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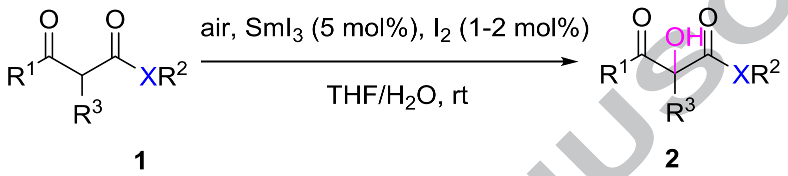

R^1, R^2 = aryl, or alkyl; R^3 = alkyl; X=O, or N

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Aerobic α-Hydroxylation of β-Keto Esters and Amides by Co-catalysis of SmI_3 and I_2 under Mild Base-free Conditions

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ABSTRACT

A clean base-free α-hydroxylation of β-keto esters and amides has been developed, in which air was used as the oxygen source and SmI_3 and I_2 were applied as the catalysts, affording the corresponding α-hydroxylated 1,3-dicarbonyl products in good to excellent yields under mild conditions. Mechanism discussion shows that both two oxygen atoms of dioxygen are utilized and incorporated into the product through a unique free-radical process.

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α-Hydroxy-β-keto esters and amides moiety is a ubiquitous, important synthetic intermediary and common structural unit of a wide range of natural products and pharmaceutical compounds, serving as an important contributor to biological activities[1] (Figure 1). Great interest of synthetic community has been received to resolve the concise syntheses of such structural motifs. Quite a number of useful methods have been developed for the preparation of α-hydroxy-β-dicarbonyl moieties,[2] including approaches based on asymmetric enol epoxidation.[3] Among these, direct oxidations of 1,3-dicarbonyl compounds with various oxidants, such as high valence metal oxides,[4] peroxide,[3a,5] peracid,[6] high-valence iodidum,[7] and molecular oxygen catalyzed by metal catalysts,[8-12] were frequently reported (Figure 2). However, many of the earlier methods often require stoichiometric amounts of organic oxidants or heavy metals and present disadvantages of high costs of materials and producing toxic wastes and byproducts. Recent report also showed that I_2 could be applied to the similar α-hydroxylation under UV irradiation.[13] It was believed that high-energy UV light plays as the initiator of the free radical process. In this work, we want to report a new direct α-hydroxylation of various β-keto esters and amides by using air (oxygen) as the clean oxidant under the catalysis of SmI_3 and I_2 (Figure 2). This new cheap and environmentally friendly method provides an easily operational and high-yielding catalytic transformation to the α-hydroxylated products (up to 95% yield) without the assistance of light and base.

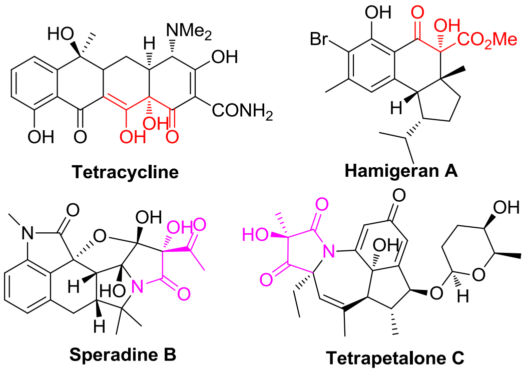


Figure 1. Several bioactive natural molecules bearing α-hydroxy-β-dicarbonyl moiety.

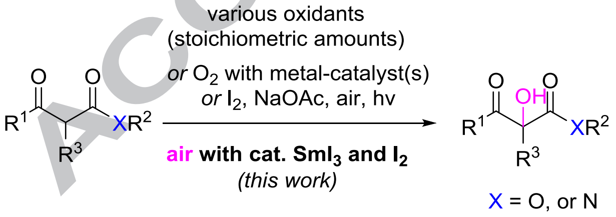
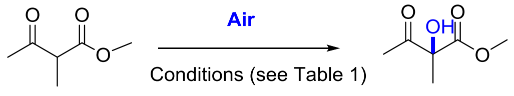


Figure 2. α-Hydroxylation of 1,3-dicarbonyl compounds.

