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Photoredox-catalyzed dicarbofunctionalization of styrenes with amines and CO₂: a convenient access to γ -amino acids†

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A visible-light-promoted carbocarboxylation of styrenes using CO₂ and amines is reported. The reaction is catalyzed by a photoredox catalyst and is compatible with a variety of amines and styrenes. This method affords highly functionalized γ -amino acids in good yields with high regioselectivity.

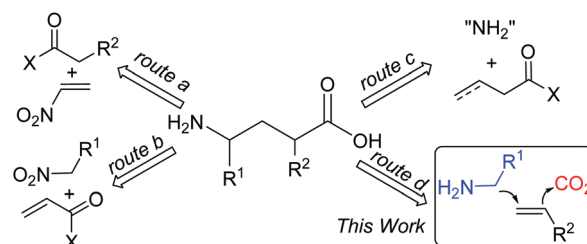
γ -Amino acids are highly valuable compounds that exist widely in pharmaceuticals and exhibit a diverse range of biological activities as agonists and antagonists of receptors for mammalian neurotransmitters in the central nervous system.¹ Thus, considerable efforts have been devoted to the synthesis of γ -amino acids,² such as Michael addition of carbonyl compounds to nitroethylenes (Scheme 1, route a)³ or conjugate addition of nitroalkanes to α,β -unsaturated carbonyl compounds (Scheme 1, route b)⁴ to afford γ -amino acids. Recently, Ye and coworkers reported γ -amination of α,β -unsaturated acyl chlorides with azodicarboxylates followed by reductive ring opening of dihydropyridazinones to afford γ -amino acids (Scheme 1, route c).⁵ Despite all these efforts, these synthetic methods suffer from limited substrate scope, multiple steps, and/or harsh reaction conditions. We envisioned that the simultaneous incorporation of both α -aminoalkyl and carbon dioxide (CO₂) to alkenes *via* dicarbofunctionalization of alkenes would serve as an ideal route to deliver γ -amino acids (Scheme 1, route d).

The evolving visible-light-mediated photoredox catalysis offers an operating strategy to access open shell radical species,⁶ leading to novel methods for difunctionalization of alkenes.⁷ Recently, photoredox-promoted single electron oxidation of amines and subsequent deprotonation to generate α -aminoalkyl radicals **B** have been described (Scheme 2).⁸ The

addition of the α -aminoalkyl radical **B** to alkenes resulted in the formation of the alkyl radical species **C**, which undergoes a single electron reduction to capture an electrophile.⁹ We anticipated that the incorporation of CO₂ as an electrophile in the reaction mixture might enable the formation of γ -amino acids.

CO₂ as a nontoxic, ubiquitous, and recyclable one-carbon source has attracted attention in organic synthesis.¹⁰ The catalytic carboxylation of unsaturated compounds with CO₂ has attracted much attention from chemists.¹¹ Compared with the widely considered hydrocarboxylation of alkene with CO₂,¹² photocatalytic functional carboxylation of alkenes with CO₂ is more challenging and rarely reported. Recently, the Martin, Yu, Wu, and Li groups demonstrated respectively the photoredox-catalyzed difunctionalization of alkenes under visible light to afford β -functionalized alkylcarboxylic acids with CO₂.¹³ Taking into account the potential of these transformations and our ongoing interest in the carboxylation of alkenes with CO₂ for the efficient dicarbofunctionalization reaction, herein, we report the photoredox-catalyzed α -aminomethylcarboxylation of alkenes with amines and CO₂. This strategy is sustainable, general, and practical, representing a rare example of redox-neutral dicarbofunctionalization of alkenes to generate important γ -amino acids with high efficiency and selectivity under mild reaction conditions.

We started the investigation by employing *N,N*-dimethylaniline **1a** and methyl 4-vinylbenzoate **2a** as model substrates

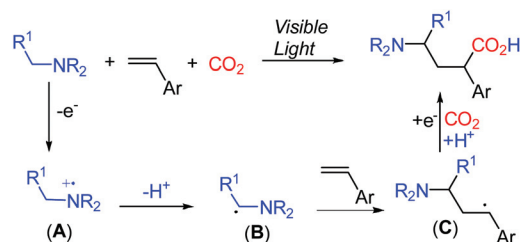


Scheme 1 Typical approaches to γ -amino acid derivatives.

