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Article

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

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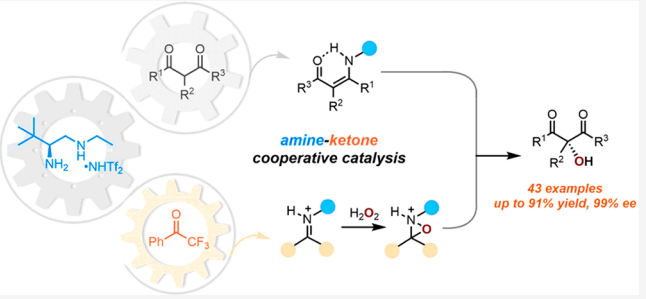
ABSTRACT: Carbonyls and amines are yin and yang in organocatalysis as they mutually activate and transform each other. These intrinsically reacting partners tend to condense with each other, thus depleting their individual activity when used together as cocatalysts. Though widely established in many prominent catalytic strategies, aminocatalysis and carbonyl catalysis do not coexist well, and, as such, a cooperative amine/carbonyl dual catalysis remains essentially unknown. Here we report a cooperative primary amine and ketone dual catalytic approach for the asymmetric α-hydroxylation of β-ketocarbonyls 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 an *in-situ*-generated ketimine. Ultimately, this enamine−oxaziridine coupling facilitated the highly controlled α-hydroxylation of several β-ketocarbonyls in excellent yield and enantioselectivity. Notably, late-stage hydroxylation for peptidyl amide or chiral esters can also be achieved with high stereoselectivity. In addition to its operational simplicity and mild conditions, this cooperative amine/ketone catalytic approach also provides a new strategy for the catalytic activation of H_2O_2 and expands the domain of typical amine and carbonyl catalysis to include this challenging transformation.



INTRODUCTION

Aminocatalysis is a fundamental activation mode in the transformations of carbonyl compounds. This catalysis has become a prevalent and enabling strategy for α- or β-functionalizations of carbonyls *via* enamine or iminium ion activation (Figure 1a).[1] On the other hand, carbonyl catalysis has recently appeared as a viable approach for the α-functionalization of glycine-type amines.[2] Like its amine counterpart, carbonyl catalysis also has its biological origin in nature's enzymes, the pyridoxal-dependent aldolases.[3] Its early successes can be traced back to before the renaissance of organocatalysis when chiral ketone or ketimine catalysts were extensively explored as metal-free oxidation catalysts.[4] In these cases, the carbonyl catalysts promoted concerted O/N atom transfer with olefins *via* dioxarine or oxaziridine intermediates, and similar catalysts have been recently used in C−H insertion reactions of alkanes.[5,6] Most of such ketone/aldehyde catalysts bear reactive carbonyls with electron-withdrawing substituents and would readily couple with nucleophilic amines. Hence, as inherent reacting partners, amines and ketone/aldehyde carbonyls are mutually exclusive for targeted catalytic transformations from a mechanistic point of view, like a yin−yang interplay. Cooperative amine and carbonyl dual catalysis remains essentially unknown.

Widely applied in industry and environmental protection as a green terminal oxidant, hydrogen peroxide is considered to be an 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.[7] 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, achieving catalytic asymmetric hydroxylation with hydrogen peroxide remains a great challenge, and successful examples along this line are extremely scarce.[8] To modulate the activity and stereoselectivity under mild conditions, catalytic activation of H_2O_2 into more electrophilic oxygen species is required because H_2O_2 itself is not electrophilic enough and can even serve as a good nucleophile under neutral and basic conditions.[9] Aside from the established metal-mediated activation strategies,[7d,8b,10] there recently appeared organocatalytic strategies that proceeded *via* dioxarine, oxaziridine, or perhydrate intermediates using either ketone or imine catalysts (Figure 1b).[5,11] To date, no enantioselective version has been developed. Herein, we report the application of ketone catalysis in the asymmetric enamine-based α-hydroxylation

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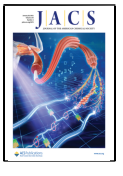

