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Enantioselective aerobic oxidative cross-dehydrogenative coupling of glycine derivatives with ketones and aldehydes *via* cooperative photoredox catalysis and organocatalysis†

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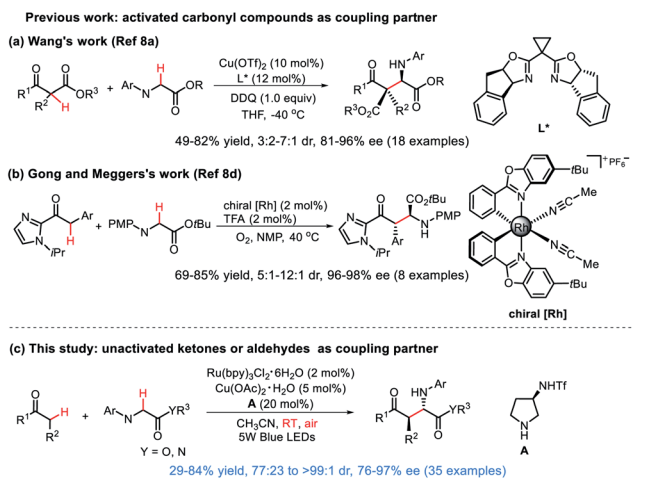
The combination of photoredox catalysis and enamine catalysis has enabled the development of an enantioselective aerobic oxidative cross-dehydrogenative coupling between glycine derivatives and simple ketones or aldehydes, which provides an efficient approach for the rapid synthesis of enantiopure unnatural α-alkyl α-amino acid derivatives in good yield with excellent diastereo- (up to >99 : 1) and enantioselectivities (up to 97% ee). This process includes the direct photoinduced oxidation of glycine derivatives to an imine intermediate, followed by the asymmetric Mannich-type reaction with an enamine intermediate generated *in situ* from a ketone or aldehyde and a chiral secondary amine organocatalyst. This mild method allows the direct formation of a C–C bond with simultaneous installation of two new stereocenters without wasteful removal of functional groups.

Introduction

The oxidative cross-dehydrogenative coupling (CDC) reaction has emerged rapidly as one of the most straightforward and atom-economical strategies for forming C–C bonds through the direct coupling of two C(sp3)–H bonds, as it does not require additional prefunctionalization of substrates, and thus largely reduces the number of reaction steps.[1–3] Among these reactions, pioneered by Li and co-workers,[4] the direct α-C(sp3)–H functionalization of readily available glycine derivatives has proved to be a powerful tool for the rapid synthesis of unnatural α-substitued α-amino acids which have significant applications in the synthesis of biologically active natural products and peptides,[5] and therefore received intense attention in recent years.[6,7] Despite the advances, the stereocontrol of such transformations is highly challenging,[8] mainly because the C(sp^3)–H oxidation process commonly requires harsh reaction conditions (*e.g.* stoichiometric amounts of strong oxidants, high temperature), which are often incompatible with the chiral catalyst system. The carbonyl moiety remains among the most utilized functional groups in organic chemistry. The direct enantioselective coupling of carbonyl compounds[9] with glycine derivatives has long been considered an elusive goal for practitioners of asymmetric catalysis. In 2011, Wang *et al.* reported a pioneering work on asymmetric CDC reaction of glycine esters with β-ketoesters in the presence of a chiral bisoxazoline/Cu(II) catalyst, producing various α-alkyl α-amino acids with good enantioselectivities (Scheme 1a).[8a] However, poor diastereoselectivities were obtained; moreover, stoichiometric amounts of strong oxidant (DDQ) was needed to complete the transformation. Recently, the Gong and Meggers research group reported an elegant oxidative asymmetric catalytic CDC reaction of 2-acyl imidazoles with glycine ester by using molecular oxygen as the terminal oxidant (Scheme 1b).[8d] However, the report was limited to only a single glycine ester.



