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Harnessing formate as a CO_2 surrogate for chiral β-hydroxy acid synthesis by photoredox hydrocarboxylation of alkenyl acetates

Xiaowen Xia,[1,2] Jiaxu Guo,[1,2] Yin Gao,[1,2] Jianming Liu,[1,2,3,*] and An-Ping Zeng[1,2,3,*]

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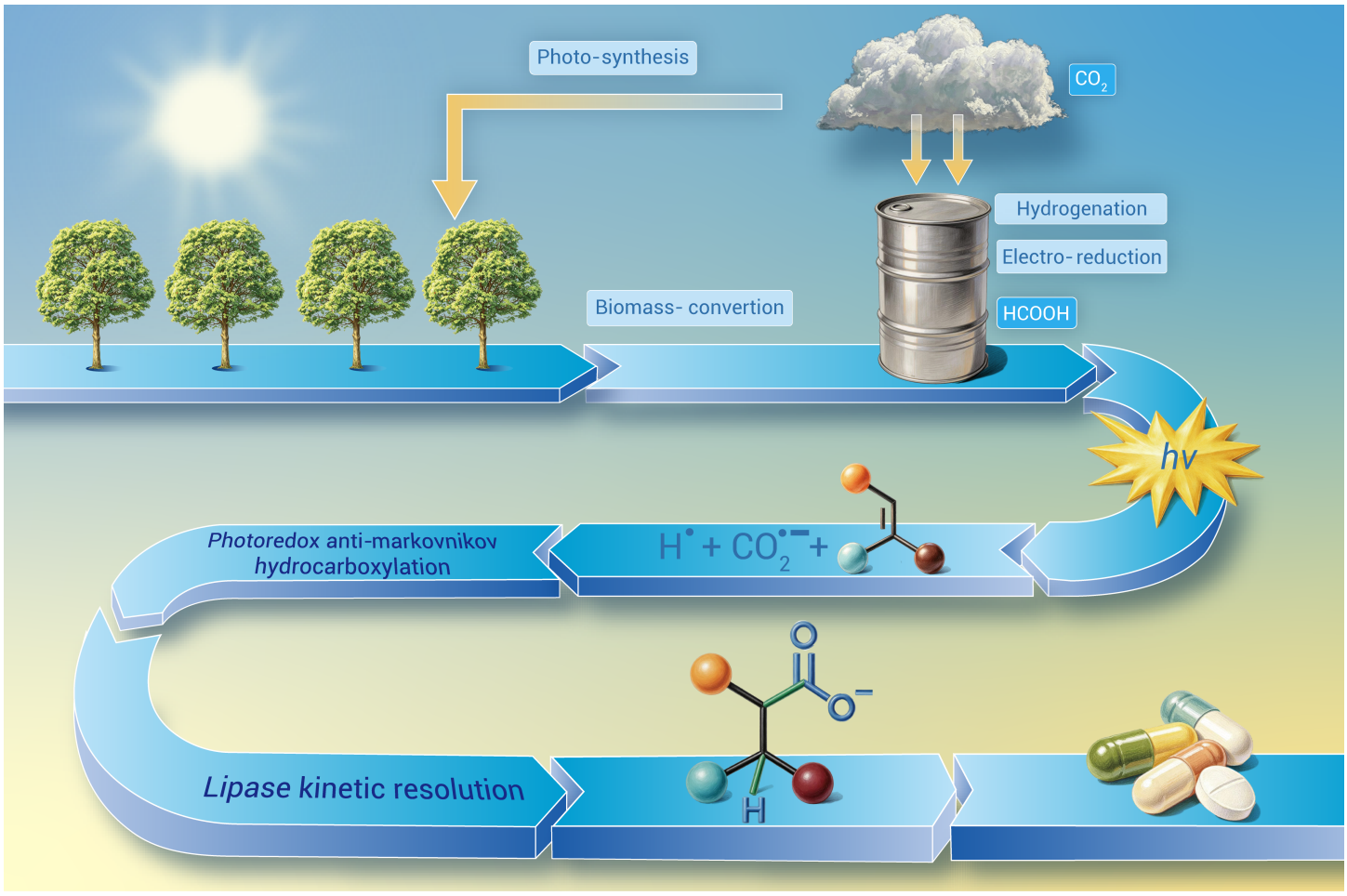
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Formate salt as sustainable C1 synthon for the carbon bond elongation reaction.
- Photoredox neutral transformation with no external reductant or oxidant.
- Anti-Markovnikov hydrocarboxylation of alkenyl acetates.
- Photo-enzymatic cascade catalysis for high value-added compound synthesis.

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Harnessing formate as a CO_2 surrogate for chiral β-hydroxy acid synthesis by photoredox hydrocarboxylation of alkenyl acetates

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Chiral β-hydroxy acids are prevalent building blocks for pharmaceuticals, making their synthesis by incorporating simple C1 feedstocks show a significant goal. In this report, we build a chemo-enzymatic cascade process that combines photoredox catalysis with biocatalysis to achieve it. The process begins with a visible-light-driven anti-Markovnikov hydrocarboxylation of diverse alkenyl acetates, formate salt was used as a sustainable C1 source and the precursor of $CO_2^{\bullet-}$. This reaction proceeds with broad functional group tolerance to afford β-acetoxy acids in good yields. Subsequently, these intermediates undergo a lipase-catalyzed kinetic resolution reaction to access valuable chiral β-hydroxy acids with moderate to good enantioselectivity. The practical utility of this strategy is demonstrated through gram-scale synthesis and the preparation of a key intermediate for the drug Ezetimibe. Mechanistic studies support a radical-mediated pathway.

