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Transition metal-free, visible-light-mediated construction of α,β-diamino esters *via* decarboxylative radical addition at room temperature†

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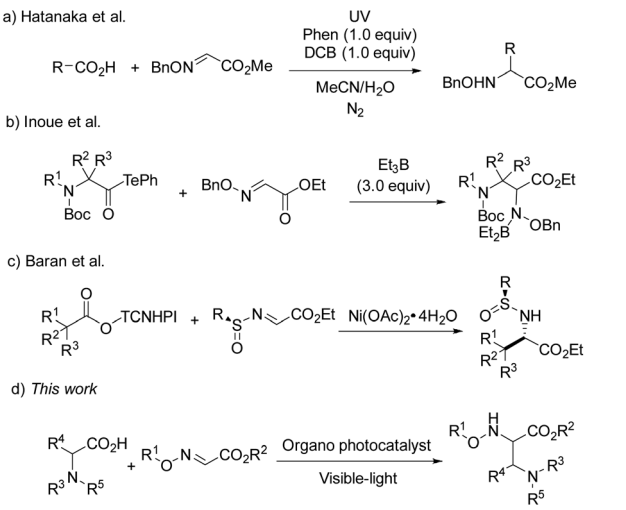
Transition-metal-free visible-light photoredox catalyzed decarboxylative radical addition has been developed for the construction of α,β-diamino esters from amino acids with glyoxylic oxime ethers under mild conditions. Cyclic and chain amino acids, dipeptides, and simple aliphatic acids are amenable to this addition as the alkyl radical source. A variety of α,β-diamino esters with broad functional groups were synthesized in satisfactory yields at room temperature. The employment of acridinium as the photocatalyst and its potential scalability also demonstrate the synthetic value in practice.

α,β-Diamino acids are essential building blocks and abundant in many bioactive compounds,[1] such as peptides, antibiotics, natural products and pharmaceuticals. Accordingly, various methods have been developed to synthesize the compounds.[2] As a powerful and efficient protocol, C–C coupling reactions are widely applied for the construction of α,β-diamino acids from simple nitrogen-containing blocks, and the typical representative is the Mannich reaction.[3] Due to its high reactivity and great tolerance of functional groups, the radical mediated Mannich reaction is drawing increasing attention. Meanwhile, stoichiometric metals and dangerous agents such as triethyl boron, rare metal indium and antimony are required for the generation of radicals.[4] Thus, a mild and environmentally friendly strategy for the generation of alkyl radicals is in urgent need for the synthesis of α,β-diamino acid derivatives.

As widely accessible and inexpensive substrates, carboxylic acids have been extensively studied as an alkyl radical source in the radical coupling reactions. Hatanaka and co-workers disclosed an efficient radical addition reaction between carboxylic acids and oxime ethers, using stoichiometric phenanthrene and 1,4-dicyanobenzene as a photosensitizer and an electron-acceptor.[5] In 2015, Inoue and co-workers developed a novel and valuable decarbonylative radical coupling for the synthesis of δ-amino and α,β-diamino acids (Scheme 1).[6] In this work, 3.0 equiv. of Et_3B were required to activate the decarboxylation of aminoacyl tellurides and form alkyl radicals. Very recently, Baran *et al.* have reported a Ni-catalyzed radical reaction between glyoxylate-derived sulfinimines and *N*-hydroxytetrachlorophthalimide-esters *in situ* generated from alkyl carboxylic acids, which paved a way for the preparation of enantiopure α-amino acids.[7]

Transition metal photoredox catalysis is a powerful tool for the decarboxylation and many excellent studies were pioneered in the radical coupling reaction.[8] The pre-functionalization of



Scheme 1 Decarboxylative radical Mannich reaction.