Scheme 1 Catalytic enantioselective CDC reaction of glycine derivatives with carbonyl compounds.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, optimization of reaction conditions, X-ray crystal structure for compound **3ae**, and spectral data for all products. See DOI: 10.1039/d0sc00683a

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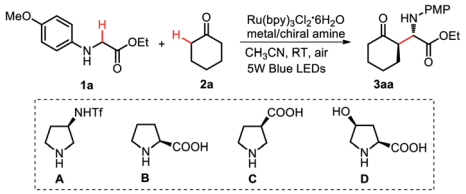
Moreover, both of these two reports are restricted to the use of highly activated carbonyl compounds as nucleophilic partners. Huang and Xie had explored the development of an asymmetric CDC reaction between glycine ester with acetone mediated by TBHP under cooperative transition metal/chiral amine catalysis, however, either the enantioselectivity (15% ee) or yield (47%) was poor.[10] So far, to our knowledge, a catalytic enantioselective CDC reaction of glycine derivatives with simple ketones or aldehydes which proceeds with both high diastereo- and enantioselectivity is unprecedented. In this respect, we wish to develop the first direct catalytic enantioselective CDC reaction of glycine derivatives with simple ketones or aldehydes (Scheme 1c). This atom economic transformation provides an efficient enantio- and diastereoselective access to chiral α-alkyl α-amino acids under mild conditions.

In the past few years, visible-light photoredox catalysis has attracted increasing interest in organic synthesis community, owing to its mild, clean, easy to handle, and environmentally benign characteristics.[11] Recently visible-light photoredox catalysis has emerged as a promising tool to trigger the CDC reaction through single-electron transfer (SET) pathways.[12–14] Despite a few recent successes have verified the feasibility of visible-light induced enantioselective CDC reaction,[15] however, such photocatalytic CDC reactions are mostly focused on the asymmetric oxidative coupling of α-C(sp3)–H bonds in cyclic amines (such as tetrahydroisoquinolines, tetrahydro-β-carbolines and 3,4-dihydroquinoxalin-2-ones). To date, to the best of our knowledge, there have been no reports on an asymmetric photoredox catalytic α-C(sp3)–H functionalization of glycine derivatives, probably due to the poor reactivity and difficulty of controlling the stereoselectivity. With our continuous interests in the visible light-driven α-C(sp3)–H functionalization of glycine derivatives,[16] herein, we describe the first visible-light-induced highly enantioselective oxidative cross coupling of glycine derivatives with simple ketones and aldehydes.

Table 1 Optimization of the reaction conditions[a]



Entry	Amine/metal	Yield[b] (%)	d.r.[c] (*anti*/*syn*)	ee[d] (%)
1	**A**/$Cu(OAc)_2 \cdot H_2O$	76	97/3	96
2	**B**/$Cu(OAc)_2 \cdot H_2O$	n.d.	—	—
3	**C**/$Cu(OAc)_2 \cdot H_2O$	57	98/2	88
4	**D**/$Cu(OAc)_2 \cdot H_2O$	n.d.	—	—
5	**A**/$Zn(OAc)_2$	n.d.	—	—
6	**A**/$Cu(OTf)_2$	63	98/2	86
7	**A**/$CuSO_4$	68	97/3	92
8	**A**/CuI	63	97/3	92
9[e]	**A**/$Cu(OAc)_2 \cdot H_2O$	80	97/3	96
10[e,f,g]	**A**/$Cu(OAc)_2 \cdot H_2O$	81	98/2	97
11[e,f,h]	**A**/$Cu(OAc)_2 \cdot H_2O$	47	95/5	94
12[e,f,g,i]	**A**/$Cu(OAc)_2 \cdot H_2O$	82	98/2	97
13[j]	**A**/$Cu(OAc)_2 \cdot H_2O$	n.r.	—	—
14	**A**/-	n.d.	—	—
15[e,f,k]	**A**/$Cu(OAc)_2 \cdot H_2O$	n.r.	—	—
16[e,f,l]	**A**/$Cu(OAc)_2 \cdot H_2O$	n.r.	—	—

[a] Reaction conditions: **1a** (0.1 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (5 mol%), Lewis acid (10 mol%), CH_3CN (2.0 mL), 5 W blue LEDs light irradiation under air at room temperature for 2 h, then **2a** (0.5 mmol) and chiral amine catalyst (20 mol%) were added. [b] Combined yield of isolated **3aa** (*syn* and *anti*). [c] Determined by HPLC on a chiral stationary phase. [d] Determined by HPLC on a chiral stationary phase. [e] 2 mol% of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ was used. [f] 5 mol% of $Cu(OAc)_2 \cdot H_2O$ was used. [g] 1.5 mL CH_3CN was used. [h] 10 mol% of **A** was used. [i] Reaction was carried out under O_2 atmosphere. [j] Reaction was performed without $Ru(bpy)_3Cl_2 \cdot 6H_2O$. [k] Reaction was carried out in the dark. [l] Reaction was carried out under argon. n.d. = not determined. n.r. = no reaction.