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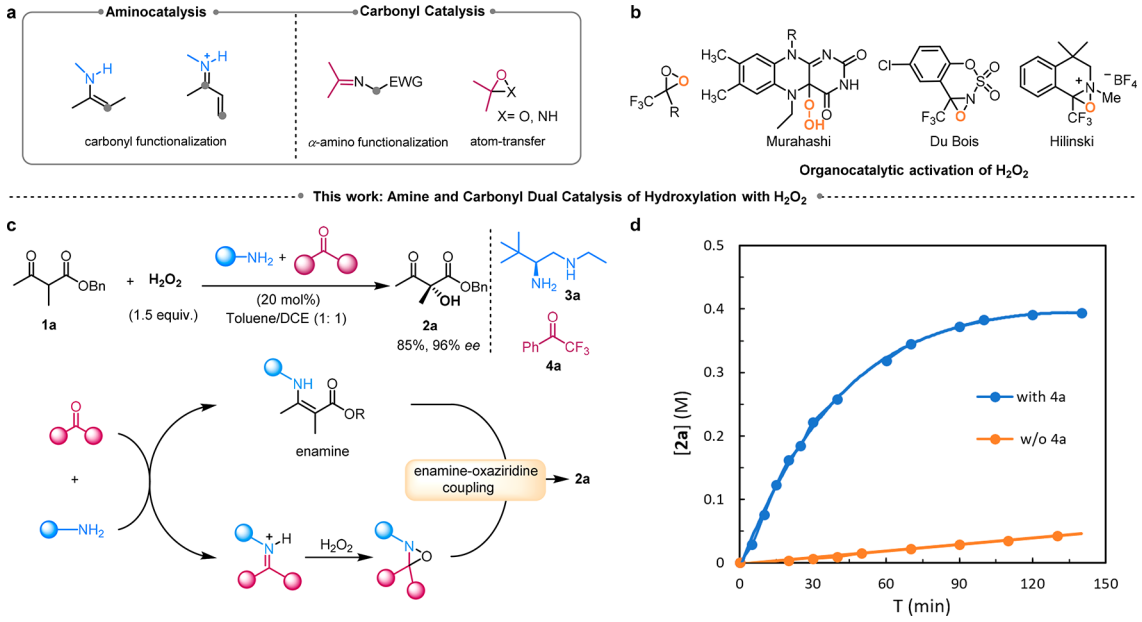
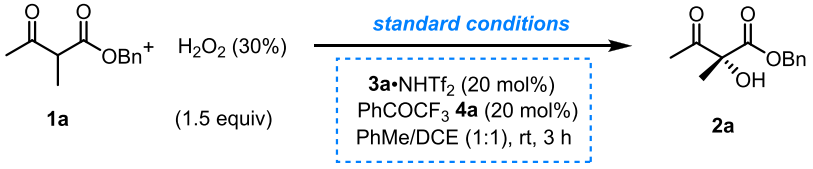


Figure 1. Organocatalytic activation of hydrogen peroxide. (a) Typical activation modes in aminocatalysis and carbonyl catalysis. (b) Active intermediates in the organocatalytic activation of H_2O_2. (c) Our concepts of amine and carbonyl dual catalysis: The chiral iminium ion generated *in situ* by 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**.

Table 1. Identification of the Amine/Ketone Dual Catalysis and Optimization[a,b,c,d]



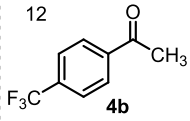
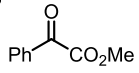
Control experiments

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

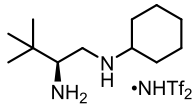
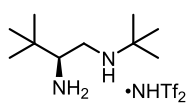
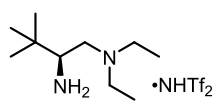
Effect of oxidant

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 product isolated for 4 h.

