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Article

α-Amino Acids and Peptides as Bifunctional Reagents: Carbocarboxylation of Activated Alkenes via Recycling CO_2

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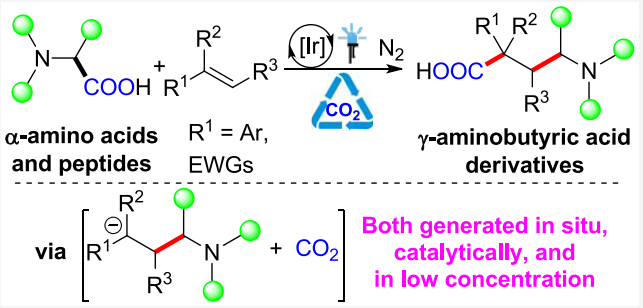
ABSTRACT: Carboxylic acids, including amino acids (AAs), have been widely used as reagents for decarboxylative couplings. In contrast to previous decarboxylative couplings that release CO_2 as a waste byproduct, herein we report a novel strategy with simultaneous utilization of both the alkyl and carboxyl components from carboxylic acids. Under this unique strategy, carboxylic acids act as bifunctional reagents in the redox-neutral carbocarboxylation of alkenes. Diverse, inexpensive, and readily available α-AAs take part in such difunctionalizations of activated alkenes via visible-light photoredox catalysis, affording a variety of valuable but otherwise difficult to access γ-aminobutyric acid derivatives (GABAs). Additionally, a series of dipeptides and tripeptides also participate in this photocatalytic carbocarboxylation. Although several challenges exist in this system due to the low concentration and quantitative amount of CO_2, as well as unproductive side reactions such as hydrodecarboxylation of the carboxylic acids and hydroalkylation of the alkenes, excellent regioselectivity and moderate to high chemoselectivity are achieved. This process features low catalyst loading, mild reaction conditions, high step and atom economy, and good functional group tolerance, and it is readily scalable. The resulting products are subject to efficient derivations, and the overall process is amenable to applications in the late-stage modification of complex compounds. Mechanistic studies indicate that a carbanion is generated catalytically and it acts as the key intermediate to react with CO_2, which is also generated catalytically *in situ* and thus remains in low concentration. The overall transformation represents an efficient and sustainable system for organic synthesis, pharmaceutics, and biochemistry.



INTRODUCTION

Carbon−carbon bond formation plays a central role in organic synthesis. Toward this end, direct cross couplings of electrophiles and nucleophiles, as well as multicomponent couplings with unsaturated bonds, are highly attractive means to generate high-value-added products.[1] In addition to many moisture-unstable and expensive organometallic reagents, carboxylic acids act as user-friendly cross-coupling partners due to their abundance and stability.[2] In addition to well-studied transition-metal-catalyzed decarboxylations of arene-carboxylic acids,[3] radical-type decarboxylations of alkyl carboxylic acids have attracted significant attention.[4−7] Notably, recent significant progress in photocatalysis has generated powerful tools to realize novel decarboxylation reactions[4,5] of alkyl-[6] and arenecarboxylic acids.[7] Generally in such processes, stoichiometric carbon dioxide (CO_2) is released as a waste byproduct and is not reutilized in the transformations (Figure 1), which leads to lower atom economy and potential safety issues at large scales. If the released CO_2, which is an inexpensive, nontoxic, and recyclable one-carbon building block,[8] could be reutilized to construct important carbonyl-containing compounds, it would represent a carbon-economical and sustainable process. Herein, we report a novel strategy for the carbocarboxylation of activated

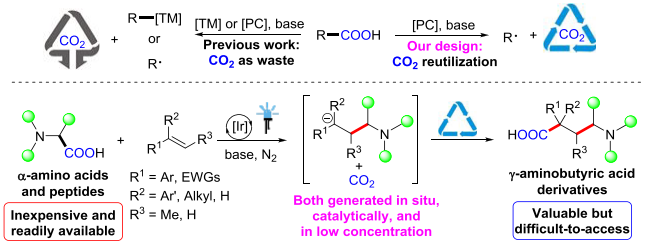


Figure 1. Strategy for carbocarboxylation of alkenes with α-AAs and peptides as bifunctional reagents. TM = transition metal. PC = photocatalyst. EWG = electron-withdrawing group.

