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Iodine Promoted α-Hydroxylation of Ketones

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A novel method for α-hydroxylation of ketones using substoichiometric amount of iodine under metal-free conditions has been described. This method has been successfully employed in synthesizing a variety of heterocyclic compounds, which are useful precursors. α-Hydroxylation of diketones and triketones are illustrated. This strategy provides a novel, efficient, mild and inexpensive method for α-hydroxylation of aryl ketones using sub-stoichiometric amount of molecular iodine.

α–Hydroxy carbonyl compounds are integral part of a number of bioactive compounds which are useful intermediates for synthesizing a variety of pharmaceutically active compounds.[1] Therefore, there is a great deal of interest in developing user-friendly methods for synthesizing α–hydroxy carbonyl compounds using the corresponding ketones as the precursors. Traditionally, α-hydroxylation of carbonyl compounds is achieved by oxidation of silylenol ethers using peracids.[2] Over the time, hypervalent iodine compounds are emerging as alternate reagents for α-hydroxylation and oxygenation of carbonyl compounds.[3] Moriarty and co-worker reported α-hydroxylation of ketones using stoichiometric amount of hypervalent iodine compounds,[3a-c] whereas Huang and co-worker employed iodobenzene and oxone for the α-hydroxylation of aryl ketones.[3g] Apart from these reports, α-hydroxylation of aryl ketones has been reported using metals such as Pd or Tl.[4] Although these methods are useful for α-hydroxylation of methyl ketones derivatives, the similar reaction with propiophenone and butyrophenone derivatives were not successful and are not compatible with many functional groups. Apart from this, some of the hypervalent iodine reagents are potentially shock-sensitive, explosives in nature, poorly soluble in common organic solvents and stoichiometric amount of reagent is required for completion of the reaction. Recently, molecular iodine has received considerable attention as an environmentally benign, inexpensive, nontoxic and readily available catalyst. Thus, there has been a strong interest in using sub-stiochiometric amount of organoiodine compounds and molecular iodine from both economic and environmental perspectives. Apart from this, a direct hydroxylation of ketones using iodine would lead to a novel and useful metal-free methodology. In pursuit of our interest in iodine and iodine derivatives catalyzed reactions,[5] and metal-free reactions,[6] herein we disclose molecular iodine promoted α-hydroxylation of aryl ketones. This strategy provides a novel, efficient, mild and inexpensive method for α-hydroxylation of aryl ketones using sub-stoichiometric amount of molecular iodine.

Results and discussion

Optimization studies were carried out using propiophenone (**1a**) as model substrate under a variety of reaction conditions (Table 1). The initial screening studies of **1a** with I_2 (50 mol %) and aq TBHP (70% solution in water) using DMSO as solvent furnished the product **2a** in 58% yield at 80 °C (entry 1, Table 1). Solvent screening studies indicated that the solvents such as CH_3CN, CH_2Cl_2, EtOAc, toluene, DMF or DMA were not compatible for the reaction (entry 2, Table 1, see Electronic Supplementary Information, ESI Table 1). Catalyst screening studies suggested that other catalysts such as KI, NaI, TBAI, TBAB, NIS, or NCS were not suitable for the reaction (entries 3-8, Table 1). Nevertheless, it was pleasing to find that the reaction of **1a** with I_2 (50 mol %) and TBHP (in decane) proceeded well to furnish the product **2a** in 70% yield (entry 9, Table 1). The similar reaction of **1a** with I_2 (50 mol%) in the presence of molecular oxygen, or H_2O_2, resulted in the formation of **3a** in low yields (entries 10-11). Further screening studies revealed that the oxidants such as cumenehydroperoxide, ditertiarybutylperoxide, *m*-CPBA, or $K_2S_2O_8$ were not helpful, and these reactions did not afford the product **3a** (see Electronic Supplementary Information). Increasing or decreasing the amount of I_2 did not bring any noticeable change as these reactions furnished product **2a** in 70 and 60% yields, respectively (entries 12-13, Table 1). Using TBHP either in 4 equiv or 2 equiv resulted in decreasing the yields of the products (entries 14 and 15). A reaction of ketone **1a** with I_2 (50 mol %) in DMSO in the absence of TBHP or

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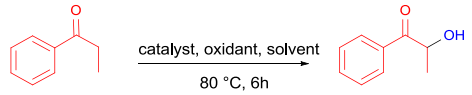
molecular oxygen (under argon atmosphere) furnished **3a** in low yield (37%) indicating that the reaction can also proceed in the absence of external oxidants such as TBHP or molecular oxygen. With these screening studies, α-hydroxylation of ketones were carried out using 50 mol% of I_2, TBHP (in decane, 3 equiv) in DMSO as sovent.