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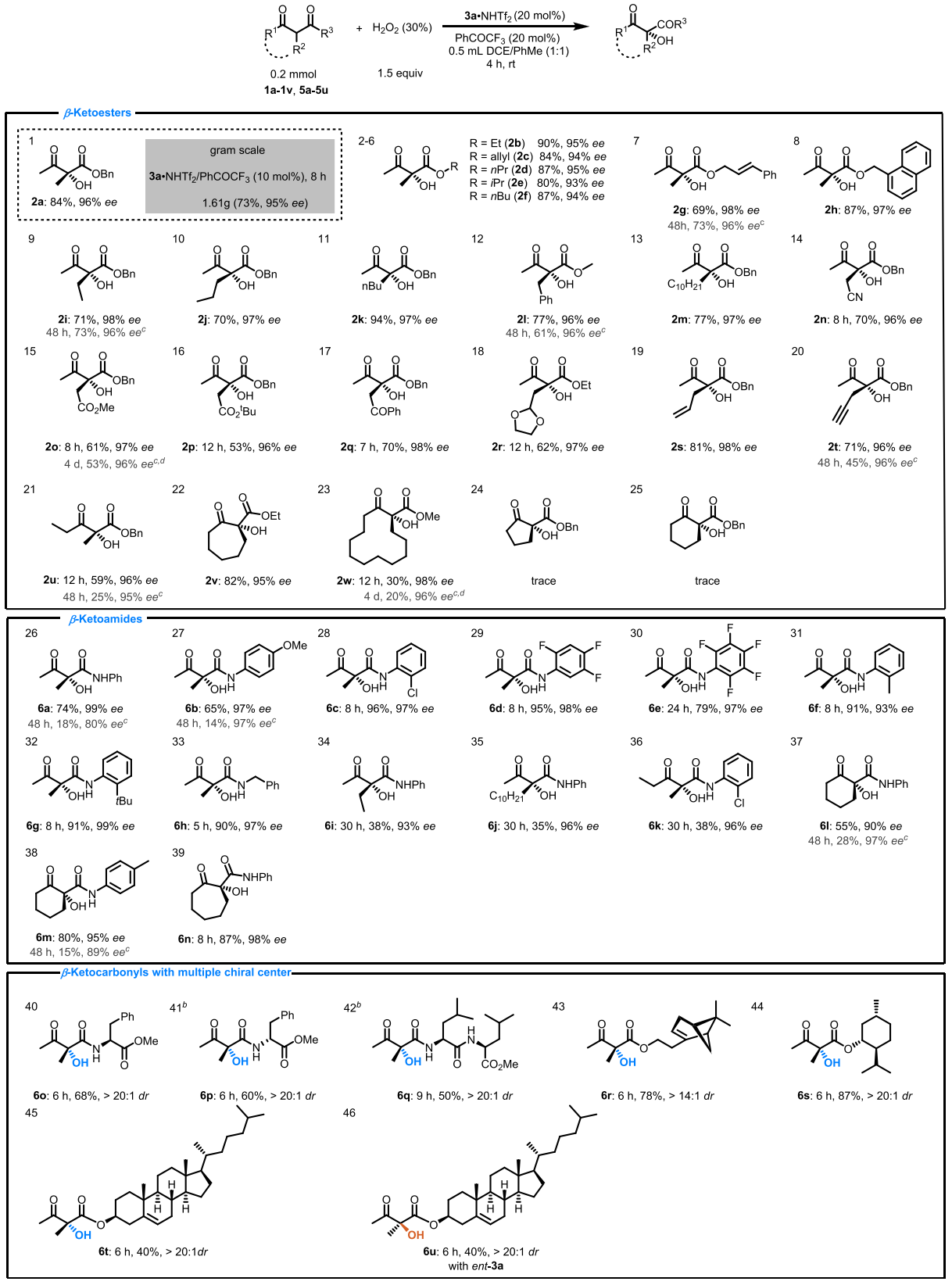
Table 2. Substrate Scope of Amine/Ketone Dual Catalysis[a,b,c,d]



[a]Condition **A**: Reactions were performed with **1** or **5** (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 of PhMe/DCE (1/1) at room temperature in air for 4 h. Yield of isolated product. The *ee* values were determined by HPLC analysis. [b]The reaction was performed on the scale of 0.1 mmol. [c]Condition **B**: Reactions were performed with **1** or **5** (0.2 mmol), **3a**/Tf_2NH (20 mol %), H_2O_2 (30 wt % in water, 0.3 mmol), and Na_2SO_4 (1.0 equiv) in 0.5 mL of PhMe/DCE (1/1) at room temperature in air for 48 h. [d]40 °C.

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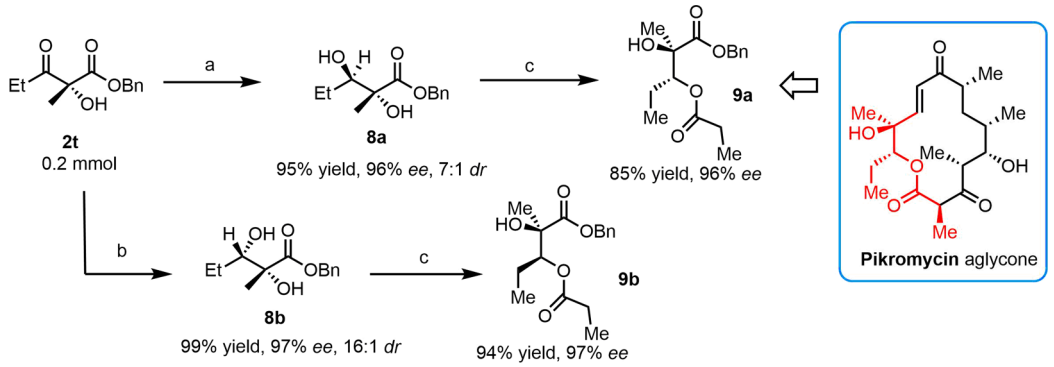

Figure 2. Synthesis application. Conditions: (a) $NaBH(OAc)_3$ (1.0 equiv), HOAc (5 mol %), DCM, 0 °C, 30 min. (b) $ZnCl_2$ (1.0 equiv), $NaBH_4$ (1.0 equiv), THF, −40 °C, 30 min. (c) Propionic anhydride (1.0 equiv), DMAP (10 mol %), Et_3N (1.0 equiv).