Results and discussion

This new visible light-induced enantioselective CDC protocol was first examined using glycine ester (**1a**) and cyclohexanone (**2a**) as the model substrates, along with photocatalyst $Ru(bpy)_3Cl_2 \cdot 6H_2O$, chiral amine **A** and $Cu(OAc)_2 \cdot H_2O$, under the irradiation of a 5 W blue LED bulb (Table 1, for details see ESI†). After preliminary manipulation of the reaction conditions, we were pleased to find that the desired asymmetric CDC reaction could be realized in the presence of 10 mol% $Cu(OAc)_2 \cdot H_2O$ and 20 mol% chiral amine **A**, to provide the coupling product **3aa** with 76% yield and excellent enantioselectivity (Table 1, entry 1, 96% ee). Encouraged by this result, we next screened a range of chiral amine catalysts (Table 1, entries 1–4) and Lewis acids (Table 1, entries 5–8). The results indicated that chiral amine **A** and $Cu(OAc)_2 \cdot H_2O$ are the optimal catalysts for this transformation (Table 1, entry 1). Different photocatalysts and solvents were also screened (for details, see ESI†). The results indicated that the reactions with $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as the photocatalyst in CH_3CN performed the best in terms of yield and ee value. Moreover, decreasing the $Ru(bpy)_3Cl_2 \cdot 6H_2O$ loading to 2 mol% (Table 1, entry 9) or decreasing the $Cu(OAc)_2 \cdot H_2O$ loading to 5 mol% (Table 1, entry 10) resulted in a slightly increase in both efficiency and enantioselectivity. In addition, a similar outcome was obtained when the reaction was conducted under O_2 (Table 1, entry 12). Finally, control experiments revealed that both the photocatalyst and $Cu(OAc)_2 \cdot H_2O$ were essential to this reaction (Table 1, entries 13 and 14), and no reaction occurred in dark or under argon conditions (Table 1, entries 15 and 16).

Having identified the optimal reaction conditions, we next investigated the scope of glycine derivative component in this new visible-light induced enantioselective CDC protocol. As revealed in Scheme 2, various glycine esters, such as methyl ester, isopropyl ester, allyl ester, *t*-butyl ester and benzyl ester, reacted well with cyclohexanone (**2a**) under the optimized conditions, and the corresponding coupling products **3aa–3af** were provided in good yields (76–81%) with excellent diastereo- and enantioselectivities (97 : 3 to >99 : 1 dr, 96–97% ee). In addition to glycine esters, glycine amide and glycine derived dipeptide can also be utilized in this transformation, providing

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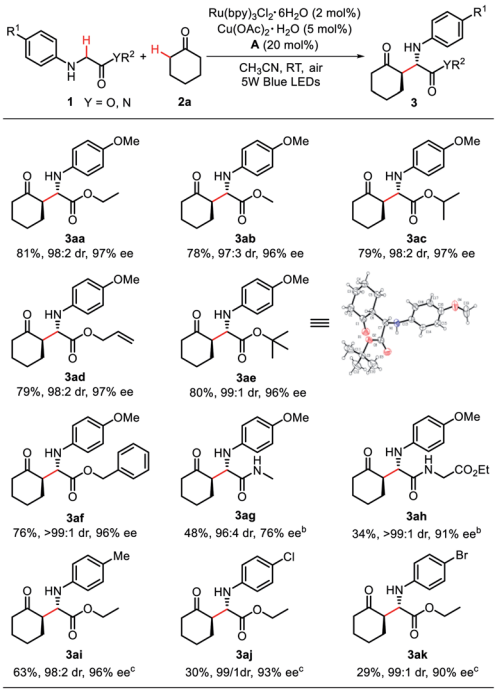
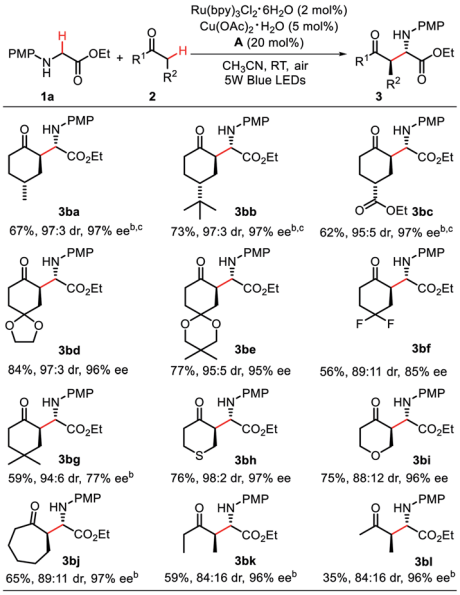