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alkenes by simultaneous utilization of both the alkyl and carboxyl components from carboxylic acids, including α-amino acids (α-AAs) and peptides. The CO_2, which is generated quantitatively *in situ* in low concentration, can be efficiently trapped by carbanion intermediates in this system, in sharp contrast to previous carboxylations with high pressure and/or high excesses of CO_2.

Amino acids (AAs), especially the readily available and inexpensive α-AAs, are important and common carboxylic acids that play a vital role in nature.[9] Another important class of AAs, γ-aminobutyric acids (GABAs), are the major inhibitory neurotransmitters in the central nervous system of mammals.[10] Structurally diverse GABAs show significant bioactivities, and variations of the scaffold exist widely in drugs and various receptor antagonists (Figure 2).[11] Despite

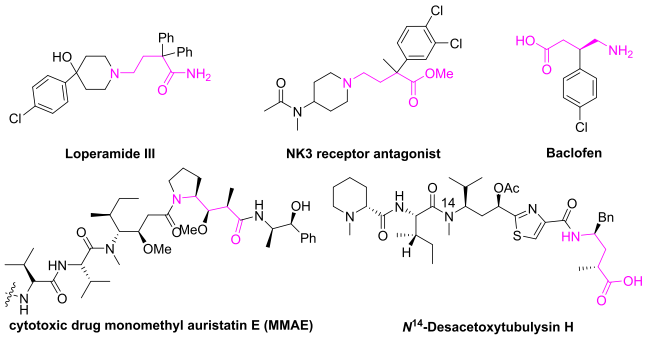


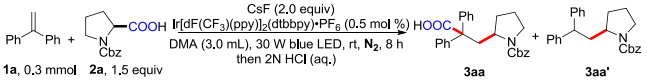
Figure 2. Selected molecules containing GABA motifs.

significant interest in their synthesis, GABAs are generally less accessible than α-AAs and their diversity is limited.[12,13] Inspired by great progress on group-transfer radical addition (GTRA)[14] and recent breakthroughs in radical-type difunctionalization of alkenes with bifunctional reagents,[15] we wondered whether we could prepare GABAs by installing both α-amino alkyl and carboxyl groups from α-AAs across the double bonds of alkenes. We hypothesized that photocatalytic decarboxylation of α-AAs or peptides in the presence of base could take place to generate α-amino alkyl radicals, which could undergo addition to activated alkenes to give more stable carbon radicals. The subsequent reduction of such radicals to carbanions and the following attack on the *in situ* generated CO_2 would generate GABAs. If successful, this process would not only turn inexpensive α-AAs into valuable GABAs but also would represent the first application of α-AAs and peptides as bifunctional reagents in the difunctionalization of alkenes and avoid the need for an excess of CO_2. However, our proposed strategy faced several challenges. First of all, there are only scarce examples of single-electron-transfer (SET) reduction of the newly generated carbon radicals in GTRA reactions,[16] which typically undergo direct couplings or oxidation to carbon cations instead.[14] Second, in comparison to common carboxylations with high pressure and/or high excesses of CO_2, it is challenging to realize efficient carboxylations via C−C bond formation with the (sub)stoichiometric amounts and low concentrations of CO_2 inherent to the proposed catalytic conditions.[17,18] Moreover, the proposed nucleophilic carbanions also would be generated catalytically in low concentrations and they could undergo undesired side reactions, such as protonation, instead of the desired carboxylation. Finally, the products, such as GABAs, could participate in similar decarboxylative transformations, including protonation, radical oligmerization, and polymerization, thus lowering the efficiency of the desired carbocarboxylation reaction.

RESULTS AND DISCUSSION

Reaction Optimization. With such challenges in mind, we initiated our investigations with the reaction between 1,1-diphenylethylene **1a** and *N*-Cbz-protected α-AA **2a** under 1 atm of N_2 and 30 W blue LED irradiation at room temperature. After substantial optimizations (Table 1), we

Table 1. Screening of Reaction Conditions[a]



entry	variation from standard conditions	yield (%)[b] 3aa	3aa′
1	**none**	**96 (81)**	**(18)**
2	4CzIPN as PC	34	40
3	$Ir(ppy)_2(dtbbpy)\cdot PF_6$ as PC	78	39
4	*fac*-$Ir(ppy)_3$ as PC	nd	nd
5	LiF instead of CsF	nd	nd
6	KF instead of CsF	73	32
7	MeCN instead of DMA	13	37
8	CO_2 (1 atm) instead of N_2	(93)	7
9	w/o CsF	nd	nd
10	w/o light	nd	nd
11	w/o PC	nd	nd
12	w/o PC/light	nd	nd