Table 1. Optimization studies[a]



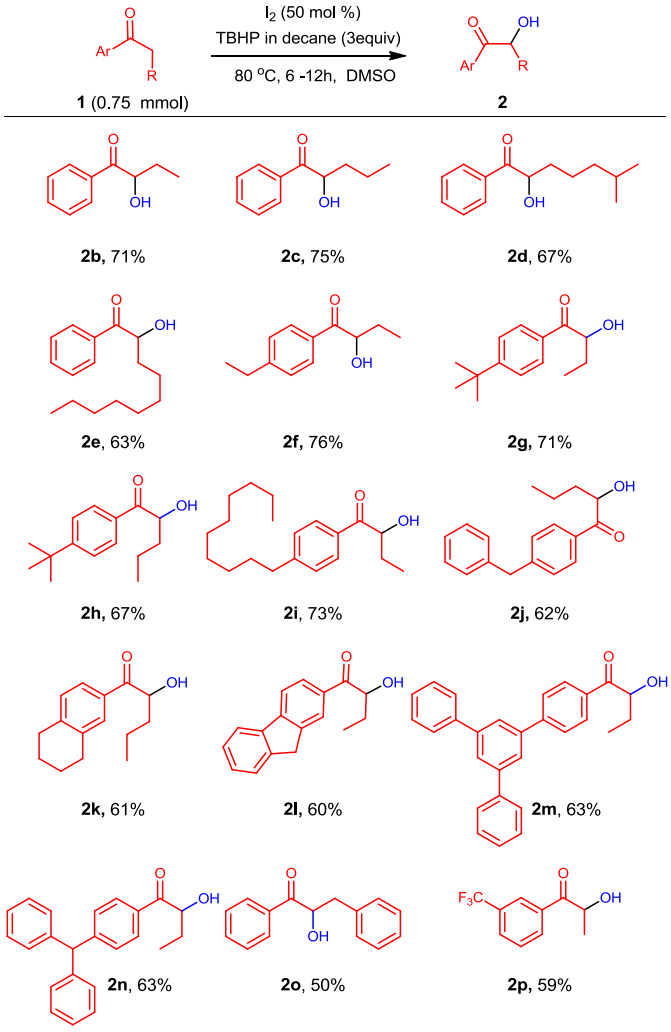
1a 2a

entry	catalyst mol%)	oxidant (3 equiv)	solvent	conversion[b]
1	I_2 (50)	aq.TBHP	DMSO	58%
2	I_2 (50)	aq.TBHP	solvent	NR[c]
3	KI (30)	aq.TBHP	DMSO	NR
4	NaI (30)	aq.TBHP	DMSO	NR
5	TBAI (30)	aq.TBHP	DMSO	NR
6	TBAB (30)	aq.TBHP	DMSO	NR
7	NIS (30)	aq.TBHP	DMSO	NR
8	NCS (30)	aq.TBHP	DMSO	NR
9	**I_2 (50)**	**TBHP in decane**	**DMSO**	**70%**
10	I_2 (50)	O_2	DMSO	41%
11	I_2 (50)	H_2O_2	DMSO	36%
12	I_2 (100)	TBHP in decane	DMSO	70%
13	I_2 (30)	TBHP in decane	DMSO	60%
14	I_2 (50)	TBHP in decane	DMSO	68%[d]
15	I_2 (50)	TBHP in decane	DMSO	58%[e]
16	I_2 (50)	(None) Ar atmosphere	DMSO	37%[f]

[a]Reaction conditions: **1a** (0.75 mmol), I_2 (0.37 mmol), oxidant (2.24 mmol) in of DMSO (1 mL) at 80 °C. [b]Isolated yield. [c] Solvents: CH_3CN, DCE, EtOAc, toluene, DMF, DMA. [d]4 Equiv of TBHP. [d]2 Equiv of TBHP. [f]The reaction was performed for 12h. DMA = *N,N*, Dimethyl acetamide. TBAI = *tetra*-n-butylammonium iodide, TBAB = *tetra*-n-butyl ammonium bromide, NIS = *N*- iodosuccinimide, NCS = *N*-chlorosuccinimide, NR = no reaction.

