Chiral Primary Amine/Ketone Cooperative Catalysis for Asymmetric *α*-Hydroxylation with Hydrogen Peroxide

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Abstract

Carbonyl and amine are yin and yang in organocatalysis that mutually activate and transform each other. As intrinsically reacting partners, carbonyl and amine tend to condensate, depleting their individual activity when employed as catalysts. Though widely established as prominent catalytic strategies, aminocatalysis and carbonyl catalysis seems not coexist well and a cooperative amine/carbonyl dual catalysis remains virtually unknown. Here we report a cooperative primary amine and ketone dual catalysis in the asymmetric *α*-hydroxylation with H_2O_2. Besides participating in the typical enamine catalytic cycle, the chiral primary amine catalyst was found to work cooperatively with a ketone catalyst to activate H_2O_2 *via* an oxaziridine intermediate derived from *in-situ* generated ketimine intermediate. The resulted enamine-oxaziridine coupling then facilitated highly-controlled hydroxylation of *β*-ketocarbonyls that are not possible with other catalytic methods. The dual catalytic approach allows for highly enantioselective *α*-hydroxylation of a broad range of *β*-ketocarbonyls. Particularly, late-stage hydroxylation for peptidyl amide or chiral esters can also

be achieved with high stereoselectivity. With its operational simplicity and mild conditions, this cooperative amine/ketone catalysis provides a new strategy in catalytic activation of H_2O_2 and expands the domain of typical amine and carbonyl catalysis to include those challenging transformations.

Introduction

Aminocatalysis is a fundamental activation mode in the transformations of carbonyl compounds. The catalysis has become a prevalent and enabling strategy for α- or β-functionalizations of carbonyls *via* enamine or iminium ion activation (Fig. 1a)[1-2]. On the other hand, carbonyl catalysis has recently appeared as a viable approach for the α-functionalization of glycine-type amines[3]. Like its amine counterpart, carbonyl catalysis also bears a biological origin from Nature's enzyme, the pyridoxal-dependent aldolases[4], and its prominent early successes can be traced back even before the renaissance of organocatalysis when chiral ketones or ketimines catalysts were extensively explored as metal-free oxidation catalysts[5-7]. In these cases, the carbonyl catalysts promoted concerted oxygen atom-transfer with olefins *via* dioxarine or oxaziridine intermediates and similar catalysis has been advanced to C-H insertion reactions of alkanes lately[8-9]. Most of such ketone/aldehyde catalysts bear reactive carbonyls with electron-withdrawing substituents, and would readily couple with nucleophilic amine. Hence, as inherent reacting partners, amine and ketone/aldehyde carbonyl are mutually-exclusive for targeted catalytic transformations from a mechanistic point of view, like a yin-yang interplay. A cooperative amine and carbonyl dual catalysis remains virtually unknown.

Widely applied in industry and environmental protection as a green terminal oxidant, hydrogen peroxide is considered as ideal oxygen source for chemical synthesis as it has the most active-oxygen content and is relatively safe and easy-to-handle with water as the sole byproduct[10-12]. Enantioselective C-H hydroxylation with H_2O_2 is arguably one of the most straightforward and atom-economic oxidation strategies in accessing

chiral alcohols. However, to achieve catalytic asymmetric hydroxylation with hydrogen peroxide remains a great challenge and successful examples along this line are extremely scarce[13-14]. In order to modulate the activity and stereoselectivity under mild conditions, catalytic activations of H_2O_2 into more electrophilic oxygen species are required as H_2O_2 itself is less electrophilic and even serves as a good nucleophile under neutral and basic conditions[15]. Besides the established metal-mediated activation strategy[12,14,16-17], there recently appeared organocatalytic strategy *via* dioxarine, oxaziridine or perhydrate intermediates with ketone or imine as the catalysts (Fig. 1b)[8-9,18-21]. No enantioselective version has been reported so far, however. Herein, we reported the application of ketone catalysis in the asymmetric enamine-based α-hydroxylation with hydrogen peroxide. Though enamine-based α-oxygenation has been extensively explored, the successful examples relied on preactivated reagents such as oxaziridines, nitrosobenzenes, benzoyl peroxide and singlet oxygen[22-25]. Catalytic direct enamine hydroxylation with hydrogen peroxide has not been achieved[26]. Ooi reported an enolate-based asymmetric α-hydroxylation with hydrogen peroxide, unfortunately the reaction required a stoichiometric trichloroacetonitrile as an activating reagent[27]. Similar reactions have also been examined with chiral Lewis base catalysis but with moderate enantioselectivity and limited scopes[28].

In our strategy (Fig. 1c), chiral primary amine catalyst worked in concert with a ketone catalyst to promote effectively α-hydroxylation of β-ketocarbonyls with excellent stereocontrol beyond reach otherwise. The joint amine/ketone catalytic protocol could be applied in the late-stage hydroxylation reaction of complicated molecules. Mechanism studies revealed that the reaction proceeded *via* an enamine-oxaziridine coupling derived from the two working catalysts and both amine and ketone catalysts participated in activation of hydrogen peroxide *via* an iminium ion intermediate (Fig. 1c).

