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Photoredox-catalyzed dicarbofunctionalization of styrenes with amines and CO_2: a convenient access to γ-amino acids†

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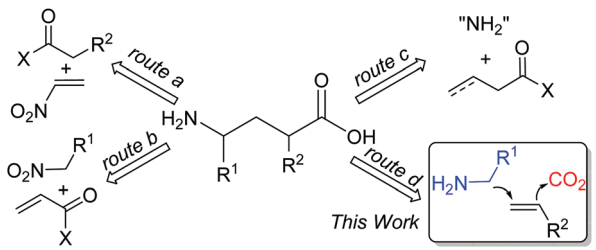
A visible-light-promoted carbocarboxylation of styrenes using CO_2 and amines is reported. The reaction is catalyzed by a photoredox catalyst and is compatible with a variety of amines and styrenes. This method affords highly functionalized γ-amino acids in good yields with high regioselectivity.

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 (CO_2) 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 CO_2 as an electrophile in the reaction mixture might enable the formation of γ-amino acids.

CO_2 as a nontoxic, ubiquitous, and recyclable one-carbon source has attracted attention in organic synthesis.[10] The catalytic carboxylation of unsaturated compounds with CO_2 has attracted much attention from chemists.[11] Compared with the widely considered hydrocarboxylation of alkene with CO_2,[12] photocatalytic functional carboxylation of alkenes with CO_2 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 CO_2.[13] Taking into account the potential of these transformations and our ongoing interest in the carboxylation of alkenes with CO_2 for the efficient dicarbofunctionalization reaction, herein, we report the photoredox-catalyzed α-aminomethylcarboxylation of alkenes with amines and CO_2. 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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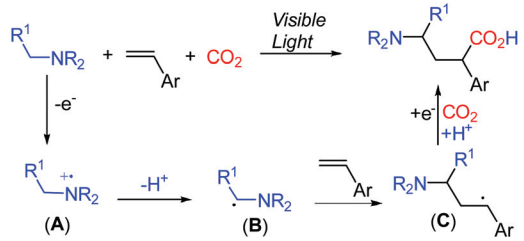


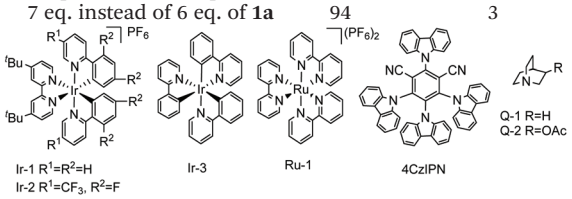
Scheme 2 Photocatalytic preparation of γ-amino acids from CO_2.

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-(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 hydroaminoalkylation product **4aa** was also detected by GC as a by-product. $Ir(ppy)_2(dtbbpy)(PF_6)$, $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$, and $Ru(bpy)_3(PF6)_2$ 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 $Ir(ppy)_3$ 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).

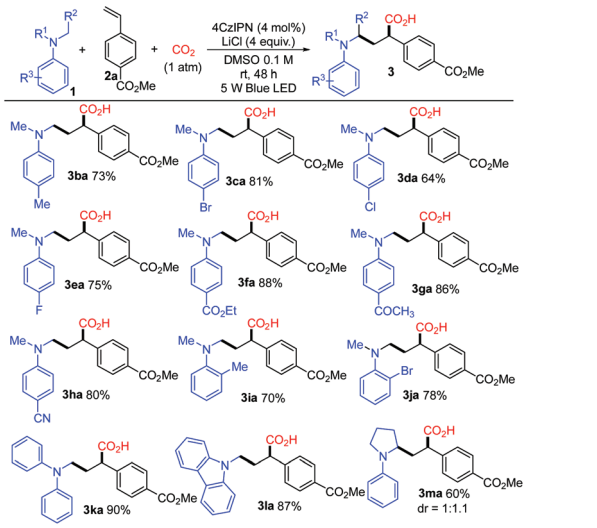
With the optimized conditions, a study on the substrate scope was carried out. Firstly, a variety of tertiary amines **1** were used in the reaction with methyl 4-vinylbenzoate **2a** to synthesize γ-amino acids with a range of substituents on anilines. The representative results are shown in Scheme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

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



[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, MeOH : 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.