[a]Standard conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), $Ir[dF(CF_3)(ppy)]_2(dtbbpy)\cdot PF_6$ (0.5 mol %), CsF (0.6 mmol), DMA (3 mL), N_2 atmosphere, 30 W blue LED, rt, 8 h. Abbreviations: LED, light-emitting diode; [dF(CF_3)ppy], 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; ppy, 2-phenylpyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; Cbz, benzyloxycarbonyl; w/o, without; nd, not detected. [b]Determined by UPLC with anisole as internal standard. The isolated yield is given in parentheses.

obtained the desired product **3aa** in 81% isolated yield by using 0.5 mol % of $Ir[dF(CF_3)(ppy)]_2(dtbbpy)\cdot PF_6$ as the PC (Table 1, entry 1). Other PCs, including 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN), $Ir(ppy)_2(dtbbpy)\cdot PF_6$, and *fac*-$Ir(ppy)_3$, turned out to be less efficient (Table 1, entries 2−4). The screening of solvents indicated that *N*, *N*-dimethylacetamide (DMA) was more suitable than others (please see more details in Table S2 in the Supporting Information). In most cases, the hydroalkylation product **3aa′** was the main byproduct with an 18% isolated yield under the optimized conditions (Table 1, entry 1). We also explored a range of bases, among which CsF proved to be the best choice (Table S4 in the Supporting Information). When the reaction was carried out in 1 atm of CO_2, the isolated yield of **3aa** was increased to 93%, indicating that decarboxylation was followed by refixation of CO_2 in the catalytic cycle. Control experiments demonstrated that neither **3aa** nor **3aa′** was detected in the absence of the PC, base, or visible light.

Substrate Scope and Synthetic Application. With the optimal reaction conditions identified, we first investigated the scope of carboxylic acids, including α-AAs, peptides, and other carboxylic acids. As revealed in Table 2, *N*-Cbz-protected proline (**3aa**) showed better reactivity in comparison to other derivatives, including *N*-Boc, *N*-Ac, and *N*-Me protection (**3ab−ad**) as well as the free amine (**3ae**).[19] Notably, the

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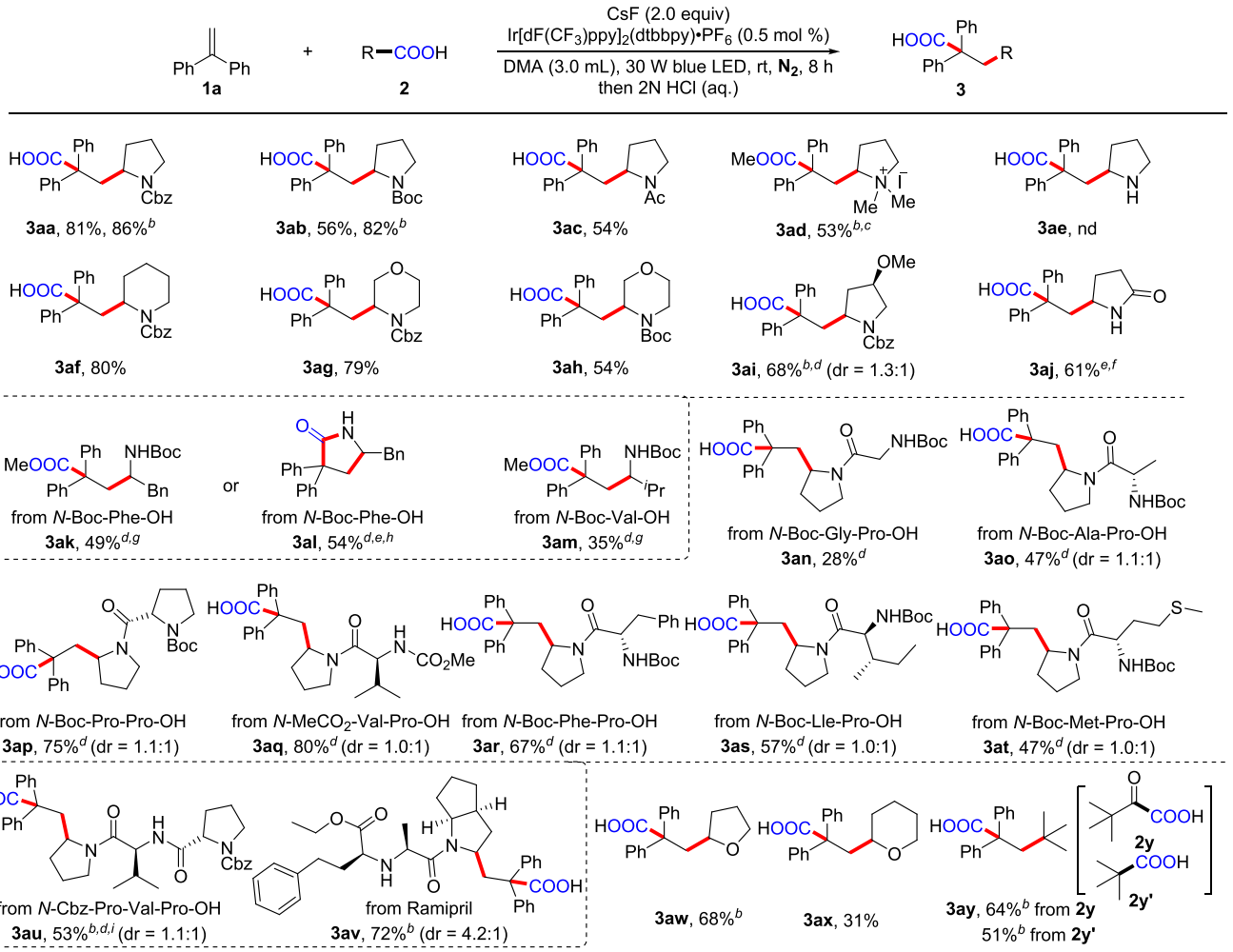
Table 2. Scope of α-Amino Acids, Peptides, and Other Carboxylic Acids as Bifunctional Reagents[a]