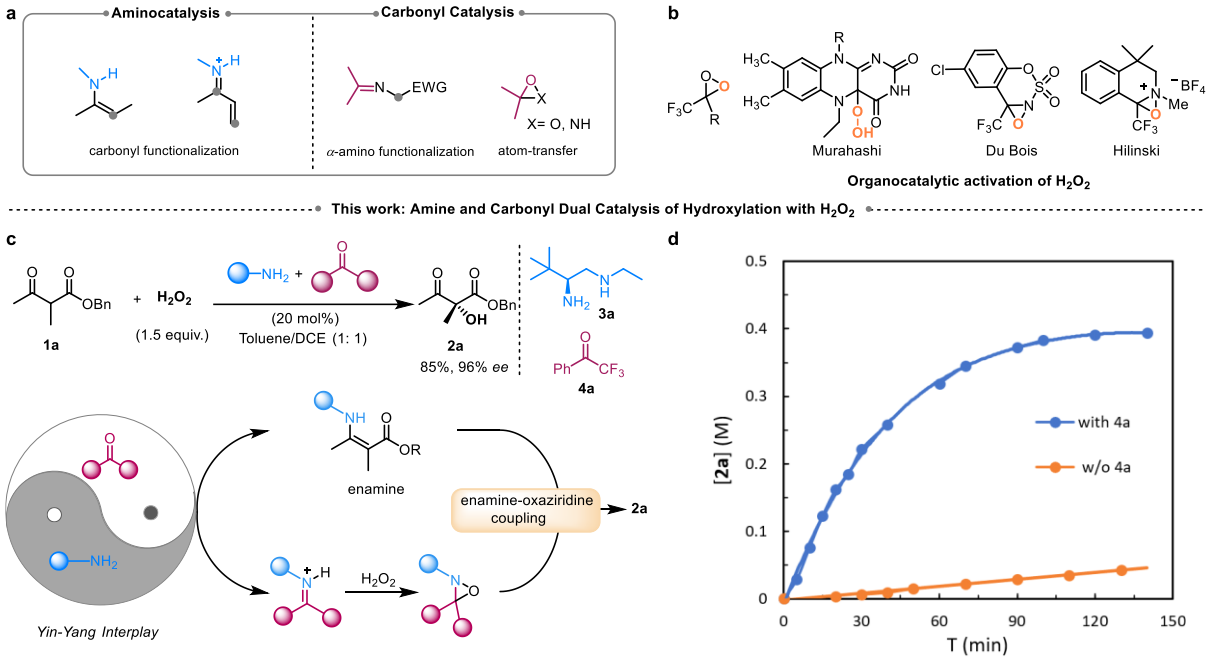


Figure 1. Organocatalytic activation of hydrogen peroxide. a, Typical activation modes in aminocatalysis and carbonyl catalysis. **b**, Active intermediates in organocatalytic activation of H_2O_2. **c**, Our concepts on amine and carbonyl dual catalysis: Chiral iminium ion *in-situ* generated by primary amine and ketone catalysts activates H_2O_2 in the form of chiral oxaziridine, which couples with enamine, also derived from amine catalysts to afford α-hydroxylation product **2a**. **d**, Kinetic profiles of ketone catalysis in the reaction of **1a**.

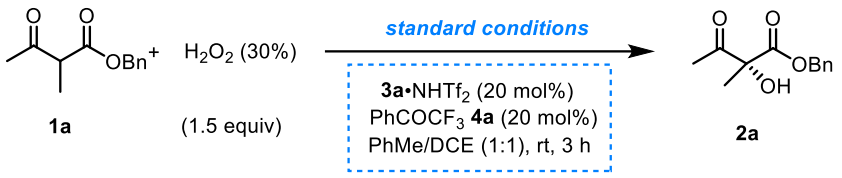
Results

Catalyst screening and reaction development. In our initial studies, we investigated the enantioselective hydroxylation of β-ketoester **1a** with primary amine catalysts developed by our group. Among different primary amine catalysts screened, primary-secondary diamines such as **3a** were identified as the preferred amine catalyst. The reaction with only amine catalyst (e.g. **3a**/Tf_2NH) was sluggish requiring at least 48 hours for complete conversion (Table 1, entry 3). At this point, the addition of a ketone catalyst was found to significantly enhance the reaction rate, and the optimal **3a**/**4a** combination led to nearly 10-times faster reaction (Fig. 1d). The reaction now gave 85% yield and 96% *ee* in 3 hours (Table 1, entry 1). Aldehydes

such as benzaldehyde was found to totally inhibit the reaction (Table 1, entry 9) and the smallest ketone, acetone showed diminished activity with maintaining enantioselectivity (Table 1, entry 10). Electron-withdrawing substitutions on the ketone carbonyl are critical to activity (Table 1, entries 11-13) and both CF_3 (**4a** or trifluoroacetone) and carboxylate (**4c**) substituted ketones showed good activity with similar enantioselectivity. The primary-secondary diamine motif (e.g. **3a-3c**) was critical to the joint catalysis as the reaction with tertiary amine (**3d**) showed rather low activity and enantioselectivity (Table 1, entries 14-16). In a control experiment, no reaction was observed in the absence of amine catalyst (Table 1, entry 2), pinpointing the decisive roles of aminocatalysis for the reaction. In consistent with well-known role of Brϕnsted acid in facilitating aminocatalysis, the use of strong acid additive such as Tf_2NH is essential for both the activity and enantioselectivity and low yield and enantioselectivity was obtained in its absence (Table 1, entry 4).

Other oxidants have also been examined in the dual catalytic system (Table 1, entries 5-8). The commonly employed oxidants such as *t*-butyl peroxide, oxone and air (or pure molecular oxygen) were virtually inactive and *m*-CPBA showed some activity but without any selectivity (Table 1, entry 6). These results indicated the current amine/ketone dual catalysis would preferentially activate H_2O_2 and facilitate the subsequent hydroxylation.

Table 1. Identifications of the amine/ketone dual catalysis and optimizations.



