H*)-one (entry **2t**). Instead of hydroxyl product, we observed an intermolecular hydrogen

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bonded enol form of the starting material whose structure was confirmed by X-ray analysis (Figure S8, SI).

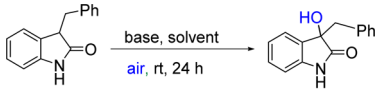
Prompted by the results obtained with ketones, the scope of this methodology was further extended with C3-substituted oxindole compounds to obtain C−H-hydroxylated product. The 3-aryl- and -alkyl-3-hydroxy-2-oxindoles have gained significant attention from the scientific community for its broad range of biological applications.[2c−e] However, reports are available in the literature for the synthesis of 3-hydroxy-2-oxindoles that use oxidant, longer reaction times, and cryogenic conditions.[12] In an investigation of the transition-metal-free C−H hydroxylation of α-substituted 2-oxindole, C3-benzyl-2-oxindole was chosen as the model substrate, and a set of experiments were performed to optimize the reaction conditions to obtain the corresponding C3-hydroxylated 2-oxindole in higher yield (Table 2). This optimization study reveals that C3-hydroxylation of **3** (3-benzylindolin-2-one) under air in the presence of a stoichiometric amount of KO-*t*-Bu in toluene furnished **4a** (3-benzyl-3-hydroxyindolin-2-one) in 93% isolated yield. To our delight, this reaction gave a fruitful result on a gram scale (5 mmol) to afford the product **4a** in 1.02 g (85%) yield.

Similarly, this hydroxylation reaction was also examined with several C3-substituted 2-oxindoles. Excellent yields were obtained with 3-(3- or 4-methoxybenzyl)indolin-2-one, providing **4b** and **4c** in 90% and 89% yield, respectively (Scheme 3). Further, compounds having substituents like the 3-(2-, 3-, or 4-methylbenzyl)indolin-2-one group furnished hydroxylated products in productive yields **4d−f** (Scheme 3). Biphenyl-substituted 2-oxindoles such as 3-([1,1′-biphenyl]-4-ylmethyl)indolin-2-one and 3-([1,1′-biphenyl]-4-ylmethyl)-1-benzylindolin-2-one produced hydroxylated products **4g** and **4p** in 91 and 98% yield, respectively (Scheme 3). Furthermore, the alkyl-substituted 2-oxindole was subjected to base-mediated aerial oxidation and also provided the respective hydroxylated products **4h−k** in moderate yield (Scheme 3). On the other hand, we explored the reactions of N−H-protected 2-oxindoles, which proceeded smoothly and furnished product **4l−o** in excellent yield (Scheme 3). The obtained products were completely characterized by spectroscopic techniques. Further, this structure was supported with the help of crystal structure of the product **4l**. Next, this C−H hydroxylation reaction was studied with several 1,3-dimethylbarbituric acid derivatives. Thus, 5-benzyl-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione was reacted with a stoichiometric amount of KO-*t*-Bu under air for 24 h to result in the formation of 5-benzyl-5-hydroxy-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione **4q** in 93% yield (Scheme 3). Other derivatives of barbituric acid were also successful for the C−H hydroxylation under these experimental conditions to afford the hydroxylated products **4r−t** in good yields (Scheme 3).

On the basis of our preliminary results, DFT computations, and previous studies, a plausible reaction mechanism involving base-induced two-step hydroxylation has been postulated (Scheme 4). Initially, compound **5** undergoes base-mediated deprotonation to give the enolate **6**. Next, the enolate **6** reacts with air (atmospheric O_2) to generate organic superoxide anion **7** that may abstract a proton from **5** to form **8** (confirmed by HRMS), which is subsequently cleaved by the in situ generated reductant enolate **6** to give the expected product **9**.[4h] Next, we performed the labeling experiment to check the source of oxygen incorporation and to support the mechanism (Scheme 5).