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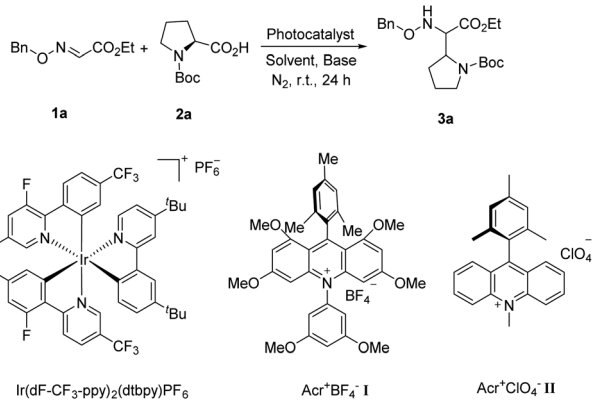
carboxylic acids was not involved in these transformations. Meanwhile, as the widely used organic photocatalyst, 9-mesityl-10-methylacridinium perchlorate ($Acr^+ClO_4^-$ **II**) is also applied in the radical reaction gradually.[9,10] However, the negative ground state reduction potential ($E_{1/2}(C/C^-)$ = −0.57 V *vs.* SCE) is weak. Furthermore, its strongly positive excited state oxidation potential ($E^*_{1/2}$ = +2.06 V *vs.* SCE) can lead to substrate decomposition through unselective oxidation processes. In addition, DiRocco *et al.* designed several novel acridinium-based photocatalysts, which have been demonstrated to have excellent photoredox capability.[11] These achievements have expanded the scope of photocatalysts with highly potential, applicable value in the organic synthesis field. Herein, we envisioned that α,β-diamino esters could be built *via* the decarbonylative radical Mannich reaction between amino acids and glyoxylic oxime ethers using an acridinium-based photocatalyst as the photosensitizer.

Results and discussion

Due to the excellent reactivity toward nucleophilic carbon radicals,[12] glyoxylic oxime ether (**1a**) was chosen as a radical acceptor to screen the optimal conditions with *N*-Boc-L-proline (**2a**). A set of solvents were evaluated in the presence of 2.0 mol% of $Acr^+BF_4^-$ **I**, and 1.5 equiv. of $K_2HPO_4{\cdot}3H_2O$, irradiated with blue LEDs at room temperature for 24 h (Table 1, entries 1–4). The results illustrated that non-polar solvent CH_2Cl_2 was the best, and toluene provided competitive yield as well (Table 1, entries 2 and 4, 73% and 72% yield, respectively). Impressively, we found that $Acr^+BF_4^-$ **I** presented appreciable catalytic efficacy in comparison with any other photocatalysts, such as Ir and Ru photocatalysts and other organic dyes, which proved to be the optimal photocatalyst (Table 1, entries 4–8). It is mainly due to the high oxidation potential value of the positive excited state of $Acr^+BF_4^-$ **I** ($E^*_{1/2}$ = +1.65 V *vs.* SCE).[11] Notably, the yield of this reaction irradiated with blue LEDs was much higher than that obtained with fluorescence light (Table 1, entries 4, 11). However, no desired product was detected in the absence of a light resource or photocatalyst, suggesting the important roles played by the light resource and photocatalyst in this conversion (Table 1, entries 9, 10 and 12). Furthermore, excellent yield was obtained when 2.5 equiv. of Cs_2CO_3 were utilized as the base instead of $K_2HPO_4{\cdot}3H_2O$ (Table 1, entries 2 and 15). Only a trace of **3a** was obtained

Table 1 Optimization of reaction conditions[a]



Entry	Light sources	Base	Solvent	Photocatalyst	Yield[b] (%)
1	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_3CN	$Acr^+BF_4^-$ **I**	64
2	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	Toluene	$Acr^+BF_4^-$ **I**	72
3	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	Acetone	$Acr^+BF_4^-$ **I**	64
4	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	$Acr^+BF_4^-$ **I**	73
5[c]	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	Ir(dF-CF_3-ppy)$_2$(dtbpy)PF_6	64
6	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	$Acr^+ClO_4^-$ **II**	40
7[d]	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	Trace
8	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	Eosin-Yellow	Trace
9[e]	Blue LEDs	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	—	0
10[e]	Fluorescence	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	—	0
11	Fluorescence	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	$Acr^+BF_4^-$ **I**	24
12[f]	—	$K_2HPO_4{\cdot}3H_2O$	CH_2Cl_2	$Acr^+BF_4^-$ **I**	0
13[g]	Blue LEDs	—	Toluene	$Acr^+BF_4^-$ **I**	5
14	Blue LEDs	Cs_2CO_3	Toluene	$Acr^+BF_4^-$ **I**	84
15[h]	Blue LEDs	Cs_2CO_3	Toluene	$Acr^+BF_4^-$ **I**	93

