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Photoredox/Enzymatic Catalysis Enabling Redox-Neutral Decarboxylative Asymmetric C−C Coupling for Asymmetric Synthesis of Chiral 1,2-Amino Alcohols

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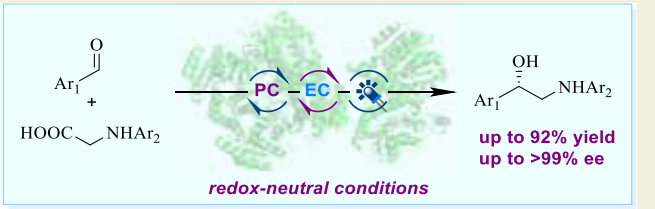
ABSTRACT: Photocatalysis offers tremendous opportunities for enzymes to access new functions. Herein, we described a redox-neutral photocatalysis/enzymatic catalysis system for the asymmetric synthesis of chiral 1,2-amino alcohols via decarboxylative radical C−C coupling of *N*-arylglycines and aldehydes by combining an organic photocatalyst, eosin Y, and carbonyl reductase RasADH. Notably, this protocol avoids using any sacrificial reductants. A possible reaction mechanism proposed is that the transformation proceeds through sequential photoinduced decarboxylative radical addition to an aldehyde and a photoenzymatic deracemization pathway. This redox-neutral photoredox/enzymatic strategy is promising not only for effective synthesis of a series of chiral amino alcohols in a green and sustainable manner but also for the design of other novel C−C radical coupling transformations for the synthesis of bioactive molecules.



KEYWORDS: *asymmetric catalysis, photoredox catalysis, enzymatic catalysis, radical C−C coupling, deracemization*

1. INTRODUCTION

A combined photoredox/enzymatic catalysis system has emerged recently as a new toolbox for asymmetric chemical transformations.[1−3] Enzymes are preeminent catalysts for natural chemical reactions because they can function under mild conditions with high efficiency and provide excellent chemo-, regio-, and enantioselectivity.[4−7] The specificity, however, limits their application to non-natural transformations. Biochemists have found that the combination with photocatalysis enables enzymes to access new catalytic functions.

Photoenzymatic asymmetric reductions of ketones,[8,9] imines,[10,11] and olefins[12,13] and reductive dehalogenation or deacetylation of α-halo- or α-acetoxycarbonyls[14−17] have been accomplished. For the C−C bond-forming reactions, Hyster and co-workers, Zhao and co-workers, and others have demonstrated asymmetric radical addition reactions enabled by flavin-dependent ene-reductases (EREDs) employing alkyl iodides or α-halo (diazo) carbonyls[18−22] as radical precursors (Scheme 1A). Wang, Zhao and co-workers subsequently reported the generation of *N*-(acyloxy)phthalimide-derived radicals and their addition to terminal alkenes catalyzed by nicotinamide-dependent ketoreductases (KREDs, Scheme 1B),[23] and Hyster and co-workers recently revealed an ene-reductase CsER-catalyzed cross-electrophile coupling (XEC) reaction between alkyl halides and nitroalkanes followed by cleavage of the nitro group.[24] Interestingly, when an engineered enzyme GkOYE-G7 was used, the product was the C-alkylated nitroalkanes (Scheme 1C).[25] The strategies mentioned above always include a NADPH recycling system, and NADPH functions in two different ways (Scheme 1D): (i) direct formation of a charge transfer (CT) complex between NADPH and the substrate within the enzyme active site; (ii) hydride transfer to the flavin mononucleotide (FMN) to form flavin hydroquinone (FMN_{hq}), which undergoes subsequent charge transfer or single electron transfer (SET) to generate the radical intermediate. Recycling of NADPH costs extra sacrificial electron donors such as isopropanol or glucose, which leads to lower atom economic efficiency, and the decomposition of them may also affect the functionality of enzymes and photocatalysts. On the other hand, the photoenzymatic redox-neutral system was just reported with limited examples.[25−28]

Carboxylic acids are abundant and inexpensive basic chemicals from nature sources. They are easy to store and handle and thus are widely used as versatile synthetic building blocks. Recent years have witnessed an upsurge in developing

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Scheme 1. Previous Studies on Photoenzymatic C−C Bond Formation and This Work