Having found the optimal reaction conditions, the scope of the coupling reaction was explored using a variety of aryl ketones. The reaction was facile with ketones such as 1-phenylbutan-1-one, 1-phenylpentan-1-one, 6-methyl-1-phenylheptan-1-one, and 1-phenyldecan-1-one furnished their corresponding α-hydroxy ketones **2b**, **2c**, **2d**, and **2e** in good yields (71, 75, 67, and 63%, respectively, Table 2). Further, 1-(4-ethylphenyl)butan-1-one, 1-(4-(tert-butyl)phenyl)butan-1-one, 1-(4-(tert-butyl)phenyl)pentan-1-one, 1-(4-decylphenyl)butan-1-one and 1-(4-benzylphenyl)pentan-1-one underwent a smooth hydroxylation to afford their corresponding α-hydroxy products **2f**, **2g**, **2h**, **2i**, and **2j** in good yields (76, 71, 67, 73, and 62%, respectively, Table 2). These examples show that a variety of electron releasing aliphatic groups such as ethyl, *tert*-butyl, decyl and benzyl group on the *para*position of phenyl ring is well tolerated. The ketones such as 1-(5,6,7,8-tetrahydronaphthalen-2-yl)pentan-1-one and 1-(9H- fluoren-2-yl)butan-1-one furnished their corresponding α-hydroxy products **2k**, and **2l** in good yields (61 and 60%, respectively, Table 2). Interestingly, the ketones such as 1-(5'-phenyl-[1,1':3',1''-terphenyl]-4-yl)butan-1-one and 1-(4-benzhydrylphenyl)butan-1-one under the optimal reaction conditions furnished the corresponding hydroxy ketones **2m**, and **2n** in 63 and 63%, respectively. Similarly, 1,3-

Table 2. Substrate Scope[a,b]



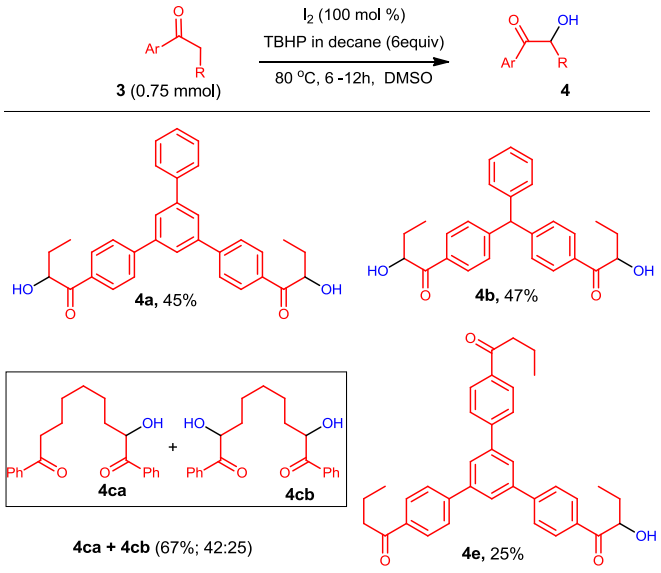
[a] Reaction conditions: ketone (0.75 mmol), I_2 (0.37 mmol), TBHP (5.5 M solution in decane), (2.24 mmol) in DMSO (1 mL) at 80 °C. [b]Isolated yield.

diphenylpropan-1-one furnished the corresponding hydroxy ketone **2o** in 50% yield. As observed, the formation of α-hydroxy ketones such as **2i**, **2j**, **2k**, **2n** and **2o** is interesting as benzylic positions in these compounds are intact under the reaction conditions. 1-(3-(Trifluoromethyl)phenyl)propan-1-one, which contains electron-withdrawing group also underwent a smooth α-hydroxylation to furnish the corresponding hydroxy product **2p** in moderate yield (59%).