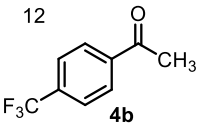
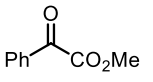
Control experiments

entry	variations[a]	yield (%)[b]	*ee* (%)[c]
1	none	85 (84)[d]	96 (96)
2	no **3a**	n.r.	
3	no **4a**	27	96
		81 (48 h)	96
4	no $NHTf_2$	18	89

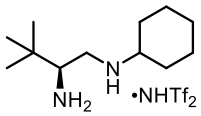
Effect of oxidant

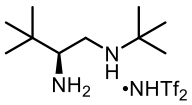
entry	oxidant[a]	yield (%)[b]	*ee* (%)[c]
5	oxone	n.r.	
6	*m*-CPBA	36	3
7	air	trace	--
8	*t*-BuOOH	trace	54

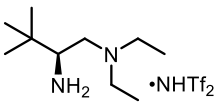
Effect of ketone catalyst

entry	ketone[a]	yield (%)[b]	*ee* (%)[c]
9	PhCHO	trace	
10	acetone	6	92
11	CF_3COCH_3	81	96
12	 **4b**	26	95
13	 **4c**	86	95

Effect of aminocatalyst

14  **3b** 71%, 95% *ee*

15  **3c** 45%, 90% *ee*

16  **3d** 52%, 61% *ee*

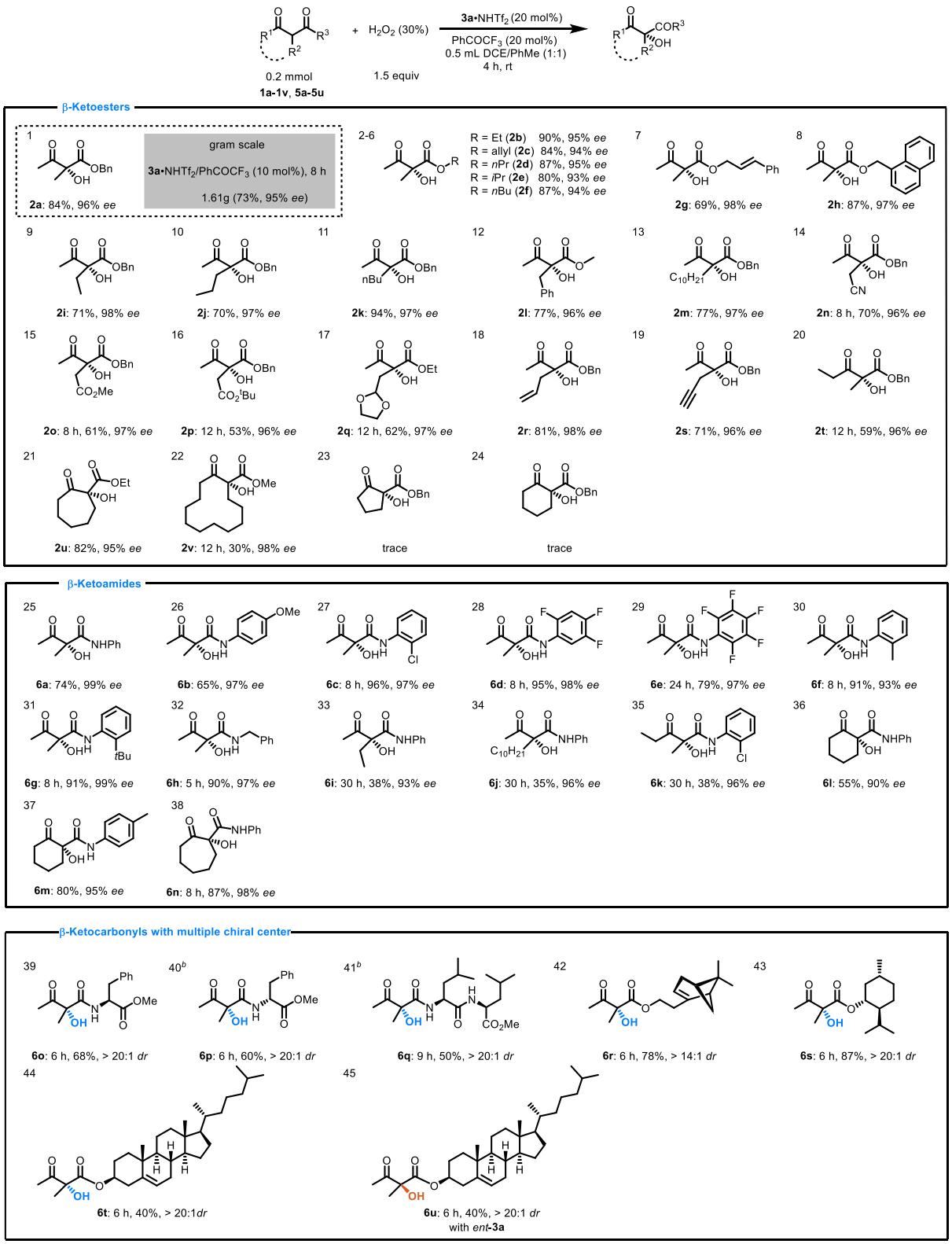
[a]Standard reaction condition: **1a** (0.2 mmol), chiral amine **3a**/$NHTf_2$ (20 mol%), $PhCOCF_3$ (20 mol%), and H_2O_2 (30 wt.% in water, 0.3 mmol) in 0.5 mL PhMe/DCE (1/1) at room temperature in air for 3 h. [b]The yield was determined by GC analysis using 1, 3, 5-trimethoxybenzene as an internal standard. [c]The *ee* value was determined by HPLC analysis. [d]Yield of isolated product for 4 hours.