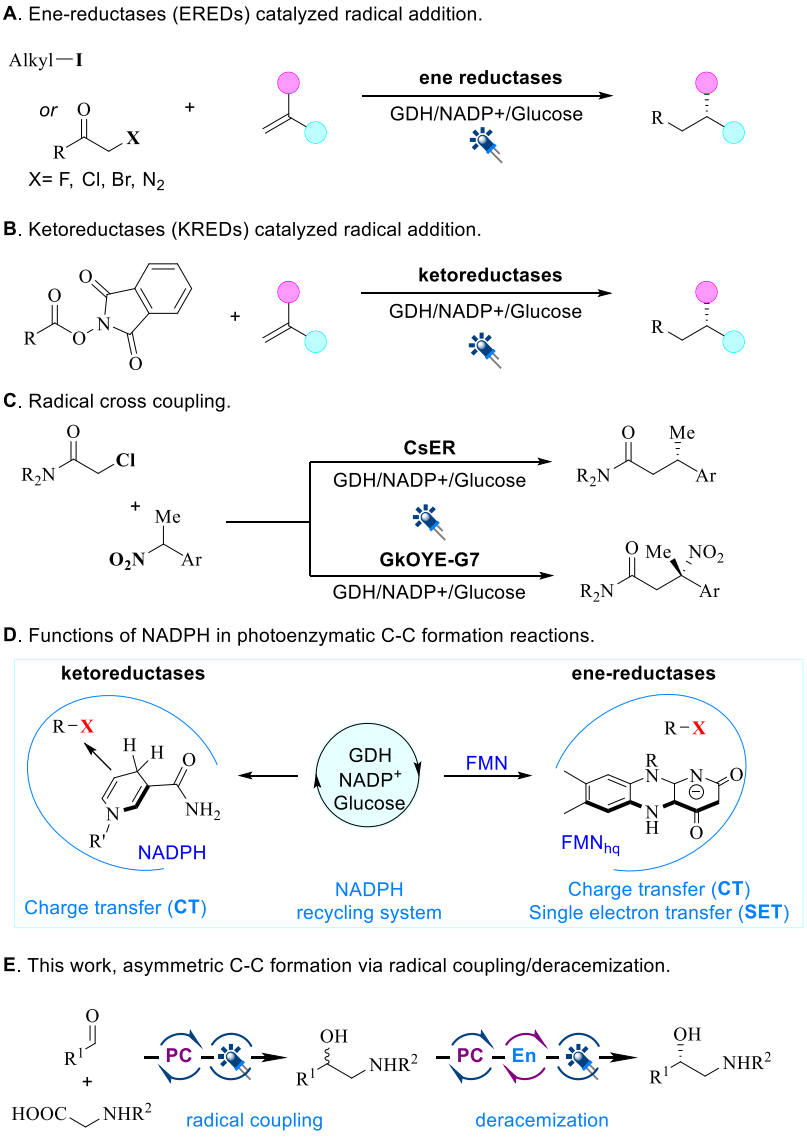
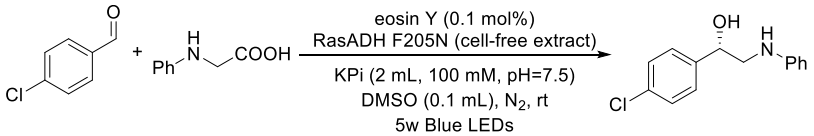


Table 1. Standard Conditions and Control Experiments[a]



1a **2a** (*S*)-**3aa**

entry	variation	yield[b]	ee (%)[c]
1	none	82	96
2	RasADH (wt)	82	23
3	performed in the dark	N.D.	
4	without enzyme	91	0
5	without eosin Y	17	99
6	without enzyme and eosin Y	N.D.	
7	open to air	N.D.	

[a]**1a** (0.02 mmol), **2a** (0.06 mmol, 3.0 equiv), eosin Y (0.1 mmol %), enzyme (cell-free extract from 50 mg of wet cells/mL), DMSO (0.1 mL), and KPi buffer (2 mL, 100 mM at pH 7.5) under the irradiation of 5W blue LEDs for 16 h. [b]Analytical yield of **3aa** determined by NMR with 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by HPLC analysis. N.D. not detected.

new decarboxylative functionalization strategies for the synthesis of valuable products.[29−32] Particularly, the photoredox-catalyzed decarboxylation reaction has gained widespread attention, and a variety of alkyl carboxylic acids can be readily