A few interesting examples of α-hydroxylation of diketones and triketones are presented in Table 3. As can be seen, the reaction diketones1,1'-(5'-phenyl-[1,1':3',1''-terphenyl]-4,4''-diyl)bis(butan-1-one), and 1,1'-((phenylmethylene)bis(4,1-phenylene))bis(butan-1-one) with I_2 (1 equiv) and TBHP (in decane, 6 equiv) resulted in the formation of their corresponding dihydroxy products **4a** and **4b** in 45 and 47%, respectively. However, the reaction of 1,9-diphenylnonane-1,9-dione with I_2 (1 equiv) and TBHP in decane (6 equiv) furnished the mixture of monohydroxyketone (**4ca**) and dihydroxy ketone (**4cb**) in 67% yield in 9:5 ratios. Our attempts to obtain either monohydroxy ketone or dihydroxy ketone

exclusively resulted in the decomposition of the starting material. Similarly, our attempt to carry out the same reaction with triketone with I_2 (1 equiv) and TBHP in decane (6 equiv) resulted in the formation of corresponding mono-hydroxylated product **4d** in 25%. Our attempts to improve the yields by using excess of I_2 and TBHP has resulted in the decomposition of the starting material.

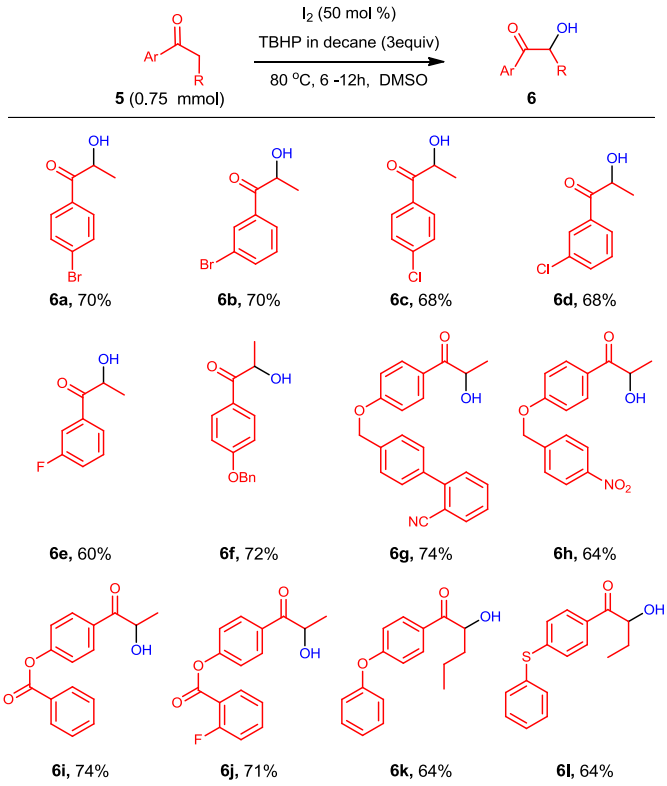
Table 3. α-Hydroxylation of diketones and triketones[a, b]



[a]Reaction conditions: ketone (0.75 mmol), iodine (0.75 mmol), TBHP (5.5 M solution in decane), (4.48 mmol) in DMSO (2 mL) at 80 °C.[b]Isolated yield.

In view of expanding the scope of α-hydroxylation reaction, a variety of aromatic ketones with substitution on aromatic ring have been subjected to the α-hydroxylation reaction under the optimal reaction conditions (Table 4). Substituents such as halide groups at *para*-position as well as *meta*-position of the aromatic rings found to have no effect on the outcome of the reaction. Hence, halogen substituted propiophenone derivatives such as 1-(4-bromophenyl)propan-1-one, 1-(3-bromophenyl)propan-1-one, 1-(4-chlorophenyl)propan-1-one, 1-(3-chlorophenyl)propan-1-one, and 1-(3-fluorophenyl)propan-1-one under the optimal conditions furnished their corresponding hydroxylated products **6a**, **6b**, **6c**, **6d**, and **6e**, in 70, 70, 68, 68 and 60% yields (Table 4). Further, the aromatic ketones substituted at *para*-positions with moderately activating groups such as alkoxy groups also underwent a smooth α-hydroxylation reaction to furnish their corresponding hydroxy ketones. Thus, the reaction of a variety of aryloxy substituted propiophenones proceeded smoothly under the optimal conditions to furnish the α-hydroxy ketones **6f**, **6g**, **6h**, **6i**, and **6j** in good yields (72, 74, 64, 74 and 71% yields, respectively, Table 4). It is worth noting that this α-hydroxylation reaction tolerates a variety of functional groups such as nitrile, nitro and ester functionalities (**6g**, **6h**, **6i** and **6j**). As anticipated, 1-(4-phenoxyphenyl)pentan-1-one reacted smoothly to afford the product **6k** in 64%. It was found from the reaction of 1-(4-(phenylthio)phenyl)butan-1-one that the sulfides are also well tolerated under the reaction conditions to form the corresponding α-hydroxy ketone **6l** in 64% and oxidation of sulfide group to sulphone or sulfoxide was not observed under the reaction conditions.