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Scheme 2 Photocatalytic preparation of γ -amino acids from CO_2 .

under the irradiation of 5 W blue light emitting diodes (LEDs) with atmospheric pressure CO_2 . Yields were determined after methyl esterification with TMSCHN_2 (Table 1). After numerous extensions of the reaction parameters, the desired product **3'aa** was obtained in 95% yield when 4 mol% of 1,2,3,5-tetrakis-

Table 1 Optimization of the reaction conditions^a

| Entry | Deviation from standard conditions | Yield of 3'aa ^b [%] | Yield of 4aa ^b [%] |
|-----------------|-------------------------------------|---------------------------------------|--------------------------------------|
| 1 | None | 95 (89) | 4 |
| 2 | Ir-1 instead of 4CzIPN | 84 | 4 |
| 3 | Ir-2 instead of 4CzIPN | 76 | 4 |
| 4 | Ir-3 instead of 4CzIPN | 12 | 1 |
| 5 | Ru-1 instead of 4CzIPN | 83 | 2 |
| 6 | Without 4CzIPN | — | — |
| 7 | LiF instead of LiCl | 44 | 3 |
| 8 | LiBF_4 instead of LiCl | 39 | 5 |
| 9 | LiOAc instead of LiCl | 43 | 7 |
| 10 | NaCl instead of LiCl | 20 | 2 |
| 11 | KCl instead of LiCl | 26 | 3 |
| 12 | Without LiCl | 62 | 3 |
| 13 | 2 eq. instead of 4 eq. of LiCl | 82 | 5 |
| 14 | Add 20 mol% Q-1 | 46 | 24 |
| 15 | Add 20 mol% Q-2 | 48 | 15 |
| 16 | DMF instead of DMSO | 80 | 15 |
| 17 | MeCN instead of DMSO | 8 | 44 |
| 18 | THF instead of DMSO | 8 | 28 |
| 19 ^c | 0.025 M instead of 0.1 M | 56 | 19 |
| 20 | 2 eq. instead of 6 eq. of 1a | 79 | 9 |
| 21 | 4 eq. instead of 6 eq. of 1a | 73 | 11 |
| 22 | 7 eq. instead of 6 eq. of 1a | 94 | 3 |

Ir-1 $\text{R}^1=\text{R}^2=\text{H}$
Ir-2 $\text{R}^1=\text{CF}_3$, $\text{R}^2=\text{F}$

Q-1 $\text{R}=\text{H}$
Q-2 $\text{R}=\text{OAc}$

^a Reaction conditions: **1a** (0.6 mmol), **2a** (0.1 mmol), 4CzIPN (0.004 mmol), LiCl (0.4 mmol), DMSO (1 mL), 1 atm CO_2 , 5 W blue LED, room temperature, 48 h, quenched with HCl (2 M) solution, after extraction with ethyl acetate, $\text{MeOH}:\text{ether} = 1:1$ (0.5 mL) and TMSCHN_2 (3 equiv.) were added. ^b Yields determined by GC using *n*-dodecane as an internal standard; isolated yield in parentheses. ^c 4 mL of DMSO was used instead of 1 mL.

(carbazole-9-yl)-4,6-dicyanobenzene (4CzIPN) was used as a photoredox catalyst and LiCl as an additive in DMSO (0.1 M) at room temperature after 48 h irradiation (entry 1). The hydro-aminoalkylation product **4aa** was also detected by GC as a by-product. $\text{Ir}(\text{ppy})_2(\text{dtbbpy})(\text{PF}_6)$, $\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})(\text{PF}_6)$, and $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ were employed as photoredox catalysts which performed less effectively than 4CzIPN (entries 2, 3 and 5). A trace amount of **3'aa** was obtained using $\text{Ir}(\text{ppy})_3$ instead of 4CzIPN (entry 4). The reaction could not proceed without the photoredox catalyst (entry 6). The choice of the additive was pivotal; LiF, LiBF_4 , LiOAc , NaCl, and KCl were used as additives to afford lower yields of **3'aa** (entries 7–11). Notably, the reaction proceeded to give the desired product **3'aa** in 62% yield in the absence of LiCl (entry 12). When two equivalents of LiCl were employed, the desired product **3'aa** was obtained in 82% yield (entry 13). Hydrogen atom transfer (HAT) is frequently involved in photocatalysis, which offers enormous opportunities for C–H activation.¹⁴ The combination of the photoredox catalyst 4CzIPN (4 mol%) with HAT catalysts such as quinuclidin-3-yl acetate and quinuclidine (20 mol%) provided the desired product **3'aa** in 46% and 48% yields, respectively (entries 14 and 15). Among the solvents examined, DMSO resulted in the best reactivity and selectivity (entries 1 and 16–18). Both reactivity and selectivity significantly decreased with the dilution of **1a** as expected (entry 19). The utilization of 6 equivalents of amine was proved to be necessary to obtain the desired product in a good yield (entries 1, 20–22).