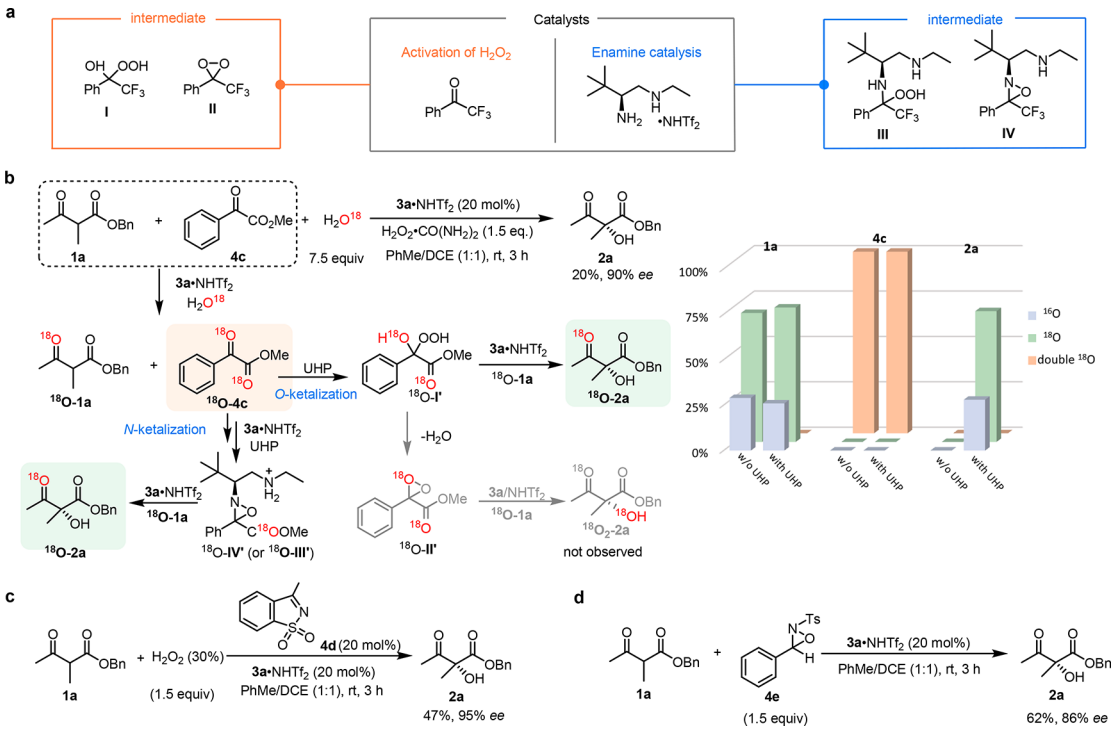

Figure 3. (a) Possible oxidative intermediates for the ketone pathway (left) and ketimine pathway (right). (b) ^{18}O-labeling experiments by $H_2{}^{18}O$. The possible labeling pathways are listed on the left, with experimental observations shown on the right. The only pathway leading to doubly labeled product $^{18}O_2$-**2a** was through a dioxirane intermediate, ^{18}O-**II′**, and the absence of $^{18}O_2$-**2a** suggested that this was unlikely. UHP: urea hydrogen peroxide. (c) Control experiment with **4d** 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 of PhMe/DCE (1/1) at room temperature in air for 3 h. (d) Control experiment with preformed oxaziridine **4e** as the oxidant. Conditions: **1a** (0.2 mmol), **3a**/Tf_2NH (20 mol %), and oxaziridine **4e** (0.30 mmol) in 0.5 mL of PhMe/DCE (1/1) at room temperature in air for 3 h.

with hydrogen peroxide. Though enamine-based α-oxygenation has been extensively explored, successful examples have relied on preactivated reagents such as oxaziridines, nitrosobenzenes, benzoyl peroxide, and singlet oxygen.[12] Direct catalytic enamine hydroxylation with hydrogen peroxide has not been achieved.[13] Though Ooi has reported an enolate-based asymmetric α-hydroxylation with hydrogen peroxide, the reaction unfortunately required stoichiometric trichloroacetonitrile as an activating reagent.[14] Similar reactions have also been examined with chiral Lewis base catalysis but with moderate enantioselectivity and limited scope.[15]

In our strategy (Figure 1c), the chiral primary amine catalyst worked in concert with a ketone catalyst to promote the effective α-hydroxylation of β-ketocarbonyls with excellent stereocontrol not obtainable by other methods. Our joint amine/ketone catalytic protocol could be applied in the late-stage hydroxylation reaction of complex molecules. Mechanistic studies revealed that the reaction proceeded *via* enamine−oxaziridine coupling derived from the two working catalysts and that both amine and ketone catalysts participated in the activation of hydrogen peroxide *via* an iminium ion intermediate (Figure 1c).