Substrate scopes. As shown in Table 2, different ester groups of acetoacetates were well tolerated (Table 2, entries 1-8). A variety of *α*-alkyl substituents ranging from methyl, ethyl to decanyl as well as benzyl all worked well to give the expected hydroxylation products with 70-94% yields and 96-98% *ee* (entries 9-13). Functional groups such as cyano (**2n**), ester (**2o, 2p**), acetal (**2q**), alkenyl (**2r**) and alkynyl (**2s**) at *α*-position were equally applicable (entries 14-19). An ethyl ketone (**2t**) is also workable with 59% yield and 96% *ee* (entry 20). Cyclic ketoesters showed divergent behavior, while smaller rings (n= 4, 5, 6) such as

cyclopentanone or cyclohexanone did not show the expected reactivity, the larger cyclic ketoesters (n = 7, 12) reacted smoothly to give the desired products in high enantioselectivity with slightly diminished reactivity (entries 21-24). A gram-scale hydroxylation reaction of *β*-ketoester **1a** was performed to probe the practicability with 10 mol% catalyst loading and comparable isolated yield and enantioselectivity were obtained in 8 h (Table 2, entry 1).

β-Ketoamides are versatile structural motifs in biologically active compounds and their direct oxidative transformations are challenging because of their oxidative compatibility. It was found *β*-ketoamides worked extremely well under our dual catalytic conditions. Both aryl and alkyl amides could be incorporated to give the expected hydroxylation adducts with 93-99% *ee* (entries 25-32). Aryl amides bearing either electron-donating group (**6b**), electron-withdrawing groups (**6c-e**) or streric *ortho*-substituent (**6g**) were equally applicable. Alkyl substituents at either *α*- or *α*'- position of ketoamides were well tolerated (entries 33-35). Cyclic ketoamides also worked well in the reactions to give the desired products in 55-87% yields and 90-98% *ee* (entries 36-38).

Table 2. Substrate scopes of amine/ketone dual catalysis[a]



[a]Reactions were performed with **1** (0.2 mmol), **3a**/Tf_2NH (20 mol%), $PhCOCF_3$ (20 mol%), and H_2O_2 (30 wt.% in water, 0.3 mmol) in 0.5 mL PhMe/DCE (1/1) at room temperature in air for 4 h. Yield of isolated product. Determined by HPLC analysis. [b]The reaction was performed on scale of 0.1 mmol.

We also challenged the current protocol in the late-stage hydroxylation of structurally complexed substrates bearing existing chiral centers. In this regard, it was shown that the hydroxylation was solely catalyst-controlled to give the expected diastereoisomers with high diastereoselectivity (entry 39 vs entry 40,

entry 44 *vs* entry 45). Peptidyl amide (**6q**) or nopyl (**6r**) and menthyl esters (**6s**) worked smoothly. The catalysis also worked with a cholesteryl ester (**6t** and **6u**) in reasonably good activity and high diastereoselectivity (entries 44 and 45).

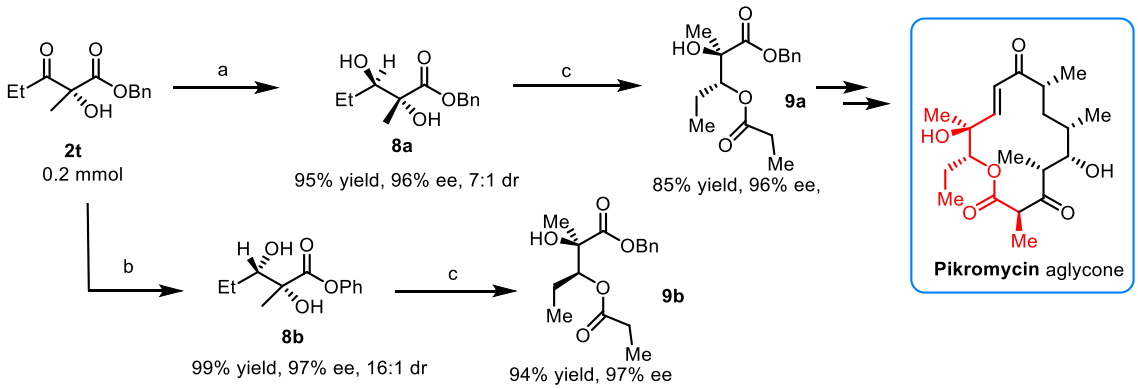


Figure 2. Synthetic application. Conditions: a) $NaBH(OAc)_3$ (1 equiv), HOAc (5 mol%), DCM, 0 °C, 30 min. b) $ZnCl_2$ (1 equiv), $NaBH_4$ (1 equiv), THF, -40 °C, 30 min. c) Acetic anhydride, DMAP, Et_3N.

Macrolide antibiotics are significantly important natural product that are wildly prescribed to treat bacterial infections. The *α*-hydroxy-carbonyl moiety in this family of antibiotics, e.g. Pikromycin, inspired us to pursue a concise synthetic path[29]. The key intermediate **2t** could by (be) synthesized by the developed catalytic asymmetric hydroxylation, and reduction of the keto moiety of **2t** followed by chemoselective acylation afforded the desired 1,2-*anti*-diol fragment **9a**. Changing the reducing condition led to a reversed configuration of 1,2-diol, producing 1,2-*syn*-diol **9b** (Fig. 2), which is also a versatile synthon in natural product synthesis[30].