INTRODUCTION

The electrochemically converting CO_2 into formate is a highly efficient carbon utilization strategy, capable of reaching over 90% faradaic efficiency approaching an industrial level.[1-6] However, its practical application and valorization have been limited by the lack of efficient methods to upgrade formate into higher-value products. Therefore, establishing formate as a sustainable C1 feedstock remains a crucial objective for effective valorization of CO_2.[7-12] Recent studies highlight the utility of formate as precursors for generating carbon dioxide radical anions ($CO_2^{\bullet-}$) under photo-mediated hydrogen atom transfer (HAT) process.[13-15] This approach bypasses the direct use of gaseous CO_2, offering a faster and more practical synthetic pathway. The in-situ generated $CO_2^{\bullet-}$acts as a highly reactive intermediate that could be involved in diverse chemical transformations. Functioning as a potent single-electron reductant ($E_{1/2}$ = −2.2 V vs. SCE) to reduce aryl halides, and initiate aryl functionalization reaction or alkene difunctionalization reactions.[16-19]Additionally, $CO_2^{\bullet-}$serves as an effective reductant for the defluorinative functionalization of trifluoromethyl derivatives.[20-22] It also directly participates in C–C bond formation via addition to unsaturated bonds. Wickens,[23-26] Li,[27,28] Zhu,[29-31] and the others,[32-36] have demonstrate the versatility of using formate salt as $CO_2^{\bullet-}$ precursors for the hydrocarboxylation, carbocarboxylation, oxycarboxylation, alkylcarboxylation, and multicarboxylation of alkenes or alkynes. Recently, the Markovnikov hydrocarboxylation of alkene using formate salt has been realized,[37] and the success of this method was based on balancing the rates of formate activation via HAT and Co-H generation. These dual roles—reductant and C1 synthon—collectively underscore its versatility and significance in modern organic synthesis. Chiral β-hydroxy acids are key intermediates in the synthesis of several bioactive compounds,[38,39] such as (*R*)-Atomoxetine,[40] Ezetimible,[41] (*S*)-Dapoxentine,[42] (Figure 1A). Consequently, developing efficient methods to synthesize these compounds from readily available starting materials, particularly by incorporating sustainable C1 units under mild conditions is highly desirable.

Alkenyl acetates are readily accessible starting materials widely employed in diverse synthetic transformations. Under Lewis acid catalysis, they act as nucleophiles in aldol-type additions,[43,44] or undergo deoxygenative nucleophilic substitution to form ketones (Figure 1B, upper right).[45-50] Furthermore, radical addition–elimination reactions of alkenyl acetates to prepare α-functionalized ketones have been extensively studied as well. Under photochemical, electrochemical, organocatalytic, or transition metal-catalyzed conditions, a variety of radicals like CF_3,[51-56] CF_2H,[57,58] R_2N,[59-61] RS,[62-64] RSO_2,[65-69] Alkyl,[70-80] alkenyl,[81] and aryl,[82-85] are compatible with this approach (Figure 1B, upper left). These compounds also serve as coupling partners for the multi-substituted alkene synthesis under transition-metal catalysis (Figure 1B, bottom left).[86-92] Additionally, the asymmetric hydrogenation,[93-98] cyclopropanation reactions of alkenyl acetates were also investigated.[99,100] Despite these advances, achieving site-selective hydrofunctionalization of alkenyl acetates while preserving the acetoxy group for the subsequent derivatization remain under developed.[101]

Chemo-enzymatic cascade catalysis, which combines the diversity of chemical transformations with the stereoselectivity of enzymatic processes, provides a powerful strategy for synthesizing value-added chiral compounds from readily available starting materials (Figure 1C).[102-110] This approach involves sequential reactions, where the product of the first reaction serves as the substrate for subsequent biocatalytic steps. A widely studied combination is the integration of lipase-catalyzed acylation of secondary alcohols or amines with metal-catalyzed racemization reaction, enabling dynamic kinetic resolution (DKR) to achieve high enantioselectivity and yield.[111-113] However, the current approaches predominantly focus on substrate resolution process,[114-116] chemo-enzymatic cascades which combine C–C bond formation with kinetic resolution to obtain the chiral molecules with more complexity and diversity remain elusive.[117-119]

In this research, a photoredox-enzymatic cascade system was established. Specifically, a photoredox anti-Markovnikov hydrocarboxylation of alkenyl acetates to synthesize β-acetoxy acids, utilizing formate as $CO_2^{\bullet-}$ precursors were achieved. Subsequently, these β-acetoxy acids then serve as substrates for lipase-catalyzed kinetic resolution process (Figure 1D).[40,120-124] With this integrated photoredox-enzymatic cascade strategy, structurally diverse chiral β-hydroxy acids are synthesized directly from alkenyl acetates and formate salt. Notably, three key challenges have been addressed: (1) The high reduction potential of $CO_2^{\bullet-}$ may promote competitive direct reduction of alkenyl acetates over C–C bond formation; (2) Radical addition intermediates are susceptible to oxidation to cations, leading to acyl group fragmentation and ketone side-product formation; (3) Residues from the hydrocarboxylation step could adversely affect lipase activity in the subsequent kinetic resolution process.

The advantage of our strategy is that it leverages the power of photocatalysis to activate the thermodynamically stable and unreactive C1 source. The excited photocatalyst drives a subsequent hydrogen atom transfer (HAT) reaction, ultimately converting the stable formate salt into the highly reactive carbon dioxide radical anion ($CO_2^{\bullet-}$). The importance of this light-driven step allows the C–C bond-forming reaction to proceed under mild conditions. Meanwhile, the simplicity of the photoreaction also reduces the interference for the subsequent enzymatic reaction.

MATERIALS AND METHODS

General procedure 1 (GP-1): Synthesis of β-acetoxy esters from alkenyl acetate and formate salt

Reaction set-up: In a nitrogen filled gloved box, an oven-dried 4 mL vial was charged with 4-DPAIPN (1.58 mg, 0.002 mmol, 2 mol%), lithium formate (20.8 mg, 0.4 mmol, 4.0 equiv). DMSO (900 uL) was injected through pipet and a 3 x 12 mm magnetic stir bar was added. Then, the alkenyl acetate