Scheme 2 Scope of the glycine derivatives component. [a] Reaction conditions: **1** (0.2 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2 mol%), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), CH_3CN (3 mL), 5 W blue LEDs light irradiation under air at room temperature for 2 h, then, **A** (20 mol%) and **2a** (1 mmol) were added. Yield is that of the product isolated by flash column chromatography on silica gel. The ee and dr was determined by HPLC. [b] 30 mol% **A** was used. [c] $Cu(OTf)_2$ (5 mol%) was used instead of $Cu(OAc)_2 \cdot H_2O$.



Scheme 3 Scope of the ketone component. [a] Reaction conditions: **1a** (0.2 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2 mol%), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), CH_3CN (3 mL), 5 W blue LEDs light irradiation under air at room temperature for 2 h, then, **A** (20 mol%) and **2** (1 mmol) were added. Yield is that of the product isolated by flash column chromatography on silica gel. The ee and dr were determined by HPLC. [b] 30 mol% **A** was used. [c] dr: ratio of the shown stereoisomer with all the other isomers, for details, see ESI.†

the corresponding products **3ag–3ah** in moderate yields (34–48%) with good diastereo- and enantioselectivities (96 : 4 to >99 : 1 dr, 76–91% ee). Glycine esters with variations on the phenyl moiety were also suitable for this transformation and gave the products **3ai–3ak** in moderate yield (29–63%) and excellent diastereo- and enantioselectivity (98 : 2 to 99 : 1 dr, 90–96% ee). The absolute configuration was determined by single-crystal X-ray diffraction of **3ae**.[17]

Next, the substrate scope of the ketone component was explored (Scheme 3). We first explored the desymmetrization process of 4-substituted cyclohexanones. It is difficult to simultaneously control the diastereo- and enantioselectivities of C2 and C4 position. Gratifyingly, all of the substrates gave the desired coupling products in good yields with excellent dr and ee values (**3ba–3bc**, 95 : 5 to 97 : 3 dr, 97% ee). Meanwhile, 4-ketalized cyclohexa-1,4-diones, 3,3-difluorocyclohexanone and 3,3-dimethylcyclohexanone were all excellent substrates for this transformation with good to excellent dr and ee values (**3bd–3bg**, 89 : 11 to 97 : 3 dr, 77–96% ee). Furthermore, in addition to cyclohexanones, other cyclic ketones, such as tetrahydrothiapyrone, tetrahydropyranone and cycloheptanone can also be utilized in this transformation, providing the corresponding products **3bh–3bj** in good yields with high dr and ee values (88 : 12 to 98 : 2 dr, 96–97% ee). Acyclic ketones had also been examined to give the desired adducts (**3bk–3bl**) with excellent enantioselectivities but lower yields. In particular, 2-butanone was found to undergo oxidative cross coupling regioselectively at the ethyl moiety, and no other isomer was observed. The poor yield was due to the unknown byproducts.

The scope of the aldehyde component in this protocol has also been investigated. As indicated in Scheme 4, an array of glycine esters reacted well with isovaleraldehyde under the optimized conditions (10 mol% **A** was used), leading to the desired products (**3ca–3cg**) in 65–82% yields with good to excellent dr and ee values (87 : 13 to 94 : 6 dr, 90–94% ee). A broad array of aliphatic aldehydes smoothly underwent this transformation, generating the desired coupling products **3ch–3cl** in moderate to good yield (58–81%) with excellent ee values (90–97% ee). Additional chemical functionalities groups (*e.g.*, chlorine, protected alcohols) were found to be inert to these mild conditions without a deleterious effect on either the efficiency or enantioselectivity, which give the potential synthetic utility for further modification.