RESULTS AND DISCUSSION

Catalyst Screening and Reaction Development. In our initial studies, we investigated the enantioselective hydroxylation of β-ketoester **1a** with primary amine catalysts developed previously by our group. Among the different

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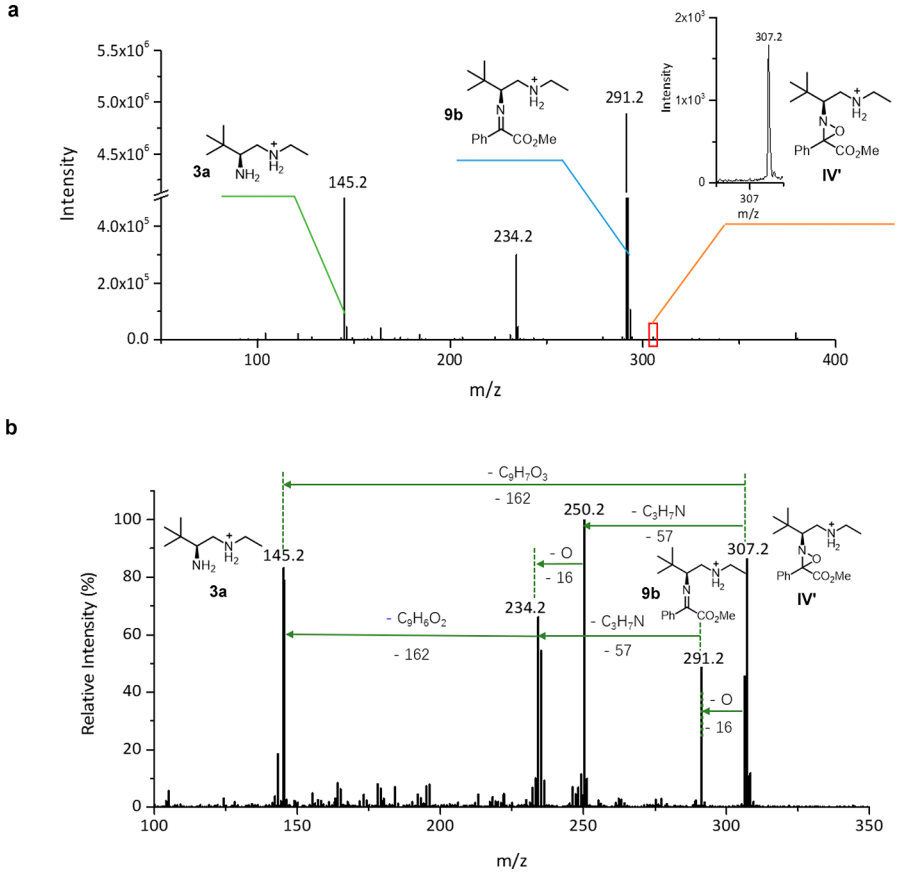

Figure 4. (a) nESI(+)-MS spectrum of the reaction of **3a**/$NHTf_2$, **4c**, and H_2O_2 (30 wt % in water) in DCE/PhMe *in situ*. (b) CID analysis of oxaziridine intermediate **IV′**.

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 h 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 a nearly 10 times faster reaction (Figure 1d). The reaction now had an 85% yield and a 96% *ee* in 3 h (Table 1, entry 1). Aldehydes such as benzaldehyde were found to totally inhibit the reaction (Table 1, entry 9), and the smallest ketone, acetone, showed diminished activity while 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 role of aminocatalysis in the reaction. Consistent with the well-known role of Brønsted acids facilitating aminocatalysis, the use of a strong acid additive such as Tf_2NH is essential for both the activity and enantioselectivity (Table 1, entry 4).

Other oxidants have also been examined in the dual catalytic system (Table 1, entries 5−8). 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 indicate that the current amine/ketone dual catalysis preferentially activates H_2O_2 to facilitate the subsequent hydroxylation.

Substrate Scope. As shown in Table 2, different ester groups of acetoacetates were well tolerated (Table 2, entries 1−8). A variety of α-alkyl substituents including methyl, ethyl, decanyl, and benzyl all worked well to give the expected hydroxylation products in 70−94% yields and 96−98% *ee* (entries 9−13). Functional groups such as cyano (**2n**), ester (**2o**, **2p**), ketone (**2q**), acetal (**2r**), alkenyl (**2s**), and alkynyl (**2t**) at the α-position were equally applicable (entries 14−20). An ethyl ketone (**2u**) is also workable with a 59% yield and 96% *ee* (entry 21). Cyclic ketoesters exhibited divergent behavior, smaller rings (n = 4, 5, 6) such as cyclopentanone and cyclohexanone did not show the expected reactivity,[16] and the larger cyclic ketoesters (n = 7, 12) reacted smoothly to give the desired products in high enantioselectivity with slightly diminished reactivity (entries 22−25). A gram-scale hydroxylation reaction of β-ketoester **1a** was performed to probe the practicability with 10 mol % catalyst loading, and comparable values of the isolated yield and enantioselectivity were obtained in 8 h (Table 2, entry 1).