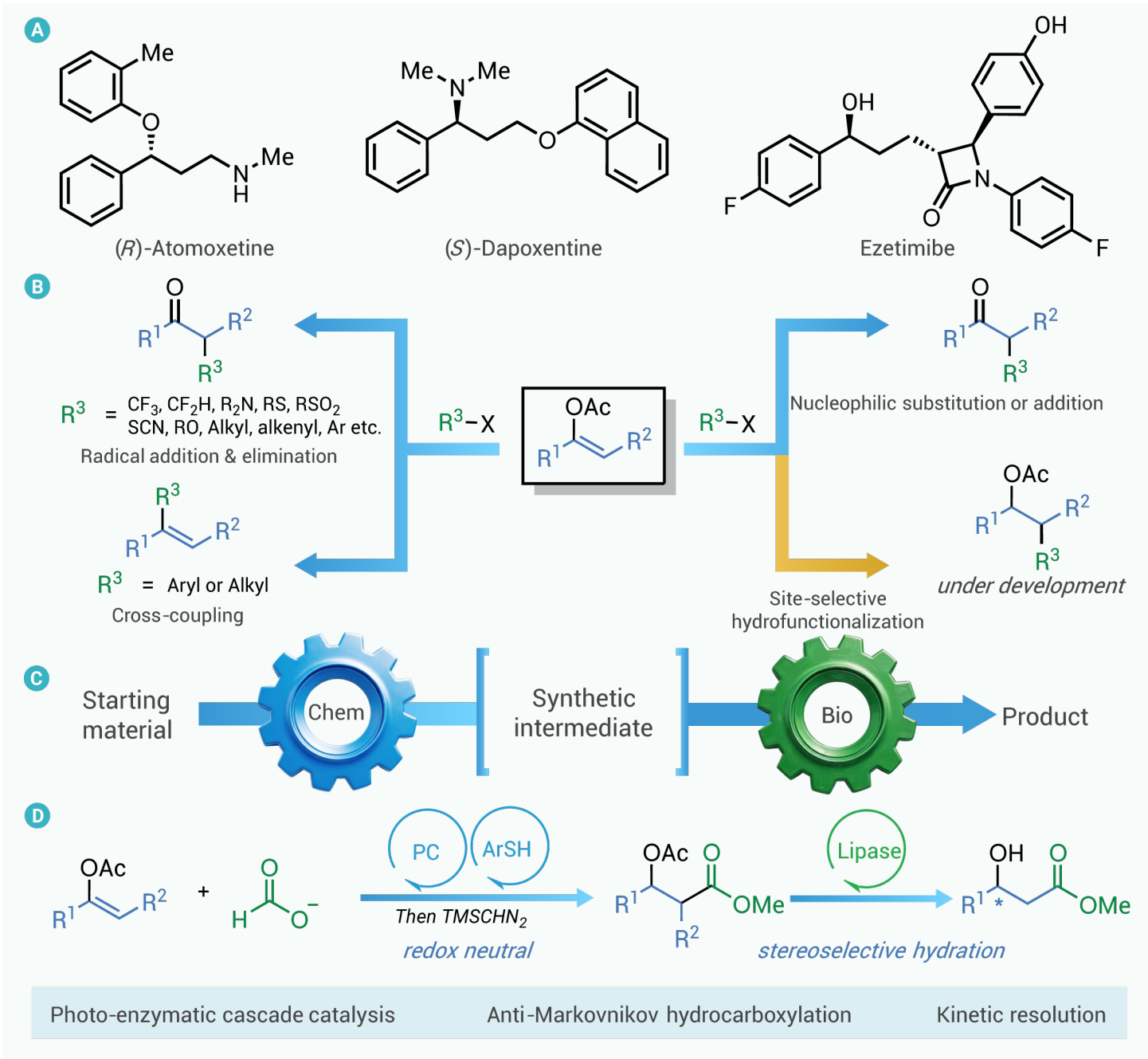

Figure 1. The importance of chiral *β*-hydroxy acid derivatives and our designed photo-enzymatic cascade catalysis system (A) Representative commercially pharmaceuticals. (B) Alkenyl acetates application. (C) Chemoenzymatic cascade catalysis. (D) Photoredox-enzymatic cascade catalysis for chiral *β*-hydroxy acetate synthesis.

(0.1 mmol, 1.0 equiv), HAT 1 (50 uL, 100 mM stock in DMSO, 0.005 mmol, 5 mol%), H_2O (50 uL) were added in succession. The resulting suspension was closed with a PTFE cap and further sealed with 2 round 3M electrical tape, taking out from the glove box. Irradiated with 440 nm blue LED at 35 °C with stirring for 20 h.

Reaction work-up: After completion, 200 uL 3N HCl was added to quench the solution. After stirring at rt for 30 min, 1 mL H_2O was added, extracted with ethyl acetate (1 mL × 3), the combine organic phase was back extracted with 1 mL brine, the upper organic phase was collected and remove the solvent under reduced pressure. The residue was redissolved in 2 mL (MeOH : Et_2O = 1:3), $TMSCHN_2$ (0.4 mL, 0.8 mmol, 2.0 M in hexane) was added dropwise, the solution was stirred at rt for 2 h. remove the solvent again, the residue was purified by preparative TLC to obtain the desired product.

General procedure 2 (GP-2): Photo-enzymatic cascade synthesis of chiral *β*-acetoxy esters from alkenyl acetate and formate salt

Reaction set-up: In a nitrogen filled gloved box, an oven-dried 4 mL vial was charged with 4-DPAIPN (3.16 mg, 0.004 mmol, 2 mol%), lithium formate (41.6 mg, 0.8 mmol, 4.0 equiv). DMSO (1800 uL) was injected through pipet and a 3 x 12 mm magnetic stir bar was added. Then, the alkenyl acetate (0.2 mmol, 1.0 equiv), HAT 1 (100 uL, 100 mM stock in DMSO, 0.01 mmol, 5 mol%), H_2O (100 uL) were added in succession. The resulting suspension was closed with a PTFE cap and further sealed with 2 round 3M electrical tape, taking out from the glove box. Irradiated with 440 nm blue LED at 35°C with stirring for 20 h.

Reaction work-up: After completion, 400 uL 3N HCl was added to quench the solution. After stirring at rt for 30 min, the resulting solution was transferred to a 10 mL glass tube, 1 mL H_2O was added, extracted with ethyl acetate (1.5 mL × 3), the combine organic phase was back extracted with 1 mL brine, the upper organic phase was collected and remove the solvent under reduced pressure. The residue was redissolved in 4 mL (MeOH : Et_2O = 1:3), $TMSCHN_2$ (0.8 mL, 0.8 mmol, 2.0 M in hexane) was added dropwise, the solution was stirred at rt for 2 h. remove the solvent again.

Enzymatic reaction set-up: The residue was then dissolved in 2 mL (Kpi

Table 1. Effect of reaction parameters.