[a]Unless specified otherwise, the reaction conditions are as shown in Table 1, entry 1; isolated yields are provided. Ratios of diastereoisomers were determined by ^{1}H NMR or LC-MS analysis. For the lower yields sometimes observed, the hydroalkylation product was the main byproduct. Boc = *tert*-butoxycarbonyl. [b]CsF (0.9 mmol), 5 Å MS (200 mg). [c]Using **2d** = *N*-Me-Pro-OH and MeI as methylation reagent; yield determined by ^{1}H NMR. [d]18 h. [e]Isolated yields for reactions using **2** (0.39 mmol) and Cs_2CO_3 (0.45 mmol) in DMF (2.5 mL). [f]Under 1 atm of CO_2. [g]Isolated yield of methyl ester using $TMSCHN_2$ as methylation reagent. [h]Workup with (1) $TMSCHN_2$, 0 °C and (2) trifluoroacetic acid, 0 °C. [i]0.2 mmol scale.

addition of 5 Å molecular sieves (MS) obviously increased the yield of **3ab** to 82% by inhibiting the hydroalkylation. Moreover, this transformation was amenable to various α-AAs to give desired products **3af**−**am** in moderate to excellent yields. When we tested the nonprotected pyroglutamic acid (H-Pyr-OH) as the starting material, the hydroalkylation product **3aj′** was obtained as the major product under the standard conditions. However, the desired product **3aj** could be obtained in 61% isolated yield under 1 atm of CO_2. When *N*-Boc-Phe-OH was employed in our reaction, the GABA **3ak** or cyclization product 5-benzyl-3,3-diphenylpyrrolidin-2-one **3al** could be obtained in moderate yields after methylation or methylation and acid-mediated deprotection/cyclization, respectively. This highlights the potential for the synthesis of cyclic peptides via three steps without isolating the intermediates. In addition to α-AAs, a series of dipeptides (**3an**−**at**) and tripeptides (**3au**,**av**) also worked well in this reaction to give the desired products in moderate to excellent yields, indicating a possible application in modifying C-terminal residues in natural peptides.[20] Notably, the α-AAs (**3aj**,**ak**,**am**) and peptides (**3an**,**ao** and **3aq**−**av**) bearing relatively acidic N−H bonds that might lead to protonation of the *in situ* generated carbanion intermediates were tolerated in this reaction, indicating the efficiency of carboxylation. Moreover, α-oxy alkyl carboxylic acids (**3aw**,**ax**), a keto acid, and pivalic acid (**3ay**) could also serve as bifunctional reagents in this transformation to give the desired products in 31−68% yields.