Table 4. α-Hydroxylation of aromatic ketones[a, b]

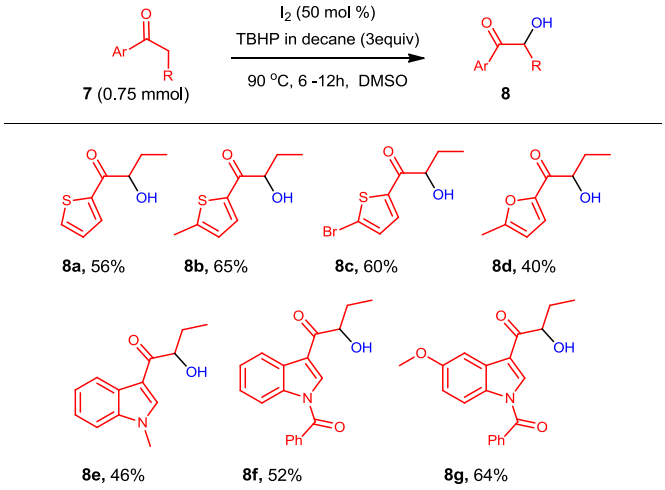


[a] Reaction conditions: ketone (0.75 mmol), I_2 (0.37 mmol), TBHP (5.5 M solution in decane), (2.24 mmol) in DMSO (1 mL) at 80 °C. [b]Isolated yield.

α-Hydroxy ketones of heterocyclic compounds are important and useful intermediates which are amenable for a variety of useful heterocyclic products. Therefore ketones of thiophenes, indoles and furan are subjected to the α-hydroxylation and the results are presented in Table 5. As can be seen, 1-(thiophen-2-yl)butan-1-one, 1-(5- methylthiophen-2-yl)butan-1-one, and 1-(5-bromothiophen-2-yl)butan-1-one underwent a facile α-hydroxylation to furnish the corresponding α-hydroxy ketones **8a**, **8b**, and **8c** in 56, 65, and 60%, respectively (Table 5). Similarly, the reaction of furan derivative such as 1-(5-methylfuran-2-yl)butan-1-one proceeded to furnish the corresponding α-hydroxy ketone **8d** in low yield (40%). As indoles are integral part of a variety of natural products,[7] it would be interesting to subject the ketones of indole and its derivatives for the α-hydroxylation reaction. As can be seen, 1-(1-benzoyl-5-methoxy-1H-indol-3-yl)butan-1-one, 1-(1-methyl-1H-indol-3-yl)butan-1-one, and 1-(1-benzoyl-1H-indol-3-yl)butan-1-one underwent a facile reaction to furnish the corresponding α-hydroxy ketones **8e**, **8f**, and **8g** in moderate to good yields (46, 52, and 64%, respectively, Table 5). However our attempts to perform

similar hydroxylation with aliphatic ketones were not successful.

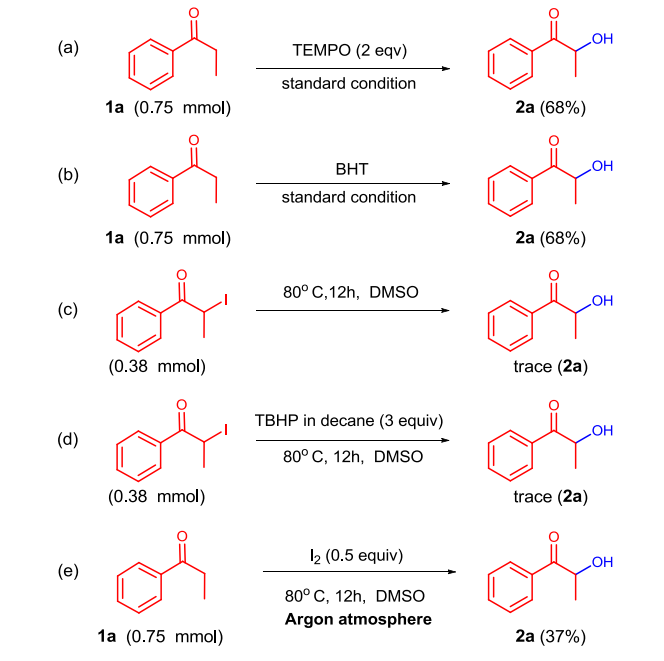
Table 5. α-Hydroxylation of heterocyclic ketones[a,b]