Entry[a]	Variation from "standard conditions"	Conv.[b] (%)	Yield[b] (%)
1	None	**> 99**	**90 (89[c])**
2	No 4-DPAIPN	30	20
3	No HAT 1	30	15
4	No Light	5	Trace
5	DMF instead of DMSO	90	83
6	ACN instead of DMSO	20	Trace
7	**4-CzIPN** instead of 4-**DPAIPN**	80	70
8	$[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ instead of 4-DPAIPN	20	Trace
9	**HAT 2** instead of **HAT 1**	80	61
10	**HAT 3** instead of **HAT 1**	75	41
11	**HAT 4** instead of **HAT 1**	95	86
12	HCOONa instead of HCOOLi	> 99	86
13	HCOOK instead of HCOOLi	> 99	89
14	No H_2O	> 99	75

[a]Reaction conditions: 1a (0.1 mmol), HCOOLi (4.0 equiv., 0.4 mmol), **4-DPAIPN** (2 mol%, 0.002 mmol), **HAT 1** (5 mol%, 0.005 mmol), DMSO (950 uL), H2O (50 uL), irradiation with 20 W 440 nm Blue LEDs at 35 °C for 20 h. [b]Conversion of **1a** and NMR Yield of **2a** were determined by crude ^{1}H NMR with 1,3,5-Trimethoxybenzene as an internal standard. [c] Isolated yield after methylation.

buffer, 100 mM, pH 7.4 : MeOH = 9:1), lipase A (from Aspergillus niger) (12.5 wt%) was added, the suspension was stirred at 40°C for a given time to achieve around 50% conversion of the substrate. The conversion was monitored by crude ^{1}H NMR.

Reaction work-up: When the conversion reach to around 50%, the suspension was extracted with ethyl acetate (2 mL × 3), the combine organic phase was back extracted with 1 mL brine, the upper organic phase was then filtered through a short silica gel column and rinsed with EtOAc (1mL × 2). All the organic phase was collected and remove the solvent under reduced pressure. The residue was purified by preparative TLC to obtain the desired product.

RESULTS AND DISCUSSION

With this ideal in mind, we initiated our investigation by optimizing the key parameters of the photochemical reaction and using *p*-fluorophenyl vinyl acetate (1a) as the starting material (Table 1). After extensive condition optimization, the optimized reaction conditions are set as follows: 1. using DMSO as solvent, 2. 4-DPAIPN as the photocatalyst and 3. methyl 2-mercaptobenzoate as the HAT reagent. 4.0 equiv. of lithium formate as C1 source, H_2O as additive, under the irradiation of 440 nm blue LED for 20 h, affording the desired product 2a in 90% NMR yield (Table 1, Entry 1). Although The BDE of formate (86 kcal/mol) is slightly higher than the HAT 1 (80 kcal/mol) which cannot be rationalized by thermodynamic parameter, but it still consistently with substantial polar effects on the HAT transition state structures.[125] Control experiments revealed the essential roles of photocatalyst, HAT reagent and light irradiation (Table1, Entries 2-4). 20% of 2a was obtained when the photocatalyst was eliminated, the thiol catalyst may undergo spontaneous oxidation to thiyl radical *in situ* to initiate the reaction, but not efficiency (Table 1, Entry 2).[24,32] $CO_2^{\bullet-}$ could be generated through SET process between formate salt and photocatalyst in the absence of thiol catalyst,[34] although the conversion and yield significantly decreased (Table 1, Entry 3). DMF was also a suitable solvent with a slight decrease of product yield, and no product was observed when acetonitrile was used as the reaction solvent (Table 1, Entries 5-6). Photocatalyst selection was important as 4-CzIPN give 70% NMR yield and [Ir] photocatalyst presents no reactivity (Table 1, Entries 7-8). Other HAT reagents and formate salts also gave the desired products but with less effectiveness (Table 1, Entries 9-13). The yield decreased when H_2O was eliminated (Table 1, Entry 14). The structure of the reagent used in Table 1 was listed in Figure 2.

After the optimal conditions established, we first evaluated the substrate scope of alkenyl acetates for the synthesis of *β*-acetoxy acids (Figure 3). A variety of aryl- and heteroaryl-substituted alkenyl acetates were evaluated (2a-2u), and the reaction demonstrated broad functional group tolerance. Substrates bearing electron-withdrawing groups (2a, 2d, 2n) exhibited adequate reactivity and provided excellent yields. Furthermore, substrates with electron-donating groups, such as methoxy, *t*-Bu, phenyl, and methylthio (2b, 2e, 2g, 2h, 2j), were also suitable for this transformation. Several heteroaryl vinyl acetates (2j, 2k, 2f) give the corresponding products in satisfactory isolated yields. Notably, both cyclic and acyclic 1,2-disubstituted alkenyl acetates proved to be suitable substrates for the photoredox hydrocarboxylation reaction (2m-2t), affording the branched *β*-acetoxy acids with moderate to excellent isolated yields, albeit with low diastereoselectivity. The product yield of 2q, 2r and 2t were relatively low due to the steric hindrance of the substrate, which may slowed down the $CO_2^{\bullet-}$ addition rate. Importantly, the method also performed successfully when applied to a fully substituted alkenyl acetate (2u).

Subsequently, we optimized reaction conditions for the photo-enzymatic cascade catalysis to synthesize chiral *β*-hydroxy esters. Various commercially available lipases were evaluated (Table S1). Following extensive optimization, lipase from *Aspergillus niger* was selected, using a mixed solvent system of methanol and potassium phosphate (KPi) buffer. This lipase selectively hydrolyzes one enantiomer of the *β*-acetoxy ester, yielding the corresponding chiral *β*-hydroxy esters alongside unreacted *β*-acetoxy esters (Figure 4, 3a-3g). This cascade catalysis platform afforded the products in moderate yield and enantioselectivity. Our approach enables a more straightforward synthesis of chiral *β*-hydroxy esters from readily available starting materials.[40,122-124]

To demonstrate the synthetic utility of this method, several productive and valuable transformations were performed (Figure 5). The photoredox anti-Markovnikov hydrocarboxylation of alkenyl acetates was readily scaled to gram quantities (Figure 5A), affording product 2a in 89% isolated yield, comparable to small-scale reactions (Figure S1). Moreover, when the purified 2a was subjected to the enzymatic kinetic resolution process, both the hydrolyzed chiral *β*-hydroxy ester 3a and the unhydrolyzed *β*-acetoxy ester (*R*)-2a were obtained with good enantioselectivity and isolated yield. Furthermore, the reduction of the product 3a to obtain the chiral diol 4 serves as a key intermediate for the synthesis of Ezetimibe (Figure 5B).[41]