Mechanism studies. To account for the dramatic promoting effect of **4a**, a H_2O_2-activation mechanism was invoked. As known, the organocatalytic activation of H_2O_2 may proceed *via* ketone mode with a dioxirane intermediate (**II**, derived from **I**, Fig. 3a) or ketimine mode with an oxaziridine intermediate **IV** (derived from **III**, Fig. 3a). ^{18}O-Labelling studies with $H_2{}^{18}O$-UHP was conducted. Under the bifunctional influence of amine-Brϕnsted acid conjugate **3a**/Tf_2NH, the carbonyl oxygen underwent fast isotope swap

with $H_2{}^{18}O$ and double ^{18}O-labelling product on both the carbonyl-O and α-hydroxyl-O would be formed if the reaction followed the dioxirane-**II** pathway (Fig. 3b). However, such a doubly-labelled product was not detected by *in-situ* HRMS analysis. In addition, control experiment indicated that preformed imine such as **4d** could effectively promote the reaction with 47% yield and 95% *ee* (Fig. 3c). The reaction with a prepared oxaziridine **4e** worked well to give the expected adduct with comparable enantioselectivity (Fig. 3d). Taken together, these results suggested that the reaction would preferentially proceed *via* the ketimine-pathway with **III** or **IV**, the ketone pathway *via* **I** or **II**, even if not entirely excluded, should be neglectable, to note that dioxirane formation between ketone and H_2O_2 normally required either strong acid or strong basic conditions[12] and amine-ketone coupling would be favored over perhydroxylation of ketone under the present acid-base bifunctional conditions. Nano-ESI-MS analysis of the reaction mixture led to the identification of the expected iminium ion intermediate **9b** and the oxaziridine intermediate **IV'** (Fig. 4a) and the structure of **IV'** was further established by collision-induced dissociation analysis (Fig. 4b), adding direct evidence to a ketimine mechanism.

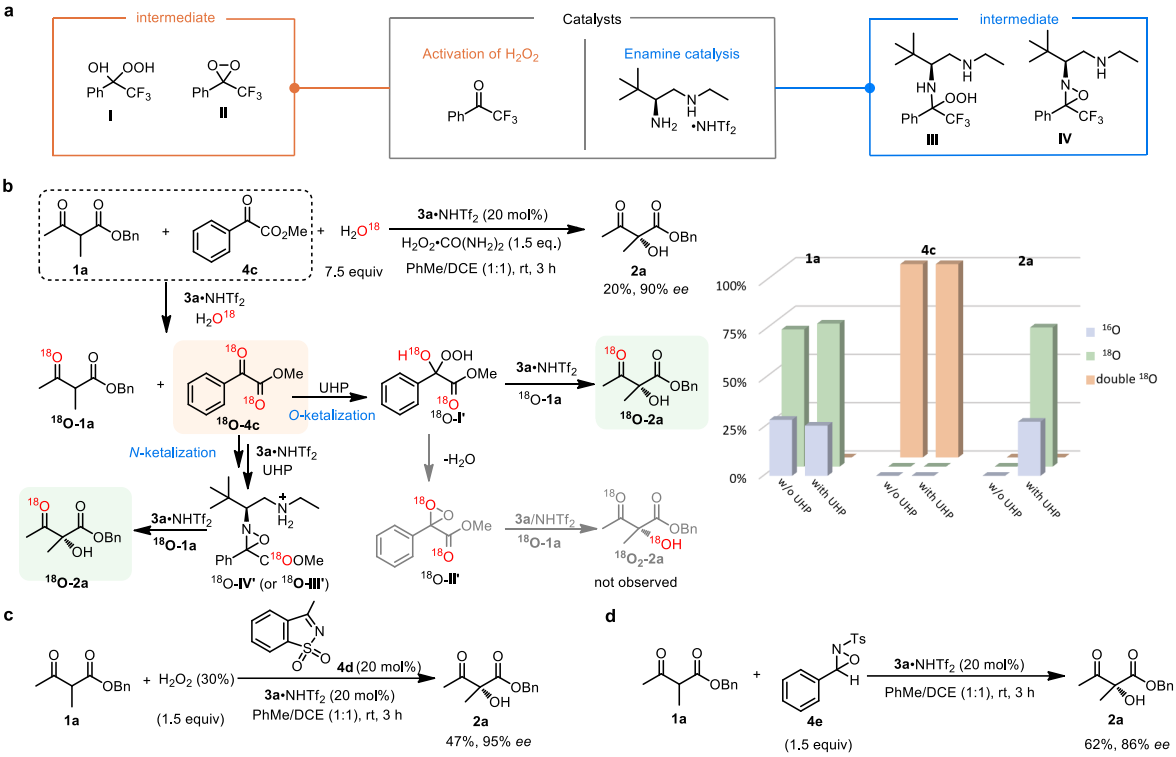


Figure 3. **a**, The possible oxidative intermediate for the ketone pathway (left) and ketimine pathway (right). **b**, ^{18}O Labeling experiments by $H_2{}^{18}O$. The possible labelling pathways were listed on the left with experimental observations showing on the right. The only pathway leading to doubly labelled product $^{18}O_2$-**2** was through a dioxirane intermediate ^{18}O-**II'**, and the absence of $^{18}O_2$-**2** suggested this was unlikely. **c**, Control experiment with **4a** as a catalyst, conditions: **1a** (0.2 mmol), **3a**/Tf_2NH (20 mol%), **4d** (20 mol%), and H_2O_2 (30 wt.% in water, 0.3 mmol) in 0.5 mL PhMe/DCE (1/1) at room temperature in air for 3 h. **d,** Control experiment with preformed oxaziridine as the oxidant, conditions: **1a** (0.2 mmol), **3a**/Tf_2NH (20 mol%) and oxaziridine **4e** (0.30 mmol) in 0.5 mL PhMe/DCE (1/1) at room temperature in air for 3h.