In order to demonstrate the generality of this strategy, we further turned our attention to the scope of the alkenes (Table 3). 1,1-Diarylethylenes bearing electron-donating groups (EDGs, e.g. **3ea**−**3ia**) at the *para* position and electron-neutral groups showed better reactivity than those with strong EWGs (e.g., CO_2Me, CF_3), which were not tolerated in this system. However, strong EWGs (e.g., CO_2Me, CF_3) at the *meta* position were tolerated to give the corresponding products in moderate to good yields. In addition, the arylalkenes bearing both strong and weak EWGs (**3ta**−**wa**) were amenable to this system. This phenomenon might arise from the balance of a stereoelectronic effect at the benzylic position, allowing facile SET reduction of benzyl radicals to the benzylic carbanions and then nucleophilic attack to CO_2 with

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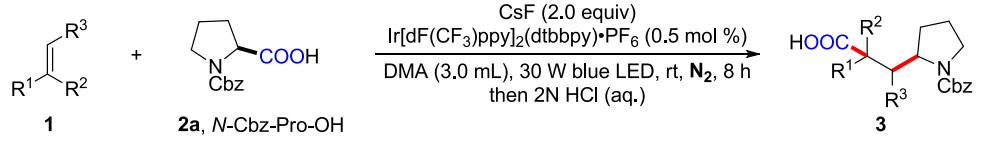
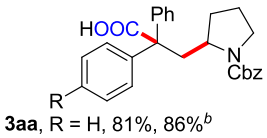
J. Am. Chem. Soc. 2021, 143, 2812−2821

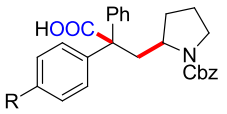
Table 3. Scope of Activated Alkenes with 2a as the Bifunctional Reagent[a]



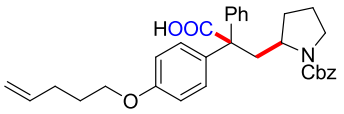
1 **2a**, *N*-Cbz-Pro-OH **3**



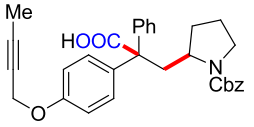
3aa, R = H, 81%, 86%[b]
3ba, R = Ph, 72% (dr = 1.0:1)
3ca, R = Me, 80%[b] (dr = 1.1:1)
3da, R = F, 80% (dr = 1.2:1)



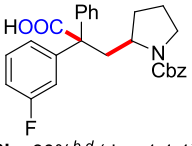
3ea, R = OMe, 85%[b] (dr = 1.2:1)
3fa, R = OPh, 74% (dr = 1.4:1)
3ga, R = SMe, 42%[c,d] (dr = 1.2:1)



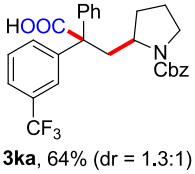
3ha, 82%[b,d] (dr = 1.1:1)



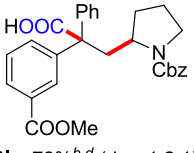
3ia, 80%[b] (dr = 1.2:1)



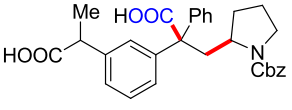
3ja, 80%[b,d] (dr = 1.1:1)



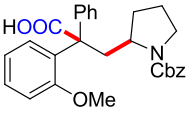
3ka, 64% (dr = 1.3:1)



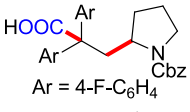
3la, 78%[b,d] (dr = 1.2:1)



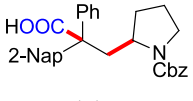
3ma, 54%[c] (dr = 1.2:1)



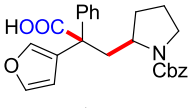
3na, 73% (dr = 4.1:1)



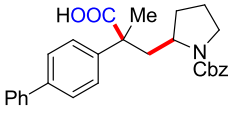
3oa, 93%[b]



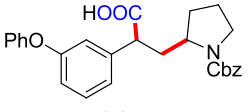
3pa, 59%[b,d] (dr = 1.2:1)



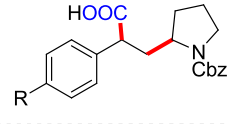
3qa, 74%[b] (dr = 1.7:1)



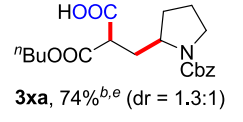
3ra, 67% (dr = 1.1:1)