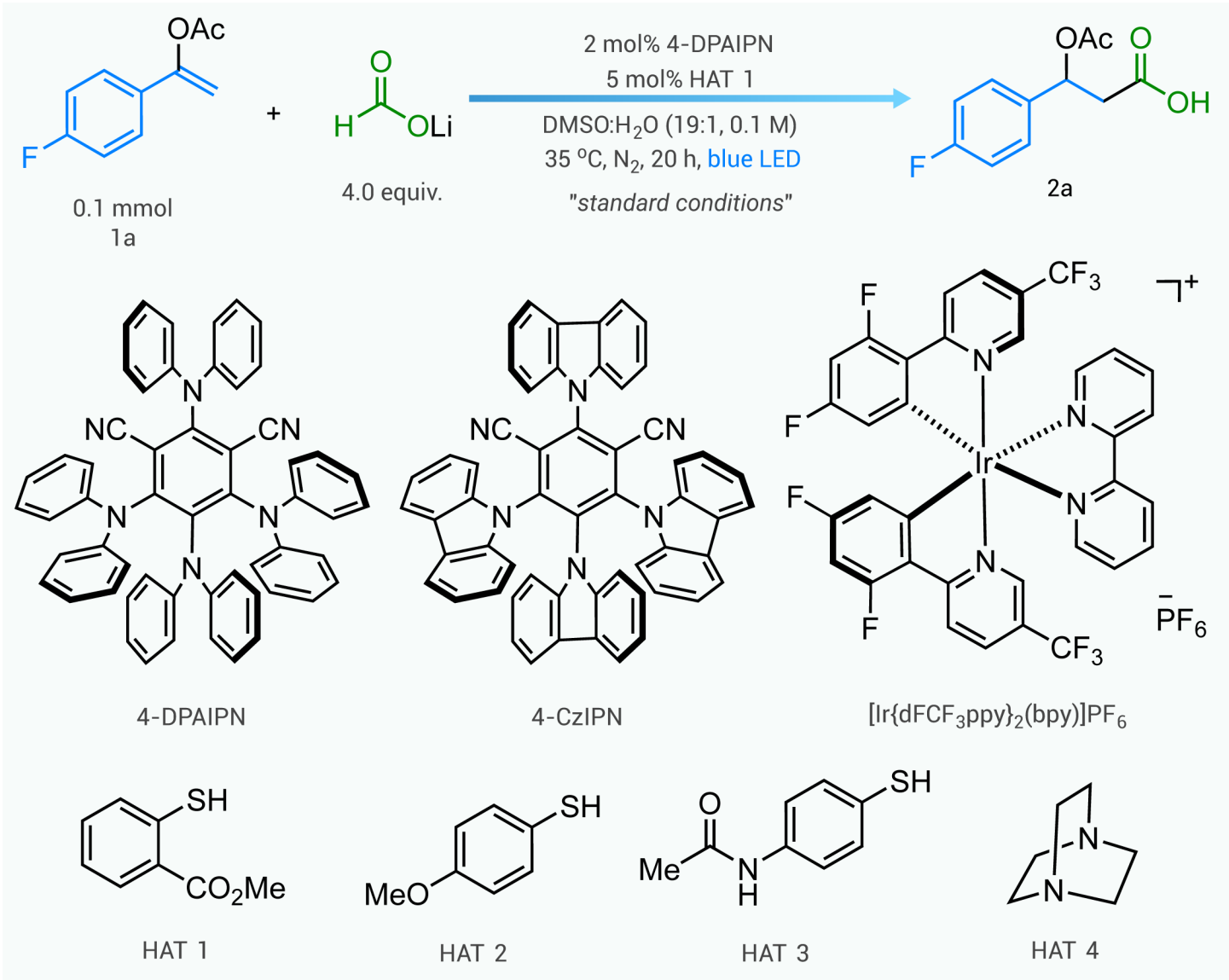

Figure 2. Reaction equation and structure of the reagent used in Table 1.

Preliminary mechanistic studies were conducted to investigate the possible reaction pathway. Adding 2.0 equiv. of TEMPO to the standard conditions and eliminating the H_2O, no desired product was observed, and the radical trapping product 5 was detected by HRMS (Figure 6A), which may indicate the generation of a benzylic radical intermediate. Deuterium incorporation was not observed when 4.0 equiv. of D-formate was applied (Figure 6B-1). However, approximately 68% deuterium incorporation was observed when H_2O was eliminated, and > 95% deuterium incorporation was achieved when sodium formate and D_2O were used as starting materials (Figures 6B-2, B-3). Meanwhile, using d_6-DMSO as the reaction solvent resulted in no deuterium incorporation (Figure 5B-4). These results suggest that proton exchange between the thiol catalyst and H_2O is likely occurring (Table S2 & Figure S2).[25] Light on/off experiments (Figure 6C) show that continuous light irradiation is necessary for the accumulation of the desired product (Table S3). Subsequently, Stern-Volmer quenching experiments indicated that the excited state of 4-DPAIPN can be quenched by either the thiol catalyst or Lithium formate (Figures S3-S8), and the thiol catalyst presents stronger quenching effect.

Based on these preliminary mechanistic studies and literature reports, we propose a plausible reaction mechanism as present in Figure 7: The major reaction pathway start from a single-electron transfer (SET) process between the thiol catalyst and the excited photocatalyst, which will produce thiol radical intermediate and reduced photocatalyst. Subsequent hydrogen atom abstraction (HAT) between thiol radical a and formate salt gives the carbon dioxide radical anion ($CO_2^{\bullet -}$) intermediate. This radical anion intermediate was then added to the alkenyl acetate to obtain intermediate b. The $PC^{\bullet -}$ could further reduce the intermediate b to intermediate d through SET process and then close the photocatalytic cycle. Finally, protonation of the intermediate d affords the final desired product. Meanwhile, the excited photocatalyst could be quenched by formate salt directly to obtain the formate radical intermediate c, as demonstrated by Stern-Volmer quenching experiments. The intermediate c will also serve as HAT reagent for the carbon dioxide radical anion ($CO_2^{\bullet -}$) intermediate generation.[27,34]

CONCLUSIONS

In summary, we have developed a chemo-enzymatic cascade system that harnesses photoenergy to transform a fundamental C1 building block. The photoredox-catalyzed anti-Markovnikov hydrocarboxylation reaction transforms multi-substituted alkenyl acetates into β-acetoxy acids under mild conditions. Integrating with lipase-catalyzed kinetic resolution in a cascade process enables the direct synthesis of valuable chiral β-hydroxy esters with good enantioselectivity. This method presents good functional group tolerance and practical utility, underscored by successful gram-scale synthesis and the preparation of a key pharmaceutical intermediate. Furthermore, this protocol provides a facile method to prepare labelled carboxylate products using D_2O as a deuterium source.