Our initial discovery was observed on the reaction of methyl 2-methyl-3-oxobutanoate (**1a**) with catalytic amount of SmI_2 (5 mol%) in the open air (Table 1). Long-time stirring of the mixture in the presence of Seignette salt (5 mol%) at room temperature afforded a high-yield single product (entry 1), which was elucidated as the corresponding α-hydroxylated product **2a** by the NMR and MS methods. The high efficiency of the observed hydroxylation reaction promoted us to further optimize and investigate this reaction, as well as the unknown catalytic capability of Sm(III) salts.

Table 1. Optimization of reaction conditions.[a]



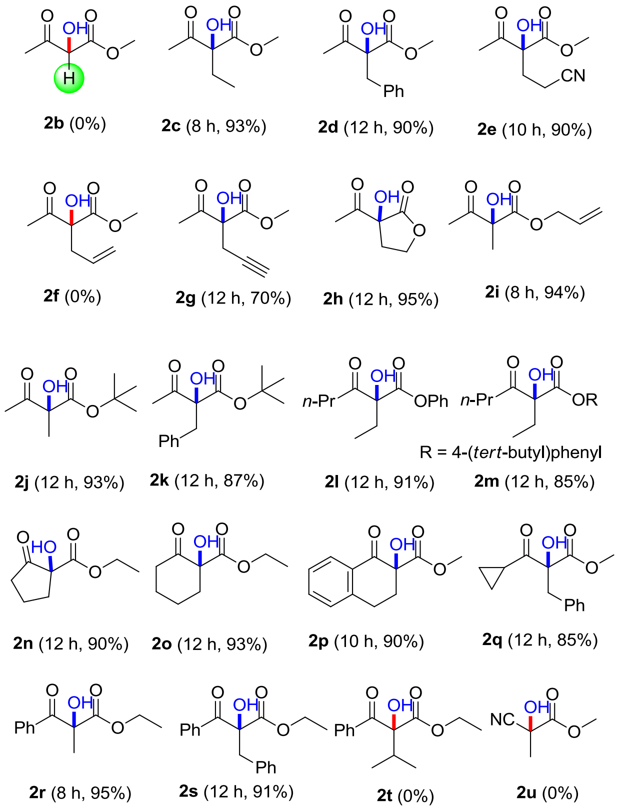
1a **2a**

Entry	Catalyst (5 mol%)	Co-catalyst or additive	Solvent(s)	T (h)	**2a** (%)
1	SmI_2	Seignette salt[b]	THF/H_2O	24	82
2	SmI_2	---	THF/H_2O	24	80
3	SmI_3	---	THF	24	50
4	SmI_3	---	THF/H_2O	24	90
5	SmI_3	I_2 (1 mol%)	THF/H_2O	8	95
6[c]	SmI_3	I_2 (1 mol%)	THF/H_2O	8	95
7	$Sm(OTf)_3$	---	THF/H_2O		NR
8	$Sm(OTf)_3$	I_2 (1 mol%)	THF/H_2O	8	95

[a] A mixure of THF and water (5:1) was used as the solvent. [b] Seignette salt (5 mol%) was applied; [c] Reaction underwent in darkness.

Optimization of the hydroxylation reaction conditions was performed upon the oxidation of substrate **1a** (Table 1). In the presence of SmI_2 (5 mol%) in THF/H_2O (5:1 v/v), similar results were achieved either in the presence and absence of Seignette salt (entries 1 and 2). Because Sm^{2+} is extremely sensitive to O_2 and could be quickly oxidized to Sm^{3+} in air, a stable Sm^{3+} salt (SmI_3) was then employed in the following reactions. Removal of water slowed down the reaction (entry 3). It mentioned that the solubility of SmI_3 and O_2 in the reaction medium might effect on the reaction efficiency, and addition of water would help to overcome such a problem (entry 4). Furthermore, application of iodide (1 mol%) as the co-catalyst significantly increased the rate of the reaction (entry 5), and even in the darkness (entry 6). In order to authenticate the role of iodine in the reaction, another salt $Sm(OTf)_3$ was applied. With or without 1 mol% of iodine, the two reactions catalyzed with $Sm(OTf)_3$ (5 mol%) showed significant difference (entries 7 and 8). These evidences clearly define that iodine also plays crucial roles in the reaction, and eventually help us to propose an appropriate reaction mechanism.