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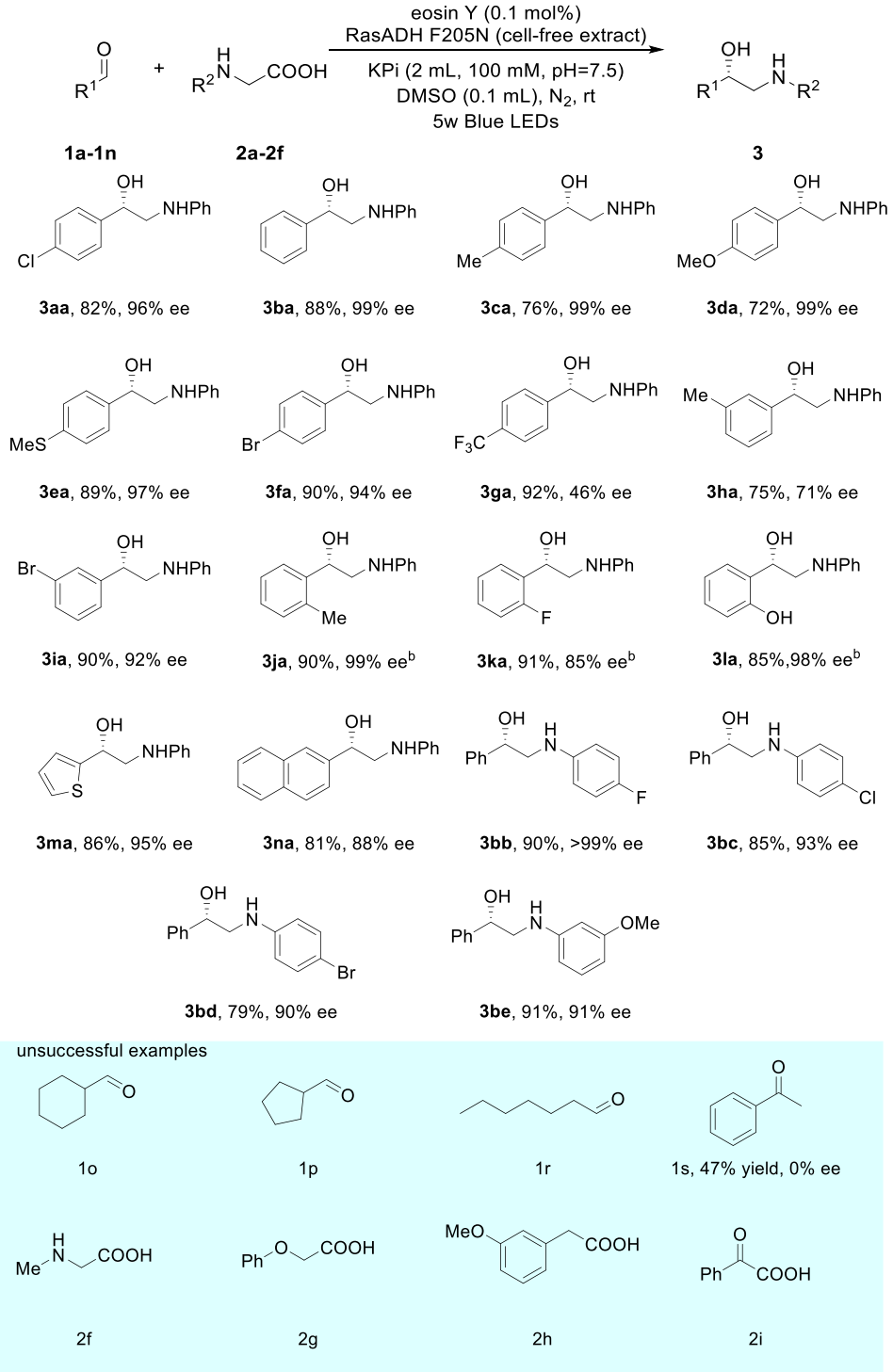
JACS Au 2023, 3, 3005−3013

Table 2. Substrate Scope Investigation[a]



[a]The conditions are the same as in Table 1. Analytical yields are determined by NMR with 1,3,5-trimethoxybenzene as the internal standard, ee values are determined by HPLC analysis. [b]RasADH F205 V was used instead of F205N.

converted to corresponding radical intermediates and then transformed into high-value products, in which only CO_2 was eliminated as a traceless byproduct.[33−38]