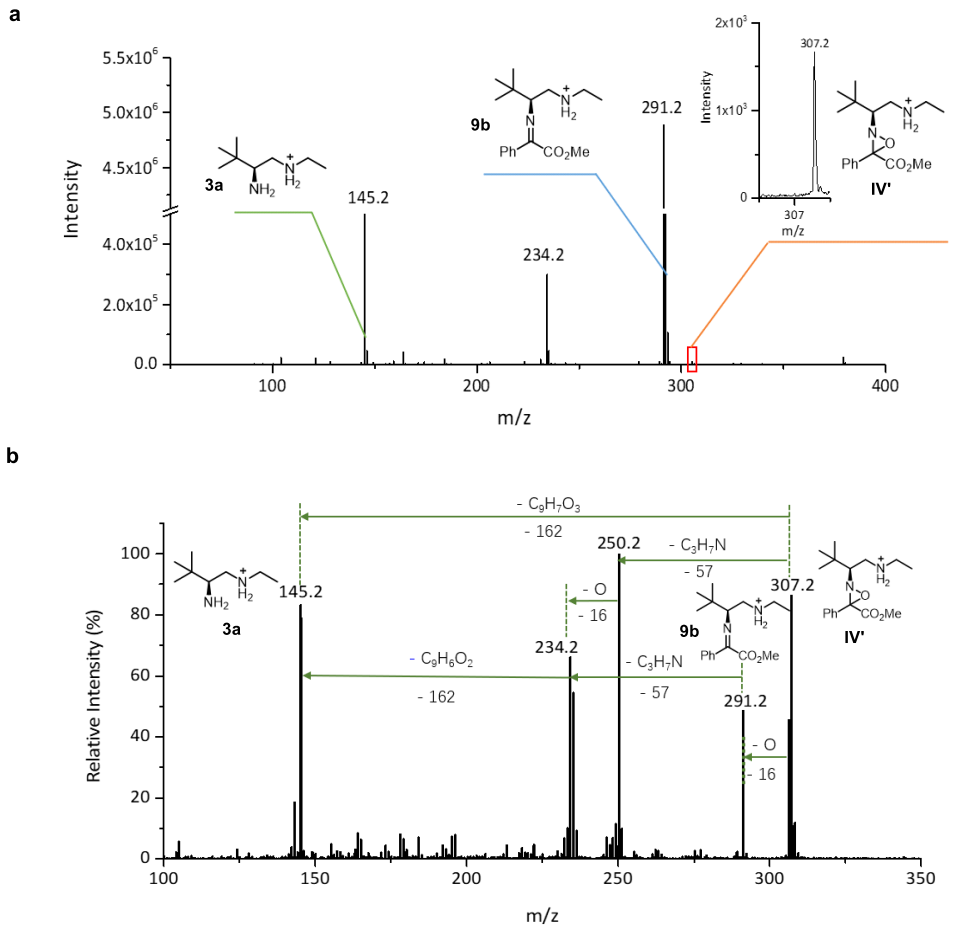


Figure 4. **a**, nESI(+)-MS spectrum of reaction of **3a**/$NHTf_2$, **4c** and H_2O_2 (30 wt.% in water) in DCE/PhMe *in situ*. **b**, CID analysis of oxaziridine intermediate **IV'**.

The kinetics was determined by measuring the initial rates with varying concentration of H_2O_2, substrate or catalysts (Supplementary Section 8). The reaction was found to be zero-order on either substrate **1a** or H_2O_2 (Fig. 5, a-b) and first-order on both amine and ketone catalysts (Fig. 5, c-d). A rate-limiting state preceding the C-O bond formation, is in line with this kinetic scenario. The non-linear effect (NLE) of the dual catalytic system was also determined and a minor negative NLE was clearly noted (Fig. 5e). Previously, negative NLE was reported in proline-catalyzed Robinson annulation by Agami[31-32], however, the existence of NLE in this reaction was later disapproved by List and Houk[33]. The observation of (-)-NLE in our reaction suggests the stereo-determining step is not a one-catalyst system. An enamine-oxaziridine coupling involving

two molecules of chiral aminocatalysts can be proposed to account for the NLE (Fig. 5f). Similar two-catalyst mode has been proposed by Kagan and Agami[31], and in this mode the reaction with the hetero-*R/S* and *S/R* combination is favored over that with homo-*R/R* or *S/S* combination. On these bases, a dual catalytic pathway involving an enamine-cycle and a ketimine cycle was proposed as shown in Fig. 5g. In this coupled cycle, ketimine formation from **3a** and **4a** is rate-limiting step, and the effective coupling between enamine **10** and intermediate **III** or **IV** leads to the hydroxylated adduct in high stereoselectivity.