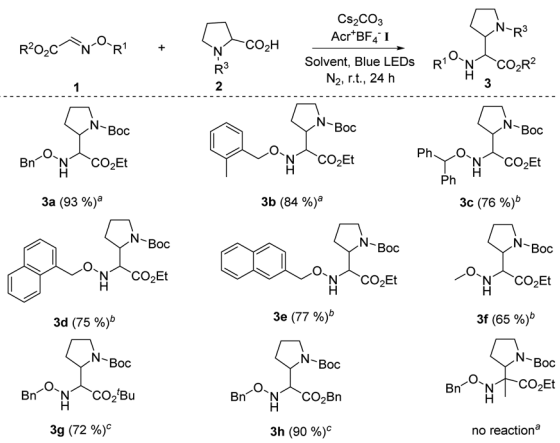
[a] Unless otherwise noted, all reactions were performed on a 0.2 mmol scale using 1 equiv. of **1a**, 1 equiv. of **2a**, 1.5 equiv. of base, 2 mol% photocatalyst, solvent (0.1 M). [b] Isolated yield. [c] Reaction performed with 3 mol% Ir(dF-CF_3-ppy)$_2$(dtbpy)PF_6. [d] Reaction performed with 3 mol% $Ru(bpy)_3Cl_2{\cdot}6H_2O$. [e] Reaction performed in the absence of the photocatalyst. [f] Reaction performed in the absence of visible light. [g] Reaction performed in the absence of the base. [h] Reaction performed with 2.5 equiv. of Cs_2CO_3.

without additive bases (Table 1, entries 13). We reasoned that the basicity of the reaction system is essential for the decarboxylation and the following formation of C–C bonds.

On the basis of the optimal reaction conditions, the scope of glyoxylic oxime ethers **1** was evaluated. As shown in Table 2, a variety of glyoxylic oxime ethers bearing different substitution patterns were well tolerated in the catalytic system (Table 2, **3a–h**, 65–93%). When the phenyl group was replaced by other aromatic moieties, the process underwent efficiently and formed the corresponding α,β-diamino esters in good to excellent yields (Table 2, **3a–3e**, 75–93%). Notably, *O*-methyl oxime ether **1f** is also the suitable radical acceptor and provided **3f** in slightly decreased yield. When the carboxyl group of glyoxylic oxime ether is protected by other groups, such as the *tert*-butyl group and benzyl group, **3g** and **3h** were synthesized in 72% and 90% yields, respectively. Unfortunately, when the ketone oxime ether substrate was involved in the reaction, no desired product was detected possibly due to the steric effect of ketone oxime ether.