Chiral 1,2-amino alcohols are privileged motifs in numerous nature products and pharmaceuticals from neurotransmitters to antivirals.[39,40] Among the tremendous efforts for the synthesis of chiral 1,2-amino alcohols, the radical decarboxylative coupling reaction of α-amino acids and carbonyls provides a redox-neutral approach. According to previous reports of Jiang and co-workers and Melchiorre and co-workers, α-amino acid would initially undergo a visible light photoredox-catalyzed SET and generate an α-amino radical upon releasing CO_2, and the resultant radical intermediate would participate in the asymmetric addition with activated ketones and alkenes enabled by chiral hydrogen-bonding catalysis[41,42] or Lewis base catalysis.[43] In light of the

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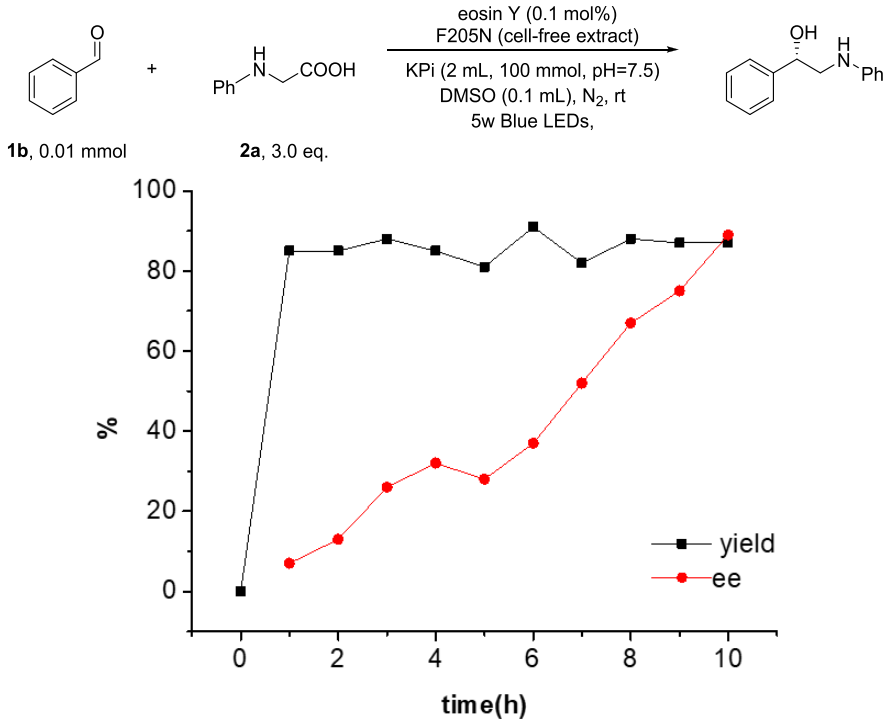


Figure 1. Yield and enantiomeric excess of product **3ba** over time.

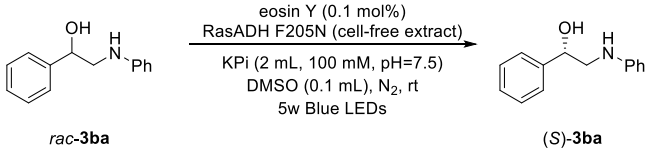
aforementioned advantages of carboxylic acids undergoing external reductant-free radical addition reactions and excellent stereocontrol of enzyme catalysis on carbonyl compounds, herein, we sought to demonstrate the synthesis of chiral 1,2-amino alcohols enabled by a redox-neutral photoredox/enzymatic catalysis system. The none-selective C−C bond formation proceeds in the first step by photocatalyzed decarboxylative radical coupling, and the resultant racemic amino alcohol undergoes a photoenzymatic deracemization pathway, furnishing chiral 1,2-amino alcohols (Scheme 1E).