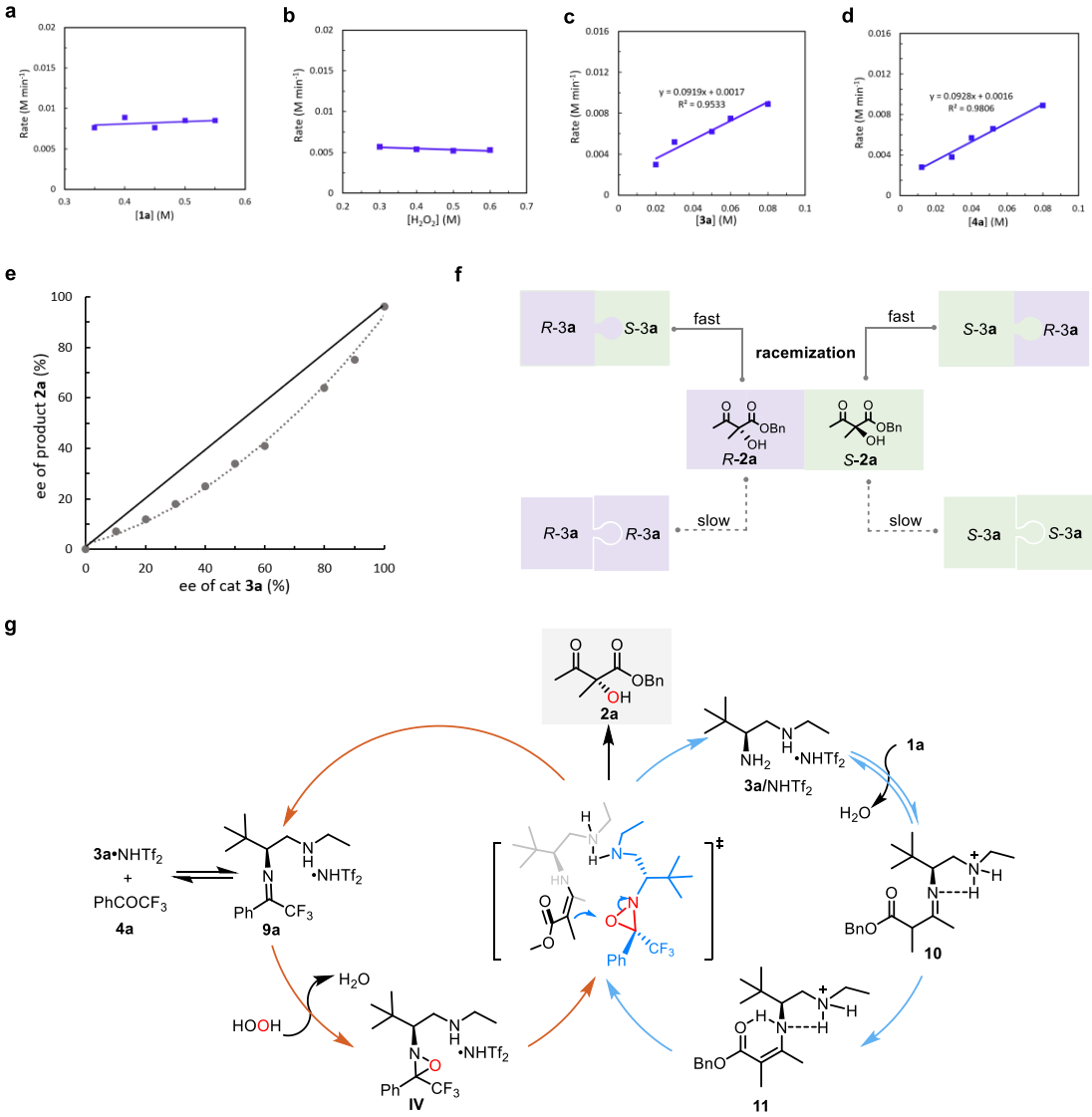


Figure 5. **a-d**, Kinetic order plots for **1a**, H_2O_2, **3a** and **4a**, respectively. Plot of initial rate against [**1a**] (from

0.35 to 0.55 M in DCE/PhMe) (**a**), [H_2O_2] (from 0.3 to 0.6 M in DCE/PhMe) (**b**), [**3a**] (from 0.02 to 0.08 M in DCE/PhMe) (**c**) and [**4a**] (from 0.01 to 0.08 M in DCE/PhMe) (**d**). **e**, Plot of enantiomeric excess of **2a** against the enantiomeric excess of **3a**, showing the existence of negative nonlinear effect (NLE). **f**, Two-catalyst model for the negative NLE with the hetero-combinations R/S and S/R reacting faster than homo-combination R/R and S/S, attenuating the enantioselectivity. **g**, Proposed catalytic cycle of synergetic catalysis of primary amine **3a** and $PhCOCF_3$ **4a**.

We further verified the reaction profile by DFT calculation (Fig. 6, see Supplementary Section 9 for details). Both the enamine (**Int3**) and ketimine (**Int5**) formation followed a bifunctional mode with the protonated secondary amine serving as the acid catalytic moiety, characteristic of the diamine-Brønsted acid catalysis as known[34]. In this coupled cycles, aminocatalyst **3a**/$NHTf_2$ played a dual role in reacting with either ketoester **1a** or ketone catalyst **4a** to form the key enamine (**Int3**) and oxaziridine (**IV**) intermediates, respectively. The ketalization with **4a** or **1a** are quickly equilibrated processes, the subsequent dehydration of ketal **Int4** is much more endergonic than **Int1**, making the former an overall rate-limiting step with an energy barrier of 20.9 kcal/mol. The down-hill re-ketalization of **Int5** with hydrogen peroxide is quite facile to give the expected perhydroxyl acetal **III** and oxaziridine **IV**. The conversion of **III** to **IV** occurred spontaneously with no obvious barrier. Both **III** and **IV** could effectively couple with the enamine intermediate **Int3** to give *R*-selective product *via* **TS9** (Supplementary Fig. 5) and **TS7**, respectively. The minor *S*-product was formed by the *E*-enamine addition to **IV**, with a calculated 99% *ee* value, which is in accordance with the experimental result. In **TS7**, an intermolecular N-H-N hydrogen bonding between two secondary amines side chains was noted, facilitating the alignment of the two reactive intermediates. Depending on the ionic status of the two intermediates, anion mediated H-bonding may also contribute and such a ternary **TS8** could also be located, showing a slightly favored energy barrier of 18.4 kcal/mol (Fig. 6)[35].