[a]Reaction conditions: ketone (0.75 mmol), I_2 (0.37 mmol), TBHP (5.5 M solution in decane), (2.24 mmol) in DMSO (1 mL) at 90 °C. [b]Isolated yield.

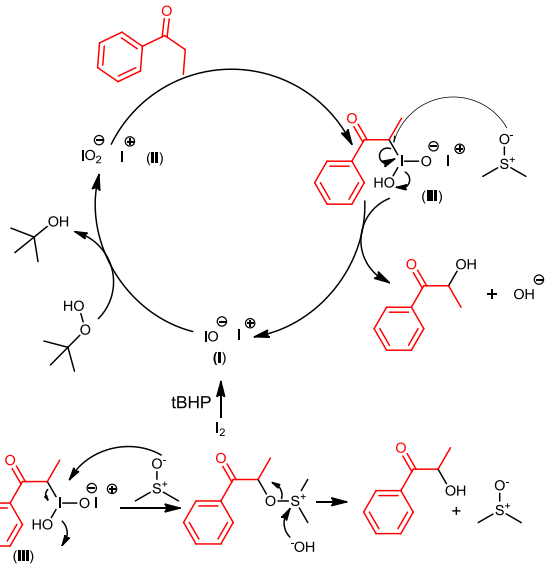
To understand the mechanism of this reaction, a few control experiments were performed. First, the reaction of propiophenone (**1a**) under the standard reaction conditions in the presence of TEMPO or BHT was found to proceed well to form the corresponding hydroxyl ketone **2b** in 68% yield (Schemes 1a and 1b) indicating that the reaction may not be proceeding through a radical mechanism. Further to find whether the 2-iodo-1-phenylpropan-1-one is an intermediate,

Scheme 1. Control experiments for mechanistic studies



two independent experiments were performed. As can be seen the reaction of 2-iodo-1-phenylpropan-1-one in the presence or in the absence of TBHP did not furnish the expected product **2a** (Scheme 1c and 1d) indicating that the iodo derivative may not be an intermediate in the reaction. It is appropriate to mention that the reaction of propiophenone **1a** under the optimal conditions in the absence of oxidants such as TBHP or O_2 (under argon atmosphere furnished the corresponding hydroxyl compounds in 37% (Scheme 1e, and also entry 16, Table 1)[8].

Based on these experiments, and the literature precedence,[9] a tentative mechanism has been proposed in Scheme 2. We believe that the reaction of I_2 with TBHP forms hypoiodite (IO^-I^+, **I**), which reacts with TBHP to form dihypoiodate ($IO_2^-I^+$, **II**).[8] The species **II** thus generated undergoes an electrophilic addition with ketone (propiophenone) to generate **III**, which upon nucleophilic displacement by DMSO furnishes **2a**. As the reaction of **1a** under optimal conditions in the absence of TBHP and O_2 (in argon atmosphere) furnished low yield of the product **2a** (37%, entry 28, Table 1), we believe that both TBHP and DMSO are necessary for the reaction to proceed well.



Scheme 2. A tentative mechanism

Conclusions

In summary, α-hydroxylation of aromatic ketones using substoichiometric amount of iodine has been described. This metal-free methodology of synthesizing α-hydroxy ketones has been demonstrated to proceed well with a variety of aromatic ketones. It is demonstrated that the method is easily adoptable for synthesizing several α-hydroxy heterocyclic compounds, which are useful precursor for a variety of heterocyclic compounds. The present protocol of α-hydroxylation of ketones has been used to synthesize dihydroxy diketone derivatives. Further, work is progress to uncover the utility of this reaction.

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