2. RESULTS AND DISCUSSION

We began our testing with commercially available 4-chlorobenzaldehyde **1a** and *N*-phenylglycine **2a** as model substrates.[44,45] As shown in Table 1, initial screening of the solvent, light source, photocatalyst, and carbonyl reductase (see Tables S1 and S2) showed that the combination of a xanthene dye eosin Y and an alcohol dehydrogenase from the bacteria *Ralstonia* species (RasADH) could efficiently catalyze the generation of amino alcohol (*S*)-**3aa** in 82% yield and 23% ee under irradiation of 5 W blue light-emitting diodes (LEDs) in a solvent mixture of 100 mM potassium phosphate buffer (pH 7.5) and DMSO (20:1 v/v) (entry 2). In our previous studies, the amino acid residue at the 205 position of RasADH greatly affects the enzyme activity and stereoselectivity in enzymatic carbonyl reductive transformations.[46,47] A further detailed investigation of RasADH mutants at the 205 position was performed to evaluate its effect on this photoenzymatic decarboxylative coupling reaction (see Table S3). When F205N was employed as the biocatalyst, product **3aa** was obtained in 82% yield with 96% ee (entry 1). Some control experiments were conducted to identify the role of each parameter. When the reaction was performed in the dark, no product was detected. In the absence of enzymes, the racemic product was generated in 91% yield (entry 4). In the absence of eosin Y, the reaction with RasADH F205N under visible light irradiation could proceed to give the product with excellent enantiomeric excess but a dramatically diminished yield (entry 5), indicating that a biocatalytic decarboxylative coupling would occur under irradiation as a minor process, probably through a charge transfer (CT) complex within the active site of the enzyme.[14,23] This was further supported by the fact that no product was detected when both the enzyme and eosin Y were omitted (entry 6). Oxygen might have a negative effect on the radical intermediate because no product was detected when it was operated open to air (entry 7).

With the best condition established, we proceeded to examine the scope of this photoenzymatic transformation by using various aldehydes and amino acids. The steric and electronic effects of the substituents on the aromatic aldehydes were first evaluated. As shown in Table 2, a series of electron-

Table 3. Control Experiments of Deracemization[a]



rac-**3ba** (*S*)-**3ba**

entry	variation	3ba[b]	ee[c]
1	none	96	98
2	performed in the dark	99	<5
3	without enzyme	91	<5
4	without eosin Y	99	<5
5	open to air	trace	

[a]*rac*-**3ba** (0.02 mmol), eosin Y (0.1 mol %), enzyme (cell-free extract from 50 mg of wet cells/mL), DMSO (0.1 mL), and KPi buffer (2 mL, 100 mM at pH 7.5) under the irradiation of 5W blue LEDs for 12 h. [b]Analytical amount of **3ba** was determined by NMR with 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by HPLC analysis.

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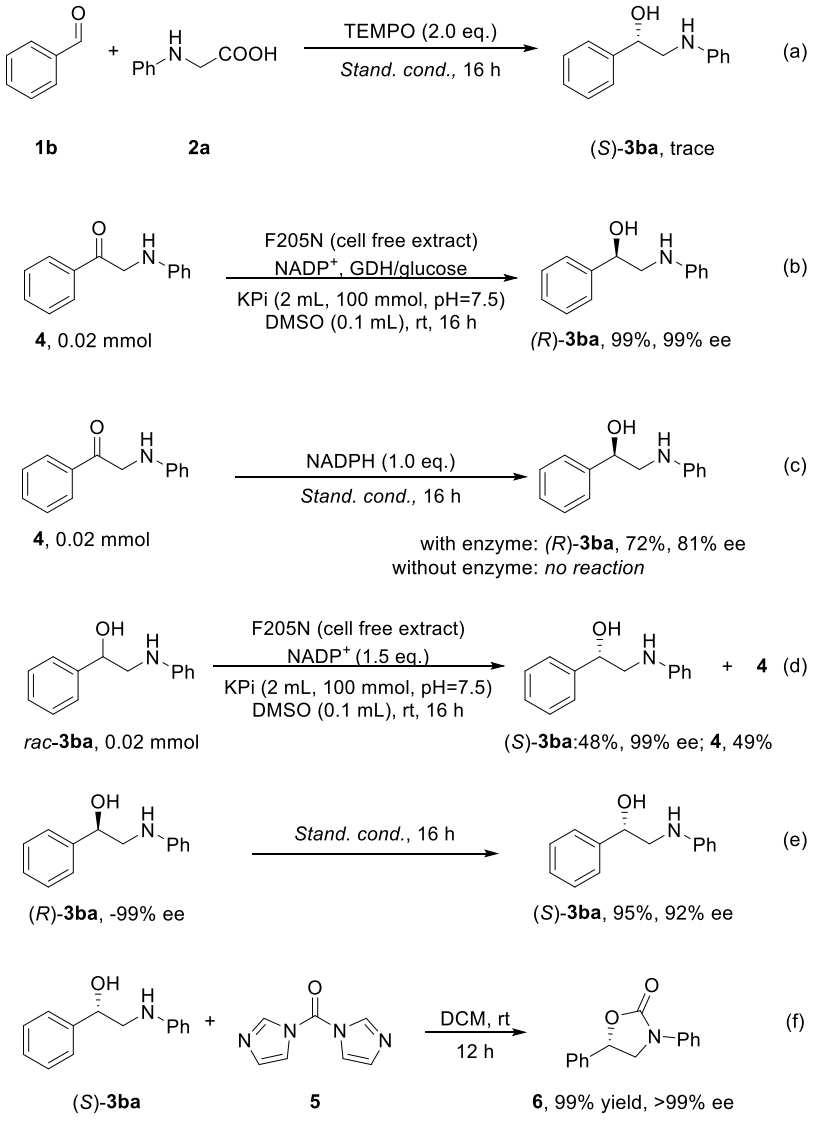
Scheme 2. (a−f) Mechanism Studies and Synthetic Application