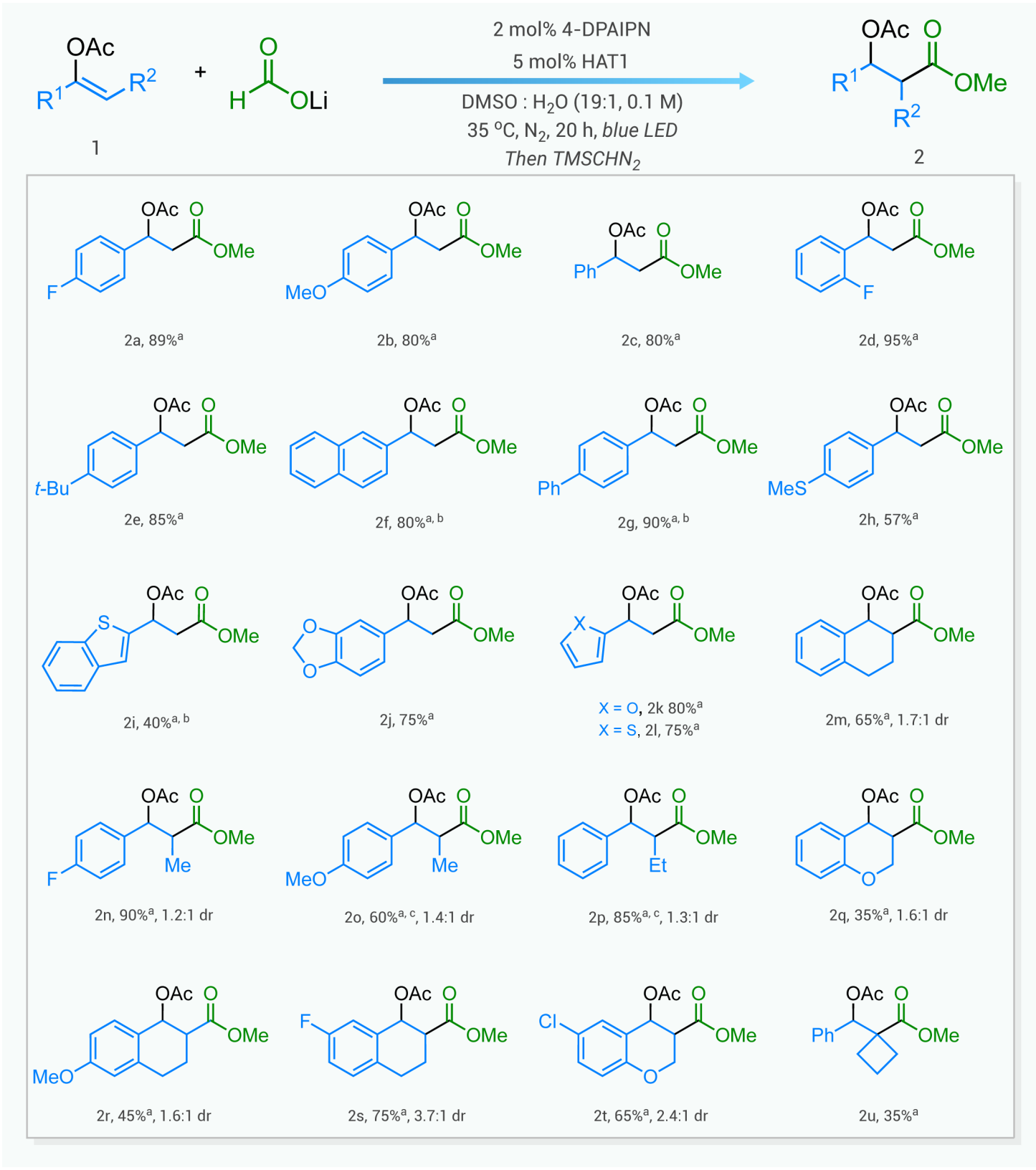

Figure 3. Scope of alkenyl acetates [a] 0.1 mmol alkenyl enolate, 4.0 equiv. of lithium formate, isolated yield after methylation. [b] 15 mol% HAT 1. [c] 40 h reaction time, the diastereoselectivity was determined using crude ^{1}H NMR analysis.