With the optimized conditions, a study on the substrate scope was carried out. Firstly, a variety of tertiary amines **1** were used in the reaction with methyl 4-vinylbenzoate **2a** to synthesize γ -amino acids with a range of substituents on anilines. The representative results are shown in Scheme 3. The



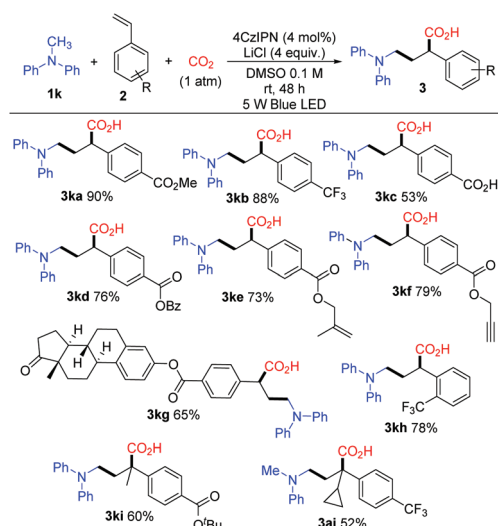
Scheme 3 Photocatalytic reactions of methyl 4-vinylbenzoate **2a** with amines. Reaction conditions: **1** (1.2 mmol), **2a** (0.2 mmol), 4CzIPN (0.008 mmol), LiCl (0.8 mmol), DMSO (2 mL), 1 atm CO_2 , 5 W blue LED, room temperature, 48 h, quenched with HCl (2 M) solution. Yields of isolated carboxylic acid **3** without esterification with TMSCHN_2 .

reaction of **2a** with dimethyldiphenylamine (**1a**) proceeded smoothly to give γ -amino acid **3aa** in 88% isolated yield without esterification with TMSCHN₂. Introduction of a substituent such as methyl, bromo, chloro, or fluoro at the *para*-position of the benzene ring did not affect much the yield of γ -amino acids **3** (**3ba** in 73%, **3ca** in 81%, **3da** in 64%, **3ea** in 75%). The amines bearing highly electron-withdrawing groups such as an ester, keto carbonyl, or cyano group at the *para*-position in the benzene ring yielded the expected products **3** in high yields (**3fa** in 88%, **3ga** in 86%, **3ha** in 80%). The substituents such as methyl or bromo located at the *ortho*-position in the benzene ring also afforded the target products **3** in good yields (**3ia** in 70%, **3ja** in 78%). To our delight, methyl-diphenylamine **1k** was well applicable and delivered the corresponding γ -amino acid **3ka** in 90% yield. γ -Amino acids with a carbazolyl group have potential in materials science; in this reaction, 9-methyl-9H-carbazole **1l** was also applicable and delivered the corresponding γ -amino acid **3la** in 87% yield. The cyclic amine 1-phenylpyrrolidine **1m** was transformed into **3ma** in 60% yield. It is noteworthy that the utilization of primary and secondary amines such as octan-1-amine and *N*-methylaniline as well as other aromatic amines such as 4-methoxy-*N,N*-dimethylaniline and *N*-dimethylnaphthalen-1-amine did not lead to the corresponding products.

Next, we examined the photocatalytic reactions with a variety of alkenes **2**; the typical results are shown in Scheme 4. A series of substituted styrenes with electron-withdrawing substituents at the *para*-position such as trifluoromethyl (**2b**), carboxyl (**2c**) and esters (**2a**, **2d**, **2e**, **2f**, **2g**, and **2i**) could be accommodated and afforded the corresponding products **3** in good yields. Remarkably, γ -amino acid **3kc** was prepared smoothly when 4-vinylbenzoic acid (**2c**) was employed. When