neutral, electron-donating (e.g., −Me, −OMe, and −SMe), and electron-withdrawing (e.g., −F, −Cl, and −Br) substituents at the *para*-position were well tolerated, giving the corresponding product **3aa**−**3fa** in good yields (72−90%) and excellent levels of enantioselectivities (92−99% ee). When there was a trifluoromethyl group at the same position, enantioselectivity was observably decreased, although the yield was excellent (**3ga**, 92% yield and 46% ee). The coupling reaction also proceeded smoothly with the substituent at the *meta*-position, furnishing products **3ha** and **3ia** with satisfactory efficiency and enantioselectivity. After noticing that the optimized enzyme F205N failed to catalyze the asymmetric transformation of phenyl aldehydes bearing a substituent at the *ortho*-position, we investigated the mutant library for a second round. To our delight, F205 V performed smoothly to produce **3ja**−**3la** in good yields and enantioselectivities. In addition, heteroaryl aldehydes such as thienyl readily participated in this reaction, affording **3ma** with 95% ee. 2-Naphthaldehyde also afforded the coupling product **3na** with 88% ee. Different aryl-bearing amino acids were also investigated, including *para*- and *meta*-substituted phenyl glycine analogues, giving corresponding products **3bb**−**3be** in generally good results.

During the examination of the substrate scope, some starting materials were proved to be unsuccessful at this stage. Alkyl aldehydes such as cyclohexanecarbaldehyde **1o**, cyclopentanecarbaldehyde **1p**, and heptanal **1r** did not react to give any product. For acetophenone **1s**, the corresponding amino alcohol product was obtained in a moderate yield but in the racemic form. It is possible to improve the enantioselectivity by discovering suitable carbonyl reductases and to extend this asymmetric transformation to aromatic ketones. Instead of **2a**, methyl-protected glycine (sarcosine) **2f**, 2-phenoxyacetic acid **2g**, benzyl carboxylic acid **2h**, and benzoyl carboxylic acid **2i** did not react with benzaldehyde **1b** to give the coupling product (Tables 2 and S4). These results suggest that the aromatic substituent is crucial for the redox nature of both aldehydes and amino acids.

To gain some insights into the reaction mechanism, we proceeded to examine the time-dependent change of the yield and enantioselectivity of the product by setting up 11 parallel reactions. It turned out that the amino alcohol was first generated as the racemic product within 1 h, producing **3ba** in