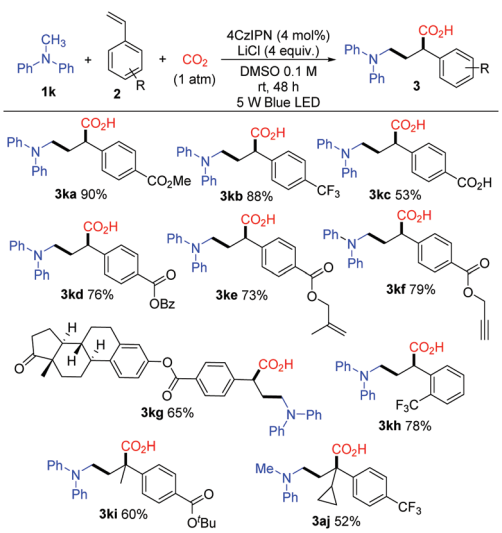


Scheme 3 Photocatalytic reactions of methyl 4-vinylbenzoate **2a** with amines. Reaction conditions: **1** (1.2 mmol), **2a** (0.2 mmol), 4CzIPN (0.008 mmol), LiCl (0.8 mmol), DMSO (2 mL), 1 atm CO_2, 5 W blue LED, room temperature, 48 h, quenched with HCl (2 M) solution. Yields of isolated carboxylic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

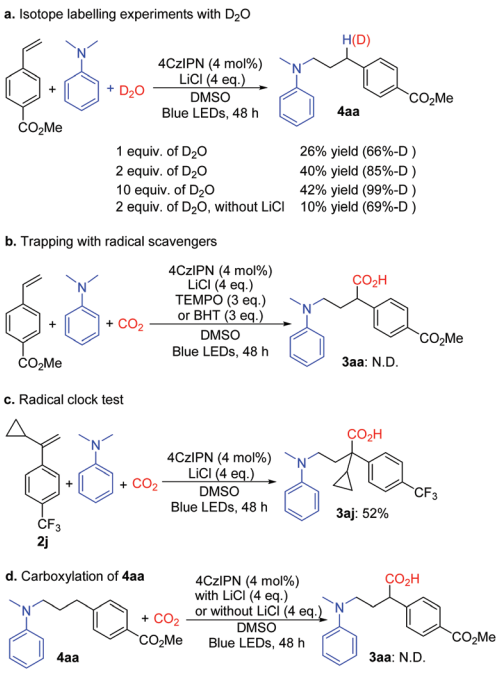
reaction of **2a** with dimethylphenylamine (**1a**) proceeded smoothly to give γ-amino acid **3aa** in 88% isolated yield without esterification with $TMSCHN_2$. Introduction of a substituent such as methyl, bromo, chloro, or fluoro at the *para*-position of the benzene ring did not affect much the 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, methyldiphenylamine **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-9*H*-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-derivatived 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.

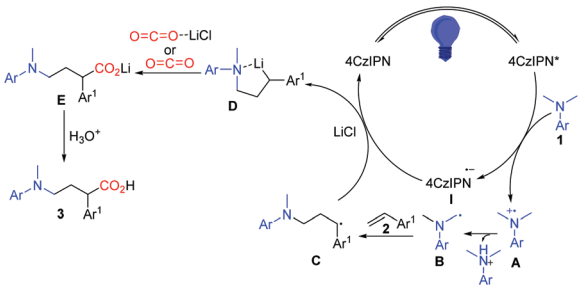
Additional experiments were performed to gain insight into the reaction mechanism. Light on–off experiments indicated that continuous light irradiation was essential to perform the reaction, and during the process, hydroaminoalkylation was restrained all the way. The quantum yield of the reaction of **1a** with **2a** under the optimized conditions was 0.0414 (see the ESI†). The isotope labelling experiments with D_2O 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 D_2O, and LiCl also played



Scheme 4 Photocatalytic reactions of methyldiphenylamine **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 CO_2, 5 W blue LED, RT, 48 h, quenched with HCl (2 M) solution. Yields of isolated products.



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-piperidinyloxyl (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 carboanion and accelerate the SET process. The nucleophilic addition to CO_2 or activated CO_2 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 CO_2 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 CO_2 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.

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