To further demonstrate the synthetic value of this visible light-induced asymmetric CDC process, transformations of the products were conducted (Scheme 5). In the presence of $NaBH_4$ and AcOH, **3cd** was transformed to alcohol **5** in 81% yield and 96% ee. Subsequently, the PMP group of **5** was removed by the treatment with ammonium cerium(IV) nitrate (CAN), leading to chiral amino alcohol **6** in 73% yield. In addition, **3ca** could also be selectively transformed into chiral γ-butyrolactone derivative **7** in 71% yield and 94% ee (>99 : 1 dr) with $NaBH_4$ as the reducing reagent.

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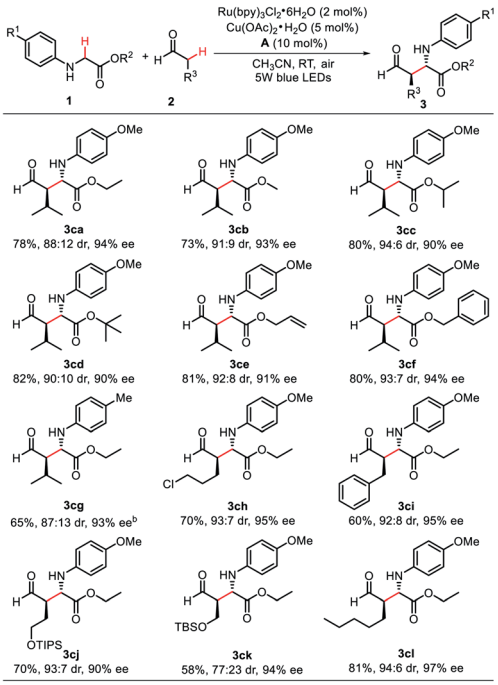
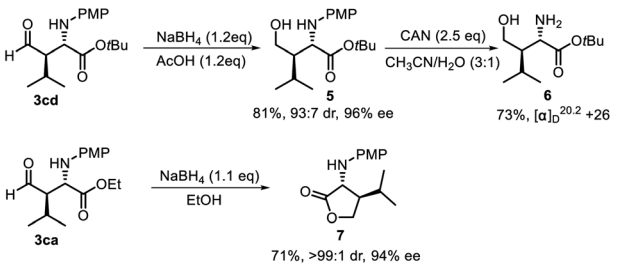
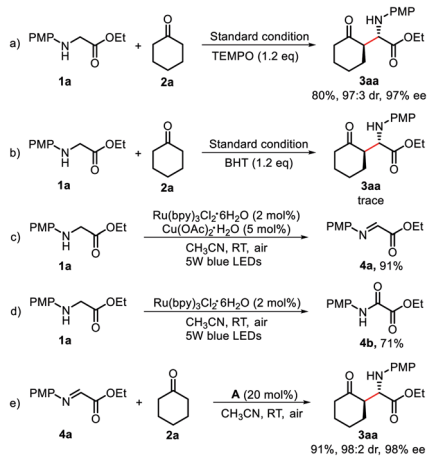


Scheme 4 Scope of the aldehyde component. [a] Reaction conditions: **1** (0.2 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2 mol%), $Cu(OAc)_2 \cdot H_2O$ (5 mol%), CH_3CN (3 mL), 5 W blue LEDs light irradiation under air at room temperature for 2 h, then, **A** (10 mol%) and **2** (0.6 mmol) were added. Yield is that of the product isolated by flash column chromatography on silica gel. The ee and dr were determined by HPLC. [b] $Cu(OTf)_2$ (5 mol%) was used instead of $Cu(OAc)_2 \cdot H_2O$.



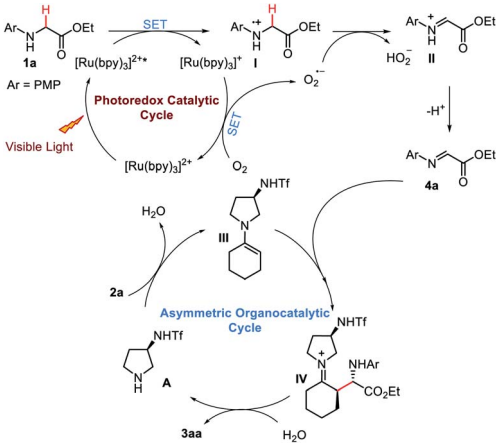
Scheme 5 Transformations of the products.