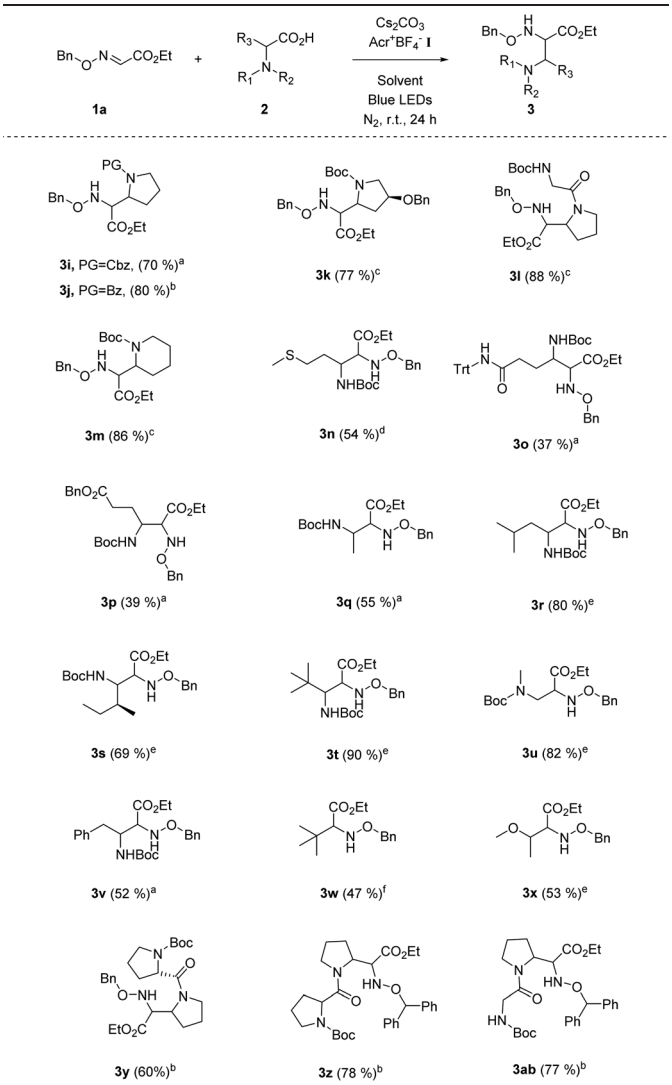
Our following task was to explore the substrate scope with respect to carboxyl acids. A number of *N*-protected five-membered cyclic amino acids (*e.g.* *N*-Cbz-proline, *N*-Bz-proline) readily participated in this radical coupling with glyoxylic oxime ether **1a**, and provided the corresponding products in good yields (Table 3, **3i–l**). The *N*-Boc protected six-membered cyclic amino acid is also the suitable alkyl radical source for this decarbonylative radical Mannich reaction (Table 3, **3m**). Moreover, a series of chain amino acids with a variety of functional groups, such as the methylthio group, ester group and *N*-Trt protected amide group, could be tolerated in this radical coupling reaction (Table 3, **3n–p**). Except for the *N*-Boc-alanine, other *N*-Boc protected natural chain amino acids (*e.g.*, Boc-protected leucine, isoleucine, sarcosine, phenylalanine) could be smoothly transformed into the target products in moderate to good yields (Table 3, **3q–v**). Intriguingly, the radical Mannich reaction was also amenable to various aliphatic acids, such as pivalic acid and 2-methoxypropionic acid (Table 3, **3w–x**). We were delighted to find that dipeptides were

Table 2 Substrate scope of glyoxylic oxime ether[a]



[a] Unless otherwise noted, all reactions were carried out using 1.0 equiv. of **1** (0.2 mmol), 1.0 equiv. of **2** (0.2 mmol), 2.0 mol% $Acr^+BF_4^-$ **I**, toluene (0.1 M), 2.5 equiv. of Cs_2CO_3, under N_2, at room temperature and irradiation with blue LEDs for 24 h. [b] Using DCE (0.1 M) as the solvent while other conditions remained the same. [c] The ratio of **1 : 2** (0.2 mmol) is 1.5 : 1.0, and using DCE (0.1 M) as the solvent, while other conditions remained the same.

Table 3 Substrate scope of alkyl carboxylic acids[a]