Under the above optimized conditions, reactions of a variety of 1,3-dicarbonyl esters were firstly examined (Figure 3). Most of the substrates including different α,γ-substituents and ester groups could be smoothly oxidized by air, giving the corresponding α-hydroxylated products in good yields, except the reactions for **2b**, **2f**, **2t**, and **2u**. A number of earlier efforts on the synthesis of **2b** through similar mechanism were also unsuccessful,[13,14] and so as in this study. The failure may be due to insufficient formation of the cyclic enolate with Sm(III) (see below text for more discussion on the mechanism). Unsuccessful synthesis of **2f** might be due to the disruption of radical process by its internal olefin functionality, while steric hindrance may be accountable in the failure of **2t**. The negative result for **2u** might be caused by the insufficient coordination ability to generate the essential cyclic transition state among carbonyl sp^2-oxygen or sp^3 ester-oxygen), cyano nitrogen, and samarium(III). Substrates having substituents with π-electron system at β-γ position to carbonyl (phenyl and vinyl) suffered with limited success, because interaction of π-electrons with samarium results in failure of forming cyclic transition state.



2b (0%) **2c** (8 h, 93%) **2d** (12 h, 90%) **2e** (10 h, 90%)

2f (0%) **2g** (12 h, 70%) **2h** (12 h, 95%) **2i** (8 h, 94%)

R = 4-(*tert*-butyl)phenyl

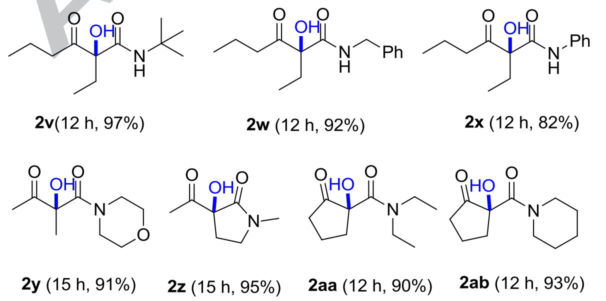
2j (12 h, 93%) **2k** (12 h, 87%) **2l** (12 h, 91%) **2m** (12 h, 85%)

2n (12 h, 90%) **2o** (12 h, 93%) **2p** (10 h, 90%) **2q** (12 h, 85%)

2r (8 h, 95%) **2s** (12 h, 91%) **2t** (0%) **2u** (0%)

Figure 3. SmI_3 (5 mol%) and I_2 (1 mol%) co-catalyzed aerobic α-hydroxylation of 1,3-dicarbonyl esters.

Unlike those for esters, less methods are available for the α-hydroxylation of amides since it is yet to be investigated thoroughly. Similar reagents were reported to apply in the transformation, including oxone,[14] high-valence iodidum,[7,15] peroxide,[16] and molecular oxygen catalyzed by metal catalysts.[11b,12b,17,18] To explore the application scope of the above aerobic hydroxylation conditions, a number of β-keto amides were also examined under the optimized conditions (Figure 4). Combinative use of 5 mol% of SmI_3 and 1 mol% of iodine did offer good yields of α-hydroxylated products. However, these reactions were found to slow down significantly. Further experimental trials showed that the reactions could be speeded up by increasing the amount of iodine up to 2 mol%. Finally, syntheses of **2v-2ab** were carried out in acceptable times using 5 mol% of SmI_3 and 2 mol% of iodine as the catalysts.[19] Again, impressive yields were observed for all the products (**Figure 4**), not only for *N-mono*-substituted amides, but also for *N,N-di*-substituted amides.



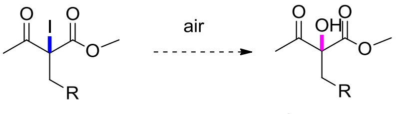
2v(12 h, 97%) **2w** (12 h, 92%) **2x** (12 h, 82%)

2y (15 h, 91%) **2z** (15 h, 95%) **2aa** (12 h, 90%) **2ab** (12 h, 93%)

Figure 4. Aerobic α-hydroxylation of 1, 3-dicarbonyl amides catalyzed with SmI_3 (5 mol%) and I_2 (2 mol%).