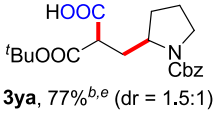
3sa, 66%[b,d] (dr = 1.1:1)



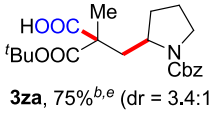
3ta, R = CN, 61% (dr = 2.0:1)
3ua, R = CF_3, 66%[b,e] (dr = 1.5:1)
3va, R = COOMe, 72%[b,d] (dr = 1.7:1)
3wa, R = Ph, 60%[b,d] (dr = 1.2:1)



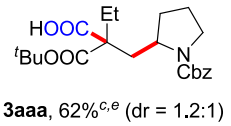
3xa, 74%[b,e] (dr = 1.3:1)



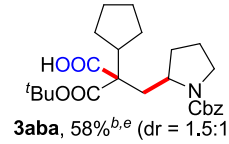
3ya, 77%[b,e] (dr = 1.5:1)



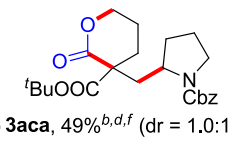
3za, 75%[b,e] (dr = 3.4:1)



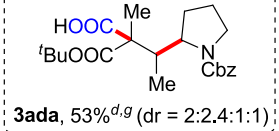
3aaa, 62%[c,e] (dr = 1.2:1)



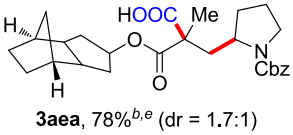
3aba, 58%[b,e] (dr = 1.5:1)



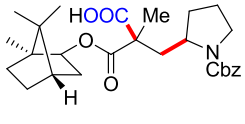
3aca, 49%[b,d,f] (dr = 1.0:1)



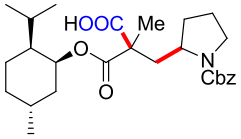
3ada, 53%[d,g] (dr = 2:2.4:1:1)



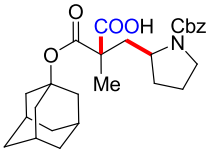
3aea, 78%[b,e] (dr = 1.7:1)



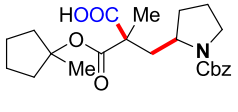
3afa, 81%[b,e] (dr = 3.5:1)



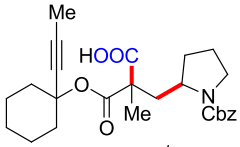
3aga, 59%[c,e] (dr = 1.5:1)



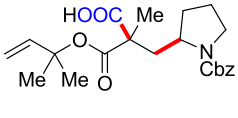
3aha, 70%[b,e] (dr = 3.6:1)



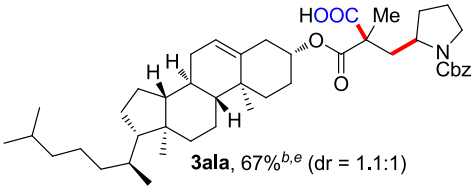
3aia, 80%[b,e] (dr = 4.3:1)



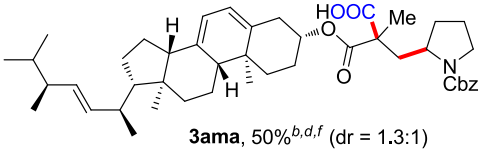
3aja, 73%[b,e] (dr = 2.2:1)



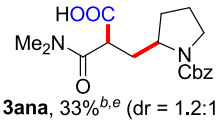
3aka, 52%[c,e] (dr = 2.8:1)



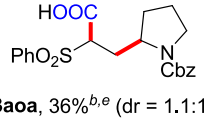
3ala, 67%[b,e] (dr = 1.1:1)



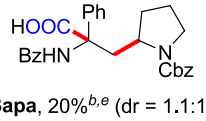
3ama, 50%[b,d,f] (dr = 1.3:1)



3ana, 33%[b,e] (dr = 1.2:1)



3aoa, 36%[b,e] (dr = 1.1:1)



3apa, 20%[b,e] (dr = 1.1:1)

[a]Unless specified otherwise, the reaction conditions are as shown as Table 1, entry 1. Isolated yields are given. Ratios of diastereoisomers were determined by ^{1}H NMR or LC-MS analysis. For the cases with lower yields, hydroalkylation products **3′** were the main byproducts. Nap = naphthyl. [b]CsF (0.9 mmol), 5 Å MS (200 mg). [c]CsF (0.9 mmol). [d]12 h. [e]4 h. [f]0.2 mmol scale. [g]**1** (0.3 mmol), **2a** (0.39 mmol), [Ir] (1 mol %), Cs_2CO_3 (0.45 mmol) in DMF (2.5 mL).

high reactivity. When a derivative of ketoprofen was subjected to this reaction, the product **3ma** was obtained in moderate yield, providing a new method to synthesize ibuprofen analogues.