β-Ketoamides are versatile structural motifs in biologically active compounds,[17] and their direct oxidative transformations are challenging because of their oxidative compatibility.[18] It was found that 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 26−33). Aryl amides bearing either an

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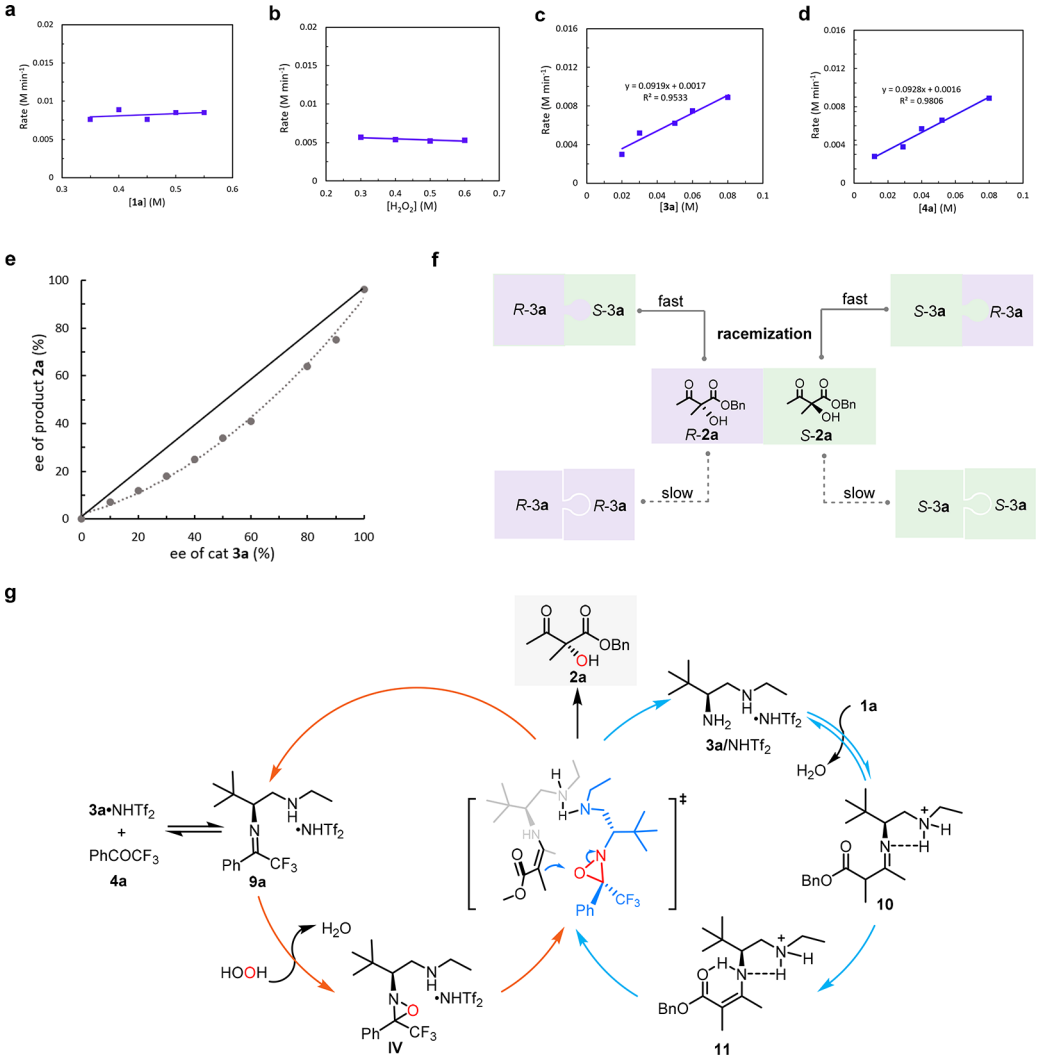

Figure 5. (a–d) Kinetic order plots for **1a**, H_2O_2, **3a**, and **4a**, respectively. (a) Plot of initial rate against [**1a**] (from 0.35 to 0.55 M in DCE/PhMe). (b) [H_2O_2] (from 0.3 to 0.6 M in DCE/PhMe). (c) [**3a**] (from 0.02 to 0.08 M in DCE/PhMe). (d) [**4a**] (from 0.01 to 0.08 M in DCE/PhMe). (e) Plot of enantiomeric excess of **2a** against the enantiomeric excess of **3a**, showing the existence of a negative nonlinear effect (NLE). (f) Two-catalyst model for the negative NLE with heterocombinations *R*/*S* and *S*/*R* reacting faster than homocombinations *R*/*R* and *S*/*S*, attenuating the enantioselectivity. (g) Proposed catalytic cycle of synergetic catalysis of primary amine **3a** and $PhCOCF_3$ **4a**.

electron-donating group (**6b**), electron-withdrawing groups (**6c–e**), or a steric *ortho* substituent (**6g**) were equally applicable. Alkyl substituents at either the α- or α'-position of ketoamides were well tolerated (entries 34–36). Cyclic ketoamides also worked well in the reactions to give the desired products in 55–87% yields and 90–98% *ee* (entries 37–39). Meanwhile, the reaction outcomes in the absence of a ketone catalyst (Table 2, condition **B**) were also listed for comparison, exhibiting generally lower yields and longer reaction time. These observations further highlight the catalytic power of this dual catalytic system.