Literature work mentioned that similar aerobic hydroxylation of 1,3-dicarbonyl compounds might proceed through a 2-iodo-intermediate **3**,[16] in which the C−I bond was broken to generated a carbon radical and furnish the final hydroxylation. To check such a possibility, compounds **3a** and **3c** were prepared[20] and examined under the standard conditions of aerobic oxidation. The results showed that the four tested reactions didn't happen and all the starting materials were recovered (Table 2). Based on such observation, a possible radical process through the C−I bond cleavage was therefore excluded.

Table 2. Transformation of iodo-intermediates 3.[a]



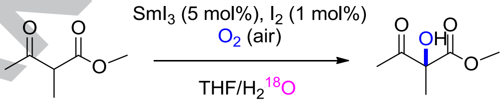
3a (R = H)
3c (R= Ph)

2a (R = H)
2c (R= Ph)

Entry	Catalyst [a]	Co-catalyst	Solvent(s)	Result
1	SmI_3	---	THF	NR
2	SmI_3	I_2	THF/H_2O	NR
3	$Sm(OTf)_3$	---	THF	NR
4	$Sm(OTf)_3$	I_2	THF/H_2O	NR

[a] 5 mol% of Sm(III) salt and 1 mol% of I_2 were used under standard conditions. NR = no reaction.

Source of the newly introduced oxygen in the products was also investigated. An experiment was conducted using ^{18}O-labelled water as the co-solvent. Oxygen isotopic abundance measurement of the product **2a** through HRMS method revealed that air was the only source of that oxygen (Scheme 1).



1a **2a**

Scheme 1. Experiment in ^{18}O-isotope labeling water.

To explain the newly developed aerobic hydroxylation of 1,3-dicarbonyl compounds by co-catalysis of SmI_3 and I_2, an appropriate mechanism was proposed based on the above results and control experiments (Figure 5). The 1,3-dicarbonyl compound should be the only reducing agent in this quick oxidation, because a single high-yielding hydroxylated product is afforded after the reaction without any additional reductant. Both oxygen atoms of dioxygen molecule are believed to be utilized and incorporated into the product, affording two equivalents of the product. Strong Lewis acidity and high oxygen-affinity of Sm(III) promotes 1,3-dicarbonyl substrate **1** to quickly undergo enolization, producing a cyclic enolate **A**,[21] in which Sm(III) prefers to coordinate with the sp^3 oxygens, and releasing one molecule of HI. Traditionally, completion of such an enolization

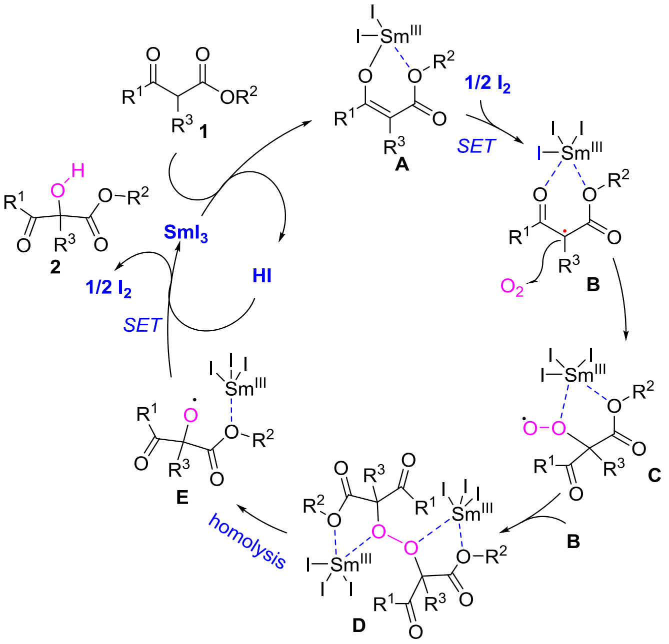


Figure 5. A proposed mechanism for the catalytic process.

needs the assistance of a base (to remove HI and move the equilibrium to the product side). According to the variable reaction times with different substrates in this study, Sm(III) is thought to predominately coordinate with sp^3 oxygens rather than sp^2 oxygens in the cyclic enolate **A**.[21] Enolate **A** then transfers an electron to iodine to form free radical species **B**, which subsequently reacts with dioxygen and generates a peroxide free radical **C**. The peroxide radical **C** couples with its precursor **B** to form a symmetrical dimeric intermediate **D**. The dimer **D** undergoes homolytic O-O cleavage, affording two molecules of oxy-radical **E**. Eventually, the oxy-radical **E** abstracts a hydrogen from previously *in situ* generated HI, furnishing the hydroxylated product **2** and dropping off half mole of iodine (Figure 5).