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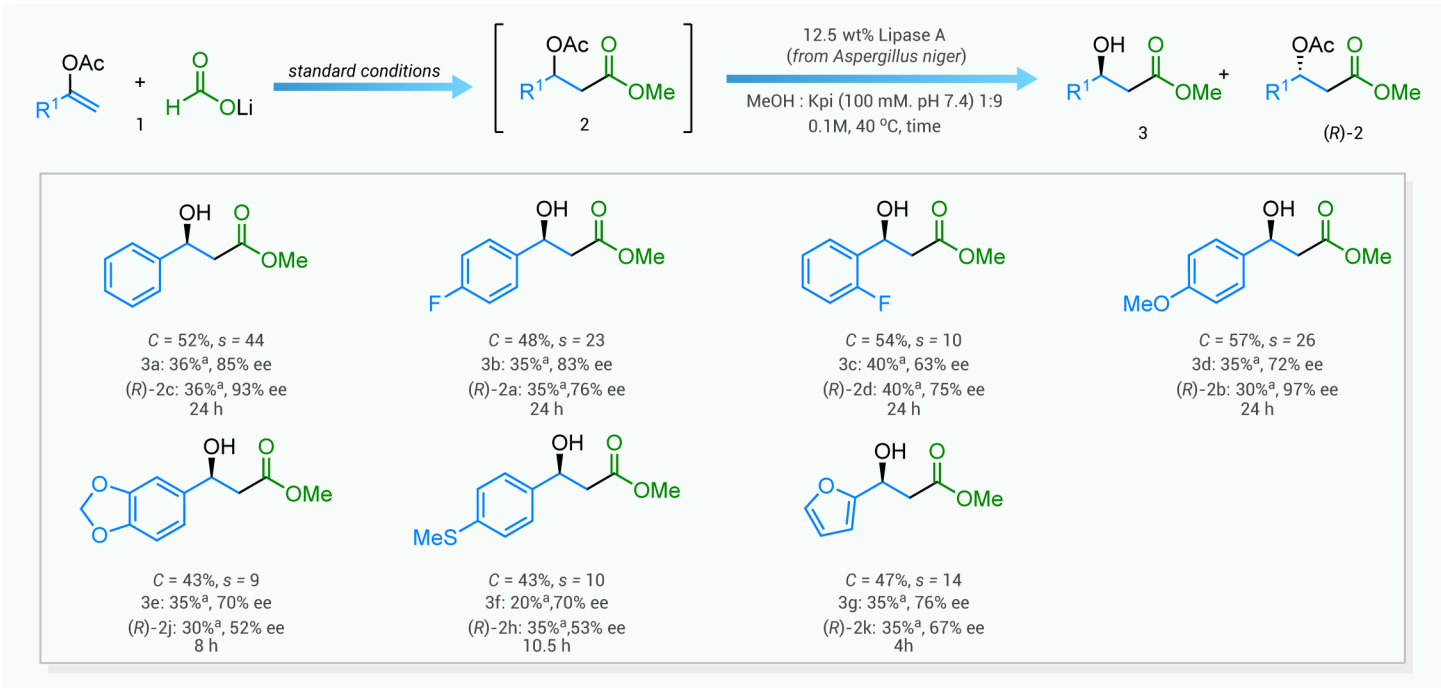

Figure 4. Scope of photoredox-enzymatic cascade catalysis [a] 0.2 mmol scale and isolated yield. The (*s*) factor was calculated by the equation $s = \ln[(1 - C)(1 - ee2)]/\ln[(1 - C)(1 + ee2)]$. $C = ee2/(ee2 + ee3)$. The ee of product 3 and the remaining substrate (*R*)-2a was determined by SFC.

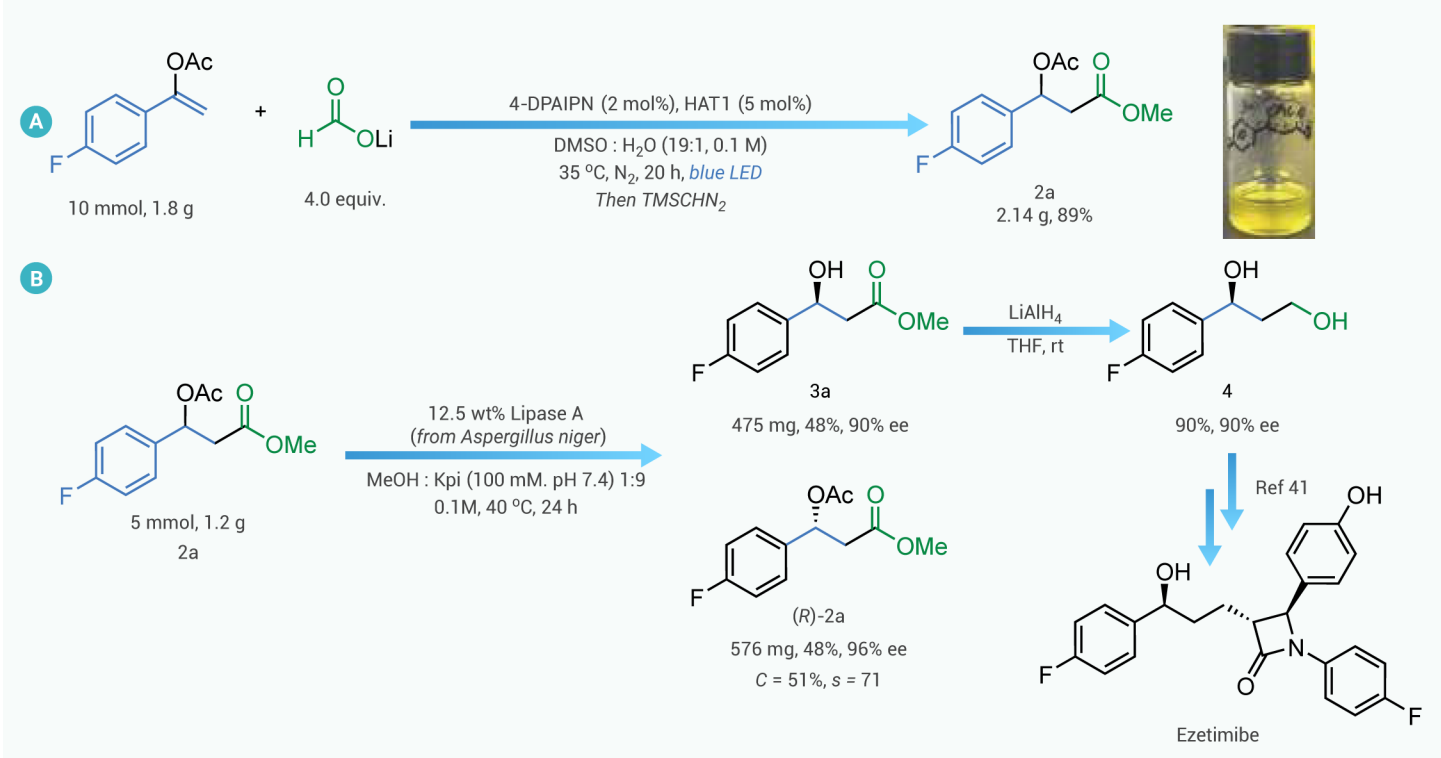

Figure 5. Method application (A) Gram scale synthesis. (B) Drug key intermediate synthesis.