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JACS Au 2023, 3, 3005−3013

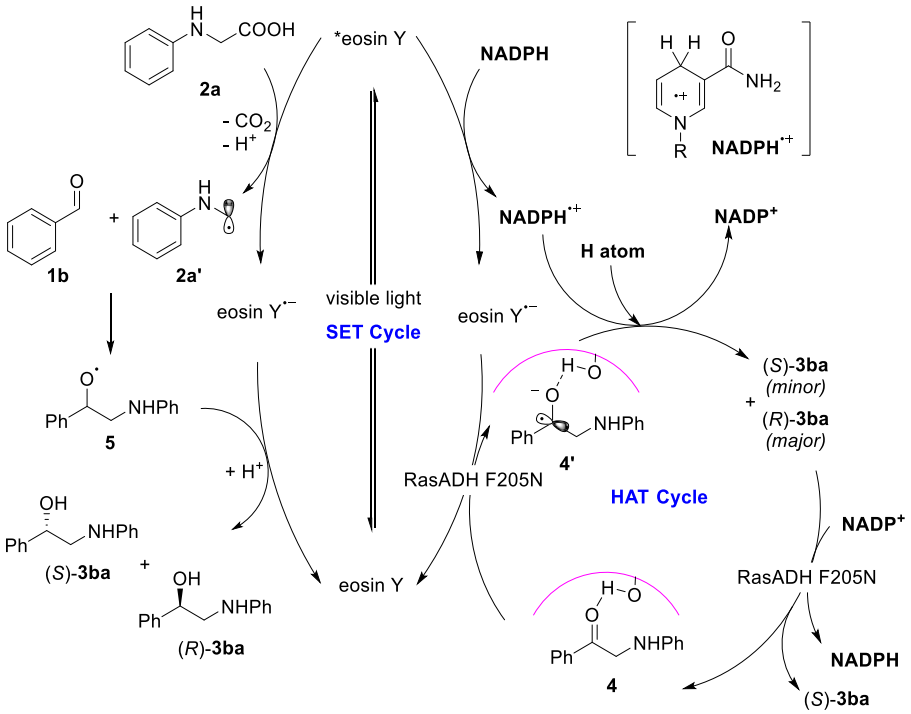

Figure 2. Possible reaction mechanism.

85% yield and 7% ee, and the enantiomeric excess value of the product increased on prolonging the reaction time, reaching 89% after 10 h (Figure 1). This result suggested that a sequential process might be involved: racemic amino alcohol was first produced from aldehydes and amino acids via a photoredox catalysis cycle, and the resulting product then underwent deracemization under the reaction conditions.

In order to confirm this hypothesis, several control experiments were conducted for the deracemization of *rac*-**3ba**. Under the standard conditions, *rac*-**3ba** was converted to (*S*)-**3ba** with 96% yield and 98% ee (Table 3, entry 1). Visible light, enzyme catalysts, and photocatalysts are all critical for this transformation since no deracemization occurred in the absence of either the light, RasADH F205N, or eosin Y (entries 2−4). The decomposition of amino alcohol was observed when the reaction was set up under an air atmosphere (entry 5).

In the presence of a stoichiometric radical quencher TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), the reaction was significantly inhibited, suggesting that radical intermediates were involved in the reaction process (Scheme 2a). Moreover, we prepared amino ketone **4** through a chemical method and subjected it to the enzymatic reduction reaction without eosin Y and light. The same enzyme F205N produced (*R*)-**3ba** instead of the (*S*)-configured product (Scheme 2b). When the reduction of amino ketone **4** was performed under the standard conditions in the presence of a stoichiometric amount of NADPH, the ee value of the product was decreased (72% yield and 81% ee, Scheme 2c). However, no reaction occurred when the enzyme was omitted. These results suggest that (*S*)-**3ba** was generated under the standard reaction conditions by a combination of photocatalysis and enzymatic catalysis. A possible process for the formation of the (*S*)-enantiomer is that photoinduced single electron transfer generates ketone anion radicals that abstract a H atom from the reaction medium, although this process may not be dominant. With a stoichiometric amount of $NADP^+$, F205N catalyzed the oxidation of racemate **3ba** in half, leaving (*S*)-**3ba** unreacted (Scheme 2d). Furthermore, (*R*)-**3ba** was readily converted to (*S*)-**3ba** with an entirely reverse chirality under standard photoenzymatic conditions (Scheme 2e). These results ruled out the possibility of a photocatalytic oxidation/enzymatic reduction mechanism for the deracemization of *rac*-**3ba**.[48−52] The synthetic importance of this amino alcohol motif was emphasized by the reaction of (*S*)-**3ba** and 1,1′-carbonyldiimidazole (**5**), and the oxazolidinone product **6** can be easily produced in 99% yield and >99% ee (Scheme 2f).

Based on the experimental results and related previous reports,[53−55] we propose a plausible mechanism for this reaction (Figure 2). Under visible light irradiation, the photocatalyst eosin Y was excited to generate its excited state (*eosin Y), and it was then reduced by **2a** via a single electron transfer (SET) process, resulting in a radical anion intermediate (eosin $Y^{\cdot-}$) and an α-amino radical after decarboxylation of $\mathbf{2a}^{\cdot-}$. This radical was then added to the carbonyl group of aldehyde **1b**, forming an oxygen-centered radical **5**. The subsequent single electron reduction by eosin $Y^{\cdot-}$ and protonation would afford the racemic amino alcohol **3ba**, along with the regenerated ground state photocatalyst. With the participation of RasADH F205N, (*R*)-**3ba** would be selectively oxidized to amino ketone **4** by $NADP^+$ (catalytic amount of the cofactor existing in the cell-free extract). The resulting NADPH could reduce excited *eosin Y to eosin $Y^{\cdot-}$, with itself being converted to the radical cation $NADPH^{\cdot+}$. The single electron transfer from eosin $Y^{\cdot-}$ to enzyme-bound amino ketone **4** generated the ketyl radical **4′**.[56] This species then abstracted a hydrogen atom from $NADPH^{\cdot+}$(or the reaction medium), generating $NADP^+$ and the amino alcohol (a mixture of (*R*)-**3ba** and (*S*)-**3ba**). (*R*)-**3ba** and (*S*)-**3ba** may not be in the ratio 50:50, according to the experiment shown in Scheme 2c. It should be pointed out that the formation of (*R*)-**3ba** would be also possibly originating (or in part) from