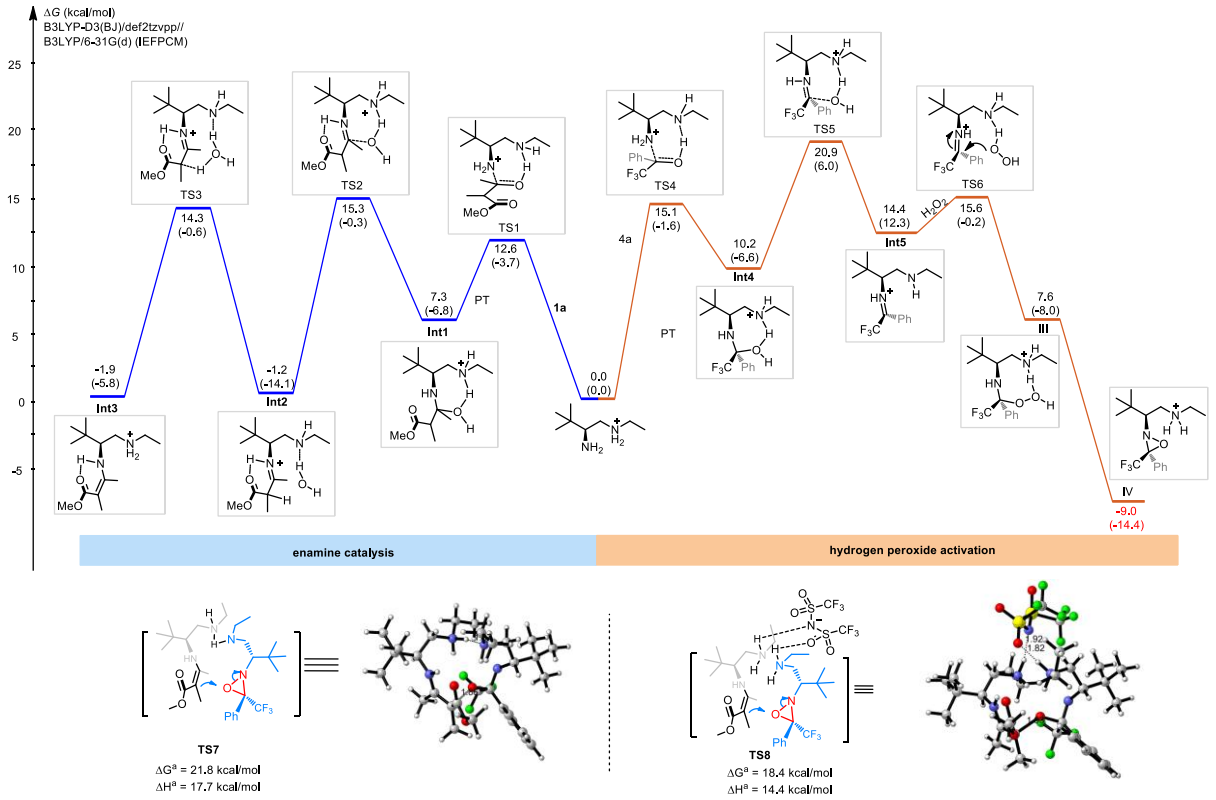


Figure 6. DFT-Calculated free-energy profiles on the activation of hydrogen peroxide and formation of enamine and the key **TS**s for the hydroxylation step.

Conclusion. In summary, we have shown that amine and ketone can work in concert to promote effectively enantioselective transformation of carbonyls. The dual amine and ketone catalysis enable an electrophilic activation of H_2O_2 *via in-situ* generated ketimine in the form of oxaziridine and allows for its effective coupling with a nucleophilic enamine intermediate. The developed dual organocatalytic protocol demonstrated high activity and enantioselectivity for a broad range of *β*-ketoeasters and *β*-ketoamides that are not possible with other catalytic approaches. The current approach represents a new organocatalytic strategy in activating hydrogen peroxide. Given its versatility and operational simplicity, further advances along this line are anticipated.

Methods

Here we describe the general procedures for the *α*-hydroxylation of carbonyl compounds through dual amine

and ketone catalysis.

General procedure for conditions: An oven-dried tube equipped with stir bar was charged with corresponding *β*-ketocarbonyls (**1**, 0.2 mmol) and aminocatalyst **3a**/$NHTf_2$ (20 mol%). After dissolution in a mixed solvent of toluene and 1,2-dichloroethane (0.5 mL, 1:1, v/v), trifluoroacetophenone **4a** (20 mol%) was added to the vial. Then H_2O_2 (30 wt.% in water, 0.3 mmol) was added via a syringe. Upon completion of the addition, the reaction was stirred at room temperature for at least 4 hours (TLC analysis). The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 20:1–4:1) to afford the desired product **2** or **6**. The enantiomeric excess was determined by HPLC.

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Contributions

S.L. designed and supervised the project. M.C. and K.X. performed the experimental studies; M.C. conducted the mechanism studies with the assistance of Z.N. and Y.L. providing ESI-MS analysis; L.Z. conducted DFT calculation. S.L., M.C. and L.Z. wrote the manuscript.

Data availability

All the data supporting the findings of this study are available within the paper and its Supplementary Information files. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics declarations

Competing interests

The authors declare no competing interests.

Additional information

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Graphic abstract