benzyl-, alkenyl-, and alkynyl-derived ester styrenes such as **2d**, **2e**, and **2f** were employed, the corresponding products **3kd**, **3ke**, and **3kf** were formed in good yields, respectively. Moreover, estrone-derived ester styrene **2g** was also tested, and the corresponding α -aminomethylcarboxylation product **3kg** was obtained in 65% yield. It is noteworthy that estrone linked with γ -amino-acid moiety could be well soluble in organic solutions while estrone cannot. Notably, the styrene with a substituent at the *ortho*-position of the benzene ring also gave the corresponding product **3kh** in 78% yield. Vinylpyridine was employed as the styrene in this reaction and a trace amount of the desired product was detected. Furthermore, α -substituted styrenes could be used resulting in the target compounds **3ki** and **3aj** with quaternary carbon centers. Unfortunately, β -substituted styrenes such as methyl (*E*)-4-(prop-1-en-1-yl)benzoate could not undergo the reaction. In addition, we did not detect the desired products when butyl acrylate and acrylonitrile were used in this reaction. In general, an electron-withdrawing group at the benzene ring of the styrene is essential to obtain the corresponding γ -amino acid in this reaction.

Additional experiments were performed to gain insight into the reaction mechanism. Light on-off experiments indicated that continuous light irradiation was essential to perform the reaction, and during the process, hydroaminoalkylation was restrained all the way. The quantum yield of the reaction of **1a** with **2a** under the optimized conditions was 0.0414 (see the ESI†). The isotope labelling experiments with D₂O implied that γ -amino benzylic anionic species could be the intermediates (Scheme 5a). It is noteworthy that the yield of **4aa** increased with increasing amount of D₂O, and LiCl also played

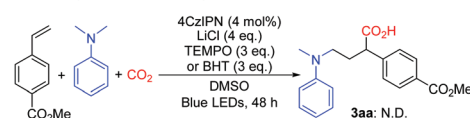


Scheme 4 Photocatalytic reactions of methyl-diphenylamine **1k** and **1a** with alkenes. Reaction conditions: **1k** or **1a** (1.2 mmol), **2** (0.2 mmol), 4CzIPN (0.008 mmol), LiCl (0.8 mmol), DMSO (2 mL), 1 atm CO₂, 5 W blue LED, RT, 48 h, quenched with HCl (2 M) solution. Yields of isolated products.

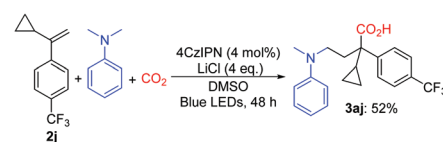
a. Isotope labelling experiments with D₂O



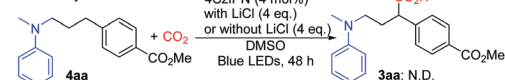
b. Trapping with radical scavengers



c. Radical clock test



d. Carboxylation of 4aa



Scheme 5 Control experiments for elucidation of the mechanism.



Scheme 6 The proposed reaction mechanism.

a vital role in this reaction. When the radical scavengers 2,2,6,6-tetramethyl-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were used in the reaction, the desired product **3aa** was not obtained (Scheme 5b) respectively; these results indicated that this transformation might rely on a radical process. Furthermore, the radical clock substrate **2j** was used under the optimal reaction conditions; however, no ring-opening product was detected (Scheme 5c), which suggested that the single electron reduction step from the benzyl radical to the benzyl anion is quite quick. Compound **4aa** was treated with standard conditions, and **3aa** was not observed and **4aa** was retained (Scheme 5d), which rules out the direct C–H carboxylation pathway.¹⁵

Based on the aforementioned results, a plausible mechanism was proposed and is shown in Scheme 6. Photo-excited 4CzIPN is reductively quenched with aniline leading to **I** and the radical cation intermediate **A**, which then deprotonates and gives α -aminoalkyl radical **B** in the presence of a base. The carbon radical **B** undergoes addition to the C=C bond of styrene **2** to selectively generate the γ -amino benzylic radical **C**. A subsequent single-electron transfer (SET) between **C** and the reduced photocatalyst 4CzIPN gives the γ -amino benzylic carbanion **D**, which is proposed as a lithium chelated species to stabilize the carbanion and accelerate the SET process. The nucleophilic addition to CO₂ or activated CO₂ by LiCl and protonation complete this reaction and yield the expected γ -amino acids.

Conclusions

In summary, we have developed a catalytic intermolecular dicarbofunctionalization of styrenes with CO₂ and amines through photoredox catalysis. The carbocarboxylation has the advantages of superior step and atom economy, broad substrate scope, and mild conditions. This study represents a rare example of the catalytic carbocarboxylation of alkenes with CO₂ in a redox-neutral fashion, which could lead to a new general alkene dicarbofunctionalization strategy using abundant and inexpensive chemical feedstock.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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