The GC−mass spectrum of the product **4a** (m/z = 239) was shifted two mass units higher to m/z = 241 (**4a′**) (91% ^{18}O labeled oxygen atom) when the reaction was carried out with $^{18}O_2$. This labeling clearly indicates the incorporation of oxygen from the molecular oxygen. To check involvement of a radical, the C−H hydroxylation reaction was performed under addition of the radical quencher 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 1,1-diphenylethylene or prop-1-en-2-ylbenzene, but this did not prevent the formation of product **4a**. This ruled out the

Table 2. Optimization for C−H Hydroxylation of 3[a]

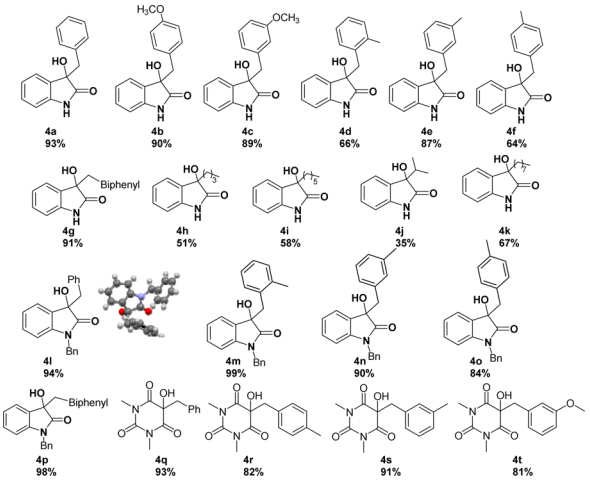


3 4a

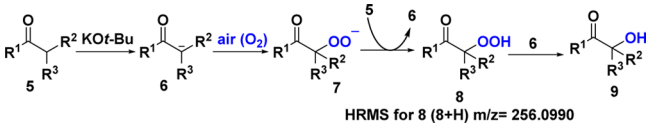
entry	base	solvent	yield (%)
1		toluene	no reaction
2	KO-*t*-Bu (0.1 equiv)	toluene	31
3	KO-*t*-Bu (0.3 equiv)	toluene	53
4	KO-*t*-Bu (0.5 equiv)	toluene	77
5	KO-*t*-Bu	toluene	93
6	KO-*t*-Bu	DMSO	40
7	NaH	toluene	67
8	Cs_2CO_3	toluene	52
9[b]	KO-*t*-Bu	toluene	no reaction
10	NaO-*t*-Bu	toluene	81
11	LiO-*t*-Bu	toluene	88

[a]Reaction conditions: base (0.25 mmol), amide (0.25 mmol), and solvent (1 mL) were stirred at room temperature for 24 h under open air conditions. [b]Reaction was carried out under Ar atmosphere.

Scheme 3. Substrate Scope of Amide C−H Hydroxylation

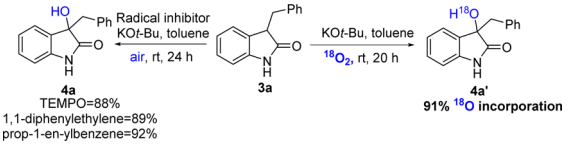


Scheme 4. Plausible Mechanism



HRMS for 8 (8+H) m/z= 256.0990

Scheme 5. Experiments for Mechanistic Studies



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involvement of free-radical intermediates (Scheme 5). It is believed that the enolate formed after deprotonation of **5** might be performing double duty to furnish the overall reaction. When Cs_2CO_3 is used as the base, a phosphine reductant is required for the reaction to occur.[9] The stronger bases used in our work appear to lead to the formation of enolate in higher concentration, which allows it to be available as a reductant for the peroxide bond cleavage, avoiding the requirement of additional phosphine reductant. To validate the proposed mechanism, computational studies were performed on a model reaction (see the SI) and the actual reaction to give the product **2a**. Transition-state structures that are first-order saddle points were obtained. The transition-state structure for the model compound (Figure S7a, SI) shows a stretched peroxide bond (R_{O4-O5} = 1.68 Å) and the simultaneous formation of a C−O bond with the reductant (R_{C7-O5} = 2.41 Å). Furthermore, a hydrogen bond between the hydrogen atom on the peroxide and the carbonyl oxygen on the reductant (R_{O9-H6} = 2.08 Å) stabilizes the transition state. The transition state for the ketone **2a** has a very similar structure (Figure S7a, SI). The calculated reaction barrier, relative stability of the product and key geometrical parameters for **2a** is shown in Figure S7a, SI. The corresponding quantities for the model reaction are shown in the SI.

In summary, we have developed a transition-metal-free, efficient method for C−H hydroxylation of various ketones and amides using inexpensive base and environmentally benign atmospheric air as an oxidant. This methodology delivers a broad array of substrates and provides an alternate route for the synthesis of hydroxylated ketones and amides by avoiding the use of hazardous phosphine-based reductant and expensive metal catalyst. The detailed mechanistic study is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01616.

Experimental procedures, DFT computations, spectroscopic data for the compounds (PDF)
X-ray data for compound **2a** (CIF)
X-ray data for compound **4l** (CIF)

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Notes

The authors declare no competing financial interest.

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