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the innate ground-state reactivity of RasADH F205N, since (*R*)-**3ba** is the major product in the reduction control experiment (Scheme 2c). With continuous irradiation, this enzymatic oxidation/photoenzymatic reduction process could lead to a redox-neutral deracemization of the racemic amino alcohol with the accumulation of (*S*)-**3ba**.[57]

3. CONCLUSIONS

In summary, we have developed a redox-neutral photoredox/enzymatic strategy for the efficient decarboxylative radical coupling of *N*-arylglycines and aldehydes, thus enabling the asymmetric synthesis of enantioenriched chiral 1,2-amino alcohols. A reaction mechanism was proposed to involve the dual characters of the photocatalyst eosin Y acting simultaneously for the racemic amino alcohol synthesis and deracemization process and the carbonyl reductase for controlling the enantioselectivity. The reaction scope could be expanded by selecting a suitable photocatalyst and biocatalyst. Other applications of this redox-neutral strategy toward the design of novel transformations are under investigation in our laboratory.

4. METHODS

4.1. Procedure for the Photoredox/Enzymatic Synthesis of Amino Alcohol Products

Aldehyde **1a** (40 μL, 500 mM stock in DMSO, 20 μmol, 1 equiv), glycine **2a** (50 μL, 1200 mM stock in DMSO, 60 μmol, 3 equiv), eosin Y (10 μL, 2 mM stock in DMSO, 0.02 μmol, 0.1 mol %), and enzyme (2 mL, cell-free extract from 50 mg of wet cells/mL in 100 mM KPi buffer, pH 7.5) were added to a 10 mL glass vial equipped with a magnetic stir bar. The resulting reaction mixture was degassed with N_2 gas bubbling for 5 min and then the vial was sealed with a cap and placed on a photoreactor. After having been irradiated for 16 h, 100 μL of 10 mg/mL 1,3,5-trimethoxybenzene in EtOAc as the internal standard was added. The reaction was extracted with EtOAc (2 mL × 2), and the combined organic extract was concentrated under reduced pressure. After NMR analysis, product **3aa** was isolated by TLC. The resulting product was dissolved in 10% isopropanol/hexanes (v/v) for chiral HPLC analysis.

4.2. Procedure for the Photoredox/Enzymatic Deracemization of Amino Alcohols

Racemic amino alcohol *rac*-**3ba** (40 μL, 500 mM stock in DMSO, 20 μmol, 1 equiv), eosin Y (10 μL, 2 mM stock in DMSO, 0.02 μmol, 0.1 mol %), and enzyme (2 mL, cell-free extract from 50 mg of wet cells/mL in 100 mM KPi buffer, pH 7.5) were added to a 10 mL glass vial equipped with a magnetic stir bar. The resulting reaction mixture was degassed with N_2 gas bubbling for 5 min and then the vial was sealed with a cap and placed on a photoreactor. After having been irradiated for 16 h, 100 μL of 10 mg/mL 1,3,5-trimethoxybenzene in EtOAc was added to serve as the internal standard. The reaction was extracted with EtOAc (2 mL × 2), and the combined organic extract was concentrated under reduced pressure. After NMR analysis, the product was isolated by TLC. The resulting product was dissolved in 10% (v/v) isopropanol/hexanes for chiral HPLC analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00366.

Experimental information and procedures, characterization data of compounds, and copies of NMR spectra and HPLC traces (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Yiyin Liu** conceptualization, data curation, funding acquisition, investigation, writing-original draft; **Liangyan Zhu** investigation, methodology, resources; **Xuemei Li** investigation, resources; **Yunfeng Cui** resources; **Atefeh Roosta** investigation; **Jinhui Feng** methodology, data curation, supervision, writing-review & editing; **Xi Chen** methodology, supervision; **Peiyuan Yao** methodology, supervision; **Qiaqing Wu** funding acquisition, supervision, writing-review & editing; **Dunming Zhu** conceptualization, data curation, funding acquisition, supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

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