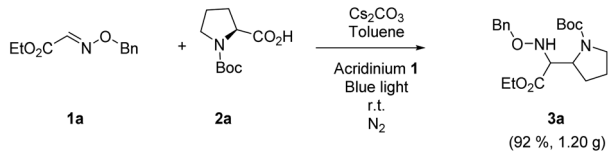


[a] Unless otherwise noted, all reactions were carried out using 1.0 equiv. of **1a** (0.2 mmol), 1.0 equiv. of **2** (0.2 mmol), 2.0 mol% $Acr^+BF_4^-$ **I**, toluene (0.1 M), 2.5 equiv. of Cs_2CO_3, under N_2, at room temperature and irradiation with blue LEDs for 24 h. [b] Using DCE (0.1 M) as the solvent while other conditions remained the same. [c] The ratio of **2 : 1a** (0.2 mmol) is 1.5 : 1.0, and using DCE (0.1 M) as the solvent, while other conditions remained the same. [d] The ratio of **2 : 1a** (0.2 mmol) is 3.0 : 1.0, and using DCE (0.1 M) as the solvent, while other conditions remained the same. [e] The ratio of **2 : 1a** (0.2 mmol) is 2.0 : 1.0, and using DCE (0.1 M) as the solvent, while other conditions remained the same. [f] Using DCE (0.1 M) as the solvent, pivalic acid as the alkyl carboxylic acid, while other conditions remained the same.

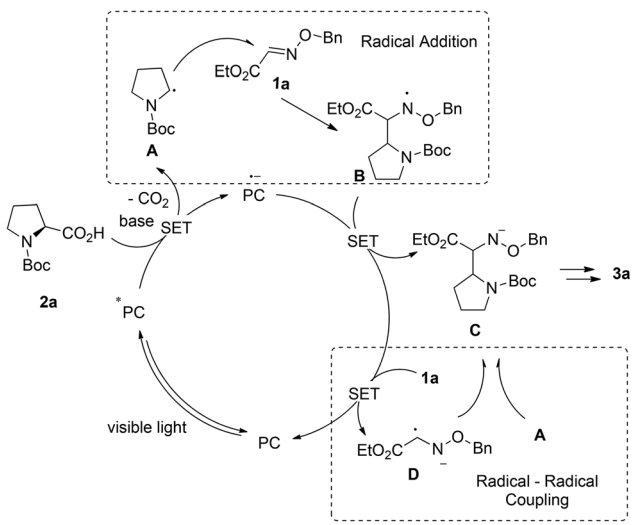
successful substrates to obtain multi-amino esters in good yields (Table 3, **3y–ab**). It provides a valuable and useful routine for the building of more complex α,β-diamino ester derivatives.

Finally, the reaction was carried out at the gram-scale. Under the standard conditions, the radical coupling between 3.37 mmol **1a** and **2a** was performed and 1.20 g **3a** was obtained in excellent yield (Scheme 2, 92%). The scalability of this protocol demonstrates great value in the practical synthesis of α,β-diamino esters.

Based on the previous reports, two plausible reaction mechanisms are shown in Scheme 3: the radical addition pathway[5,13] and the radical–radical coupling pathway.[14] Irradiation of $Acr^{+}BF_4^{-}$ **I** with visible light generates photoexcited state Acr*. Alkyl acid **2a** can be deprotonated and then oxidized by Acr* ($E_{1/2}(C/C^{-}) = -0.82$ V *vs.* SCE in MeCN) which will be transformed into Acr^{*-}, affording alkyl radical **A** following the decarboxylation process. On the one hand, the radical addition of **A** to Glyoxylic oxime ether **1a** provides nitrogen radical **B**, which could be stabilized by the neighboring oxygen atom. Subsequently, the single electron transfers between B and $Acr^{*\bullet-}$, generating glyoxylic oxime ether anion **C** and Acr. On the other hand, glyoxylic oxime ether **1a** is reduced by $Acr^{*\bullet-}$ to produce glyoxylic oxime ether radical anion **D**. Then it undergoes radical–radical coupling with **B** to afford nitrogen anion **C**. The final product **3a** is obtained *via* the following protonation of **C**.



Scheme 2 Gram-scale reaction of the radical Mannich reaction.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have developed a novel protocol to construct α,β-diamino esters *via* the radical Mannich reaction using alkyl carboxylic acids as radical precursors under mild photoredox conditions. This method is subjected to a wide range of substrates with broad functional group tolerance. Moreover, the gram scale reaction also maintains an excellent yield.

Conflicts of interest

The authors declare no competing financial interest.

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