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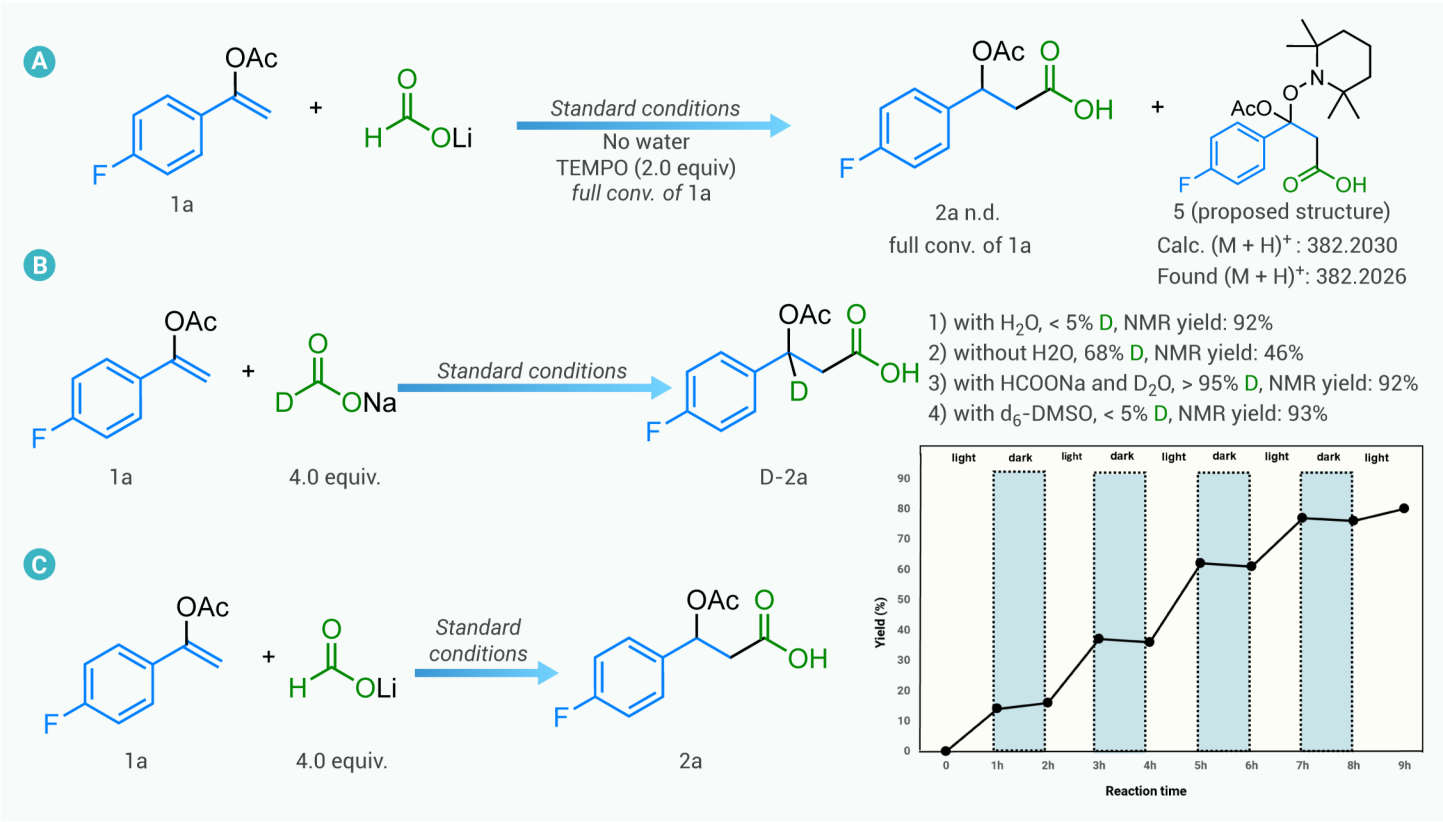

Figure 6. Mechanism study (A) Radical trapping experiment. (B) Deuterium labeling experiment. (C) Light on/off experiment.

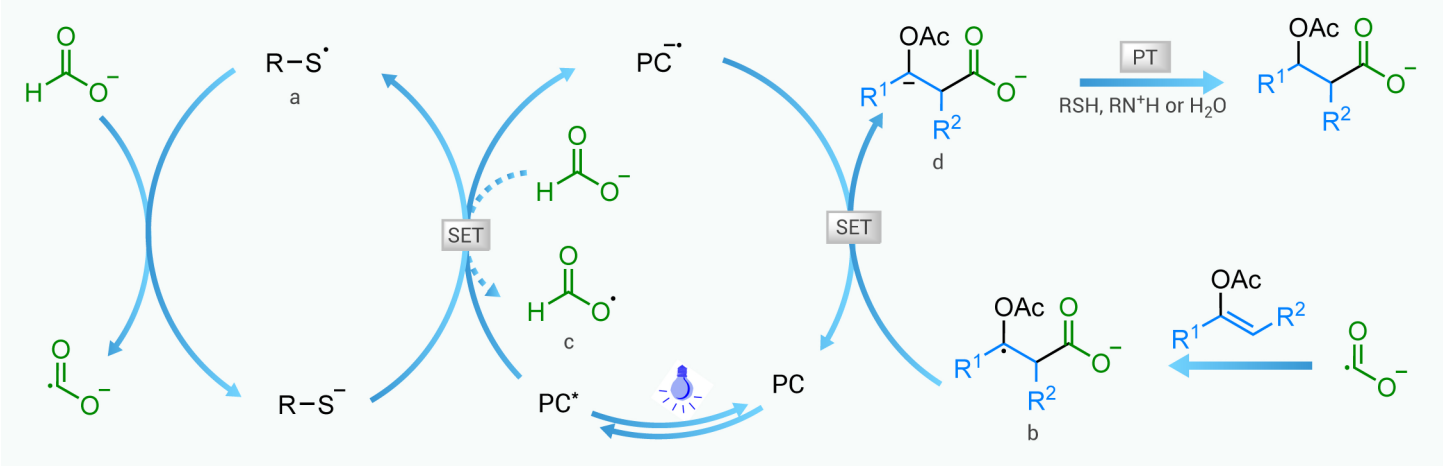

Figure 7. Proposed reaction mechanism.

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AUTHOR CONTRIBUTIONS

Xiaowen Xia: equal the conceptualization, lead the data curation, equal the formal analysis, equal the investigation, lead the methodology, lead the original draft, writing the original manuscript. Jiaxu Guo: Supporting the data curation, compounds synthesis. Yin Gao: Supporting the data curation, formal analysis and methodology. Jianming Liu: Lead the conceptualization, lead the investigation, equal the project administration, revise the original manuscript, equal the funding the acquisition. An-Ping Zeng: lead the funding the acquisition, equal the conceptualization, lead the supervision, lead the project administration, revise the original manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.