A series of control experiments were conducted to gain some insight into the mechanism of this reaction (Scheme 6). First, when the radical scavenger TEMPO (1.2 equiv.) was added to the standard reaction system, the reaction proceeded without interruption, both the yield and the stereoselectivity of the desired product **3aa** was almost the same as those in standard conditions, and the radical captured by TEMPO was not detected either, indicating that this transformation was not a radical process. However, only trace product **3aa** was observed when 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction. The observed BHT inhibition may be probably due to the preferential oxidization of the electron-rich phenol, hence suppressing the desired pathway. Next, upon irradiation of **1a** with visible-light in the presence of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ and $Cu(OAc)_2 \cdot H_2O$, the imine **4a** could be isolated in 91% yield.



Scheme 6 Control experiments.

While in the absence of $Cu(OAc)_2 \cdot H_2O$, the oxidative product **4b** was obtained in 71% yield, and only trace **4a** could be observed. Subsequently, the obtained imine **4a** could readily react with cyclohexanone under the catalysis of chiral amine **A**, affording **3aa** in 91% yield (98 : 2 dr, 98% ee). These results revealed that **4a** is a significant intermediate of this reaction. Moreover, Wu *et al.* recently reported that $Cu(OTf)_2$–glycine complex could be acted as the photoredox species.[18] We therefore carried out additional studies to explore the role of Cu(II) in this transformation. As shown in Fig. S1,† both substrate **1a** and Cu(II) salt showed no absorption in the range of visible light, and no bathochromic shift was observed in the UV-vis spectrum of the mixture of **1a** and Cu(II) salt (The Cu(II) salt used here refers to $Cu(OAc)_2 \cdot H_2O$, for details, see ESI†). In addition, no reaction was observed in the absence of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (Table 1, entry 13). These results indicated that Cu(II)–glycine complex was not the photoredox species of this reaction. The role of Cu(II) in this transformation should be to suppress the formation of oxidative product **4b** and stabilize the imine intermediate **4a** as well.[14c,19]



Scheme 7 Proposed mechanism.

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On the basis of these observations and the precedent literatures, a possible mechanism for this enantioselective photocatalytic CDC reaction was proposed (Scheme 7). Initially, the irradiation of $[Ru(bpy)_3]^{2+}$ with visible-light would render the $*[Ru(bpy)_3]^{2+}$ excited state, which should readily accept a single electron from **1a** to produce $[Ru(bpy)_3]^{+}$ and the radical cation **I**. Rapid oxidation of $[Ru(bpy)_3]^{+}$ by O_2 would then close the photoredox catalytic cycle while regenerating $[Ru(bpy)_3]^{2+}$. Meanwhile, the active species $O_2^{-\bullet}$ formed during this process may abstract a hydrogen atom from radical cation **I** to produce the iminium ion **II**, which then eliminates a proton and forms imine **4a**. Within the same time frame, condensation of **2a** with chiral amine **A** should form a nucleophilic enamine intermediate **III**, which would then intercept the electrophile **4a** to enantioselectively forge the new C–C bond.[20] Finally, subsequent hydrolysis of iminium intermediate **IV** would regenerate the organocatalyst **A** while providing the enantioenriched coupling product **3aa**.

Conclusions

In conclusion, we have developed the first visible-light-induced asymmetric cross-dehydrogenative coupling between glycine derivatives and simple ketones or aldehydes through a novel cooperative photoredox catalysis and asymmetric organocatalysis. This operationally simple and mild protocol provides a powerful means for the synthesis of diverse chiral unnatural α-alkyl α-amino acid derivatives with good yield and excellent diastereo- (up to >99 : 1) and enantioselectivities (up to 97% ee). Significantly, the strategy was also successfully applied in the enantioselective alkylated modification of dipeptide. The process is noteworthy in that it represents an unprecedented report on visible-light photoredox catalytic C(sp3)–H asymmetric functionalization of glycine derivatives. Moreover, this protocol employs molecular oxygen as the sustainable oxidant, thereby avoids the undesired byproducts associated with typical oxidation processes. The further extension of substrate scope and application of this novel CDC process to the synthesis of complex molecules are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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