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 40 vs entry 41, entry 45 vs entry 46). Peptidyl amide (**6q**) or nopyl (**6r**) and menthyl esters (**6s**) worked smoothly. The catalysis also worked with a cholesteryl ester (**6t** and **6u**) with reasonably good activity and high diastereoselectivity (entries 45 and 46).

The obtained α-hydroxy β-oxo skeletons are prevalent structural motifs in natural products and pharmaceuticals and could also serve as valuable synthons for synthetic transformations.[19] The vicinal diol moiety of macrolide antibiotics (e.g., pikromycin) inspired us to pursue a concise synthesis path to assemble the fragment.[20] Key intermediate **2t** could 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** (Figure 2), which is also a versatile synthon in natural product synthesis.[21]

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**, Figure 3a) or ketimine mode with an oxaziridine intermediate (**IV**, derived from **III**, Figure 3a). ^{18}O-labeling studies with $H_2{}^{18}O$-UHP were conducted. In this

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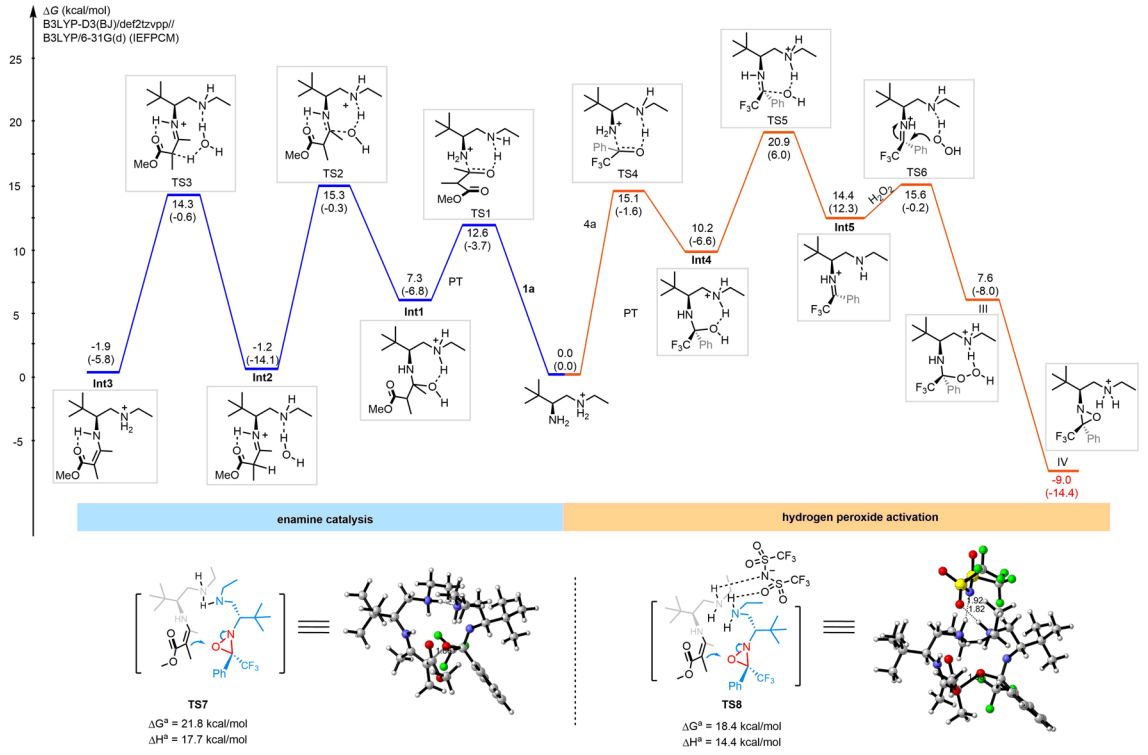

Figure 6. DFT-calculated free-energy profiles of the activation of hydrogen peroxide and formation of enamine and the key **TS**s for the hydroxylation step.