A possible alternative supramolecular mechanism is also proposed to explain this type of C-H hydroxylation reaction (Figure 6). Dimerization of *in situ* generated enolate **A** happens through exchanging one of the ligation oxygens of Sm(III), providing a symmetrical head-to-tail macrocycle intermediate **F**. To release the unfavorable repulsion of internal negative charges, enolate **F** is then oxidized with iodine through a single-electron-transfer (SET) process, giving a bis-Sm(III)-coordinated bi-radical intermediate **G**.[22,23] However, these two radicals in **G** is too far away or sterically crowded to approach each other, and molecular oxygen perfectly serves as a proper bridge between the two radicals through its coordination with two Sm(III) in the macrocyclic intermediate **H**. Unlike the stepwise formation of **D** (Figure 5), a symmetrical dimeric peroixde **I** could be provided by direct reaction of **G/H** with dioxygen simultaneously. Eventually, the O-O bond cleavage of dimer **I** is carried out by reaction with previously produced HI, affording two molecules of product **2** and regenerating both two catalysts SmI_3 and I_2.[3g]

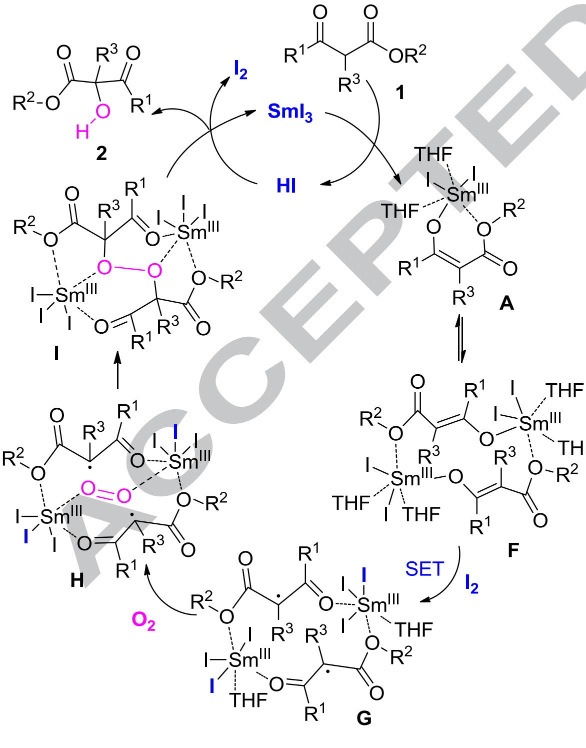


Figure 6. An alternative possible supramolecular mechanism.

In summary, we have developed a new aerobic hydroxylation of β-keto esters and amides by co-catalysis of SmI_3 and I_2 under mild base-free conditions in this work. Possible mechanisms were proposed to explain the crucial catalytic roles of Sm(III) and I_2 based on experimental evidences. This newly developed method, using air as the clean oxidant, not only presents wide applicability and good functional group tolerance, but also shows great advantages of high-yielding, economic green process and ease of operation. We believe it is valuable in future organic synthesis and helpful to understand the unknown catalytic capability of samarium(III).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at xxxxxx.

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Highlights for MS#TETL-D-16-00728

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Shun-Ming Yu, Kai Cui, Fei Lv, Zhen-Yu Yang,* and Zhu-Jun Yao*

- Clean base-free α-hydroxylation of β-keto esters and amides with air.
- The first report of new binary catalytic system of SmI_3 and I_2.
- Wide scope of substrates, excellent yields, mild conditions.
- Both two oxygen atoms of dioxygen are utilized and incorporated into the product through a unique free-radical process.