case, ketone **4c**, with catalytic performance similar to that of **4a** (Table 1, entry 1 vs 13), was used for the convenience of ESI-MS detection. Under the bifunctional influence of amine-Brønsted acid conjugate **3a**/Tf_2NH, the carbonyl oxygen underwent a fast isotope swap with $H_2{}^{18}O$, and the double ^{18}O-labeling product on both the carbonyl-O and α-hydroxyl-O would be formed if the reaction followed the dioxirane-**II** pathway (Figure 3b). However, such a doubly labeled product was not detected by *in situ* HRMS analysis. In addition, the control experiment indicated that preformed imine such as **4d** could effectively promote the reaction with 47% yield and 95% *ee* (Figure 3c). The reaction with a prepared oxaziridine, **4e**, worked well to give the expected adduct with comparable enantioselectivity (Figure 3d). Taken together, these results suggest that the reaction preferentially proceeds *via* the ketimine pathway with **III** or **IV**. The ketone pathway *via* **I** or **II**, even if not entirely excluded, should be neglectable because dioxirane formation between ketone and H_2O_2 normally requires either strongly acidic or strongly basic conditions.[4] Additionally, amine−ketone coupling would be favored over the perhydroxylation of ketone under the present acid−base bifunctional conditions. Nano-ESI-MS analysis of the reaction mixture led to the identification of expected iminium ion intermediate **9b** and oxaziridine intermediate **IV′** (Figure 4a), and the structure of **IV′** was further established by collision-induced dissociation analysis (Figure 4b), adding direct evidence to a ketimine mechanism.

The kinetics were determined by measuring the initial rates with a varying concentration of H_2O_2, substrate, or catalysts (Supporting Information, Section 8). The reaction was found to be zeroth order in either substrate **1a** or H_2O_2 (Figure 5a,b) and first order in both amine and ketone catalysts (Figure 5c,d). A rate-limiting state preceded the C−O bond formation, in line with this kinetic scenario. The nonlinear effect (NLE) of the dual catalytic system was also determined, and a minor negative NLE was clearly noted (Figure 5e). Previously, negative NLE was reported in proline-catalyzed Robinson annulation by Agami;[22] however, the existence of NLE in this reaction was later disapproved by List and Houk.[23] The observation of (−)-NLE in our reaction suggests that the stereodetermining 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 (Figure 5f). A similar two-catalyst mode has been proposed by Kagan and Agami.[22] According to this model, the catalysis with the hetero-*R*/*S* and *S*/*R* combination is favored over that with the homo-*R*/*R* or *S*/*S* combination in the stereogenic step, hence leading to attenuation of the overall enantioselectivity. On these bases, a dual catalytic pathway involving an enamine cycle and a ketimine cycle was proposed as shown in Figure 5g. In this coupled cycle, ketimine formation from **3a** and **4a** is the rate-limiting step, and the effective coupling between enamine **10** and intermediate **III** or **IV** leads to the hydroxylated adduct in high stereoselectivity. It is noted that the chirality of oxaziridine intermediate **IV′** may also contribute to the stereocontrol.[24] However, the observation of significant enantioselectivity with a racemic oxaziridine **4e** (Figure 3d) suggested that the chiral effect of **IV** should be minor, and the chiral induction was mainly determined by the enamine intermediate.

We further verified the reaction profile by DFT calculations (Figure 6, see Supporting Information Section 9 for details). Both enamine (**Int3**) and ketimine (**Int5**) formation followed a bifunctional mode with the protonated secondary amine serving as the acid catalytic moiety, characteristic of diamine Brønsted acid catalysis as known.[25] In these coupled cycles, aminocatalyst **3a**/$NHTf_2$ played a dual role in reacting with either ketoester **1a** or ketone catalyst **4a** to form the key

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enamine (**Int3**) and oxaziridine (**IV**) intermediates, respectively. Ketalization with **4a** or **1a** is a quickly equilibrated processes, and the subsequent dehydration of ketal **Int4** is much more endergonic than that for **Int1**, making the former an overall rate-limiting step with an energy barrier of 20.9 kcal/mol. The downhill reketalization of **Int5** with hydrogen peroxide is quite facile to give 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 enamine intermediate **Int3** to give the *R*-selective product *via* **TS9** (Supporting Information Figure 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**, intermolecular N−H−N hydrogen bonding between two secondary amine 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 contributed and such a ternary **TS8** could also be located, showing a slightly favored energy barrier of 18.4 kcal/mol (Figure 6).[26]

CONCLUSIONS

We have shown that amine and ketone can work in concert to promote the effective enantioselective transformation of carbonyls. Dual amine and ketone catalysis enable the 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-ketoesters andβ-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 can be anticipated.

METHODS

Here we describe the general procedures for the α-hydroxylation of carbonyl compounds through dual amine and ketone catalysis.

General procedure for the conditions: An oven-dried tube equipped with stir bar was charged with the 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 h (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 desired product **2** or **6**. The enantiomeric excess was determined by HPLC.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11787.

General information, substrates and reagents synthesis, optimization details, general experimental procedures and compound characterization, determination of the absolute configuration, synthesis transformations, mechanistic studies, and HPLC and NMR spectra (PDF)

Details of DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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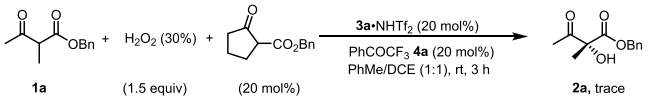

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