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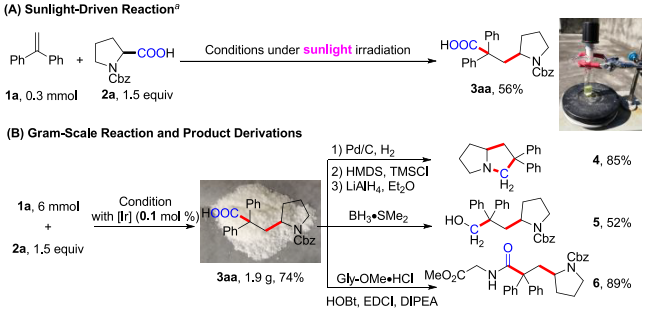
J. Am. Chem. Soc. 2021, 143, 2812−2821

Although styrenes and other activated alkenes, such as acrylates, have been widely investigated as radical acceptors in visible-light-mediated decarboxylative hydroalkylations with α-AAs,[21] we found that diverse acrylates also underwent selective GTRA in our case with CO_2 reutilization under slightly modified reaction conditions (Table 3). This unusual chemoselectivity is in contrast with previous reports,[21] which might call attention to the possible but unpredicted reactions such as this CO_2 elimination−fixation reaction in the decarboxylative radical additions. As shown in Table 3, increasing the steric hindrance at the α-position of the *tert*-butyl acrylates decreased the isolated yields of the products (**3ya**−**3aba**). In addition to monosubstituted acrylates, an α,β-disubstituted variant (**3ada**) also worked in this reaction. A variety of acrylate esters of natural products, including isobornyl (**3afa**), menthol (**3aga**), cholesterol (**3ala**), and ergosterol (**3ama**), were suitable substrates in our system. Notably, the ergosterol analogue, which is known to easily transform to vitamin D_2 under light irradiation, survived the reaction conditions without appreciable photoisomerization.[22] It merits mentioning that unconjugated alkenes (**3ha**, **3aka**−**ama**) and alkynes (**3ia**, **3aja**) as well as a 1,3-diene (**3ama**) were untouched when selective carboxylation occurred at the C=C bond of styrenes and acrylates. Moreover, a variety of functional groups, OMe (**3ea**,**na**), SMe (**3ga**), ester (**3la**,**va**, **3xa**−**3ama**), carboxylic acid (**3ma**), furan (**3qa**), and nitrile (**3ta**), were all compatible with the reaction conditions and delivered the targeted GABAs in moderate to excellent yields. Additionally, alkenes bearing EDGs, which were not suitable substrates in previously reported dicarbofunctionalizations of styrenes with amines and CO_2,[13] worked well in our system, thus indicating a higher functional group tolerance and more general substrate scope of this transformation. Moreover, other functionalized alkenes (e.g., **3ana**−**apa**) could also give the desired products, albeit in lower yields. All of these results demonstrate the potential of this method as an alternative to synthesize GABAs and as a valuable tool for the late-stage diversification of bioactive molecules with a GABA moiety.

In order to demonstrate the utility of this method, we tested the use of sunlight irradiation, gram-scale reaction conditions, and further product derivatizations (Scheme 1). First, we conducted the standard reaction under sunlight irradiation, resulting in a 56% yield of **3aa** along with 22% of **3aa′**. Then, to our delight, a gram-scale reaction with lower catalyst loading (0.1 mol %) worked smoothly to give **3aa** in 74% yield, highlighting the potential utility of this method. With GABA **3aa** now available in gram quantities, we further synthesized product **4**, which represents the necine base component present in pyrrolizidine alkaloids, in 85% yield via smooth deprotection of the Cbz group, condensation, and reduction.[23] 4-Aminobutanol **5** could be generated in 52% yield by the reduction of **3aa** with borane. Moreover, the GABA **3aa** could be converted to the dipeptide **6** following standard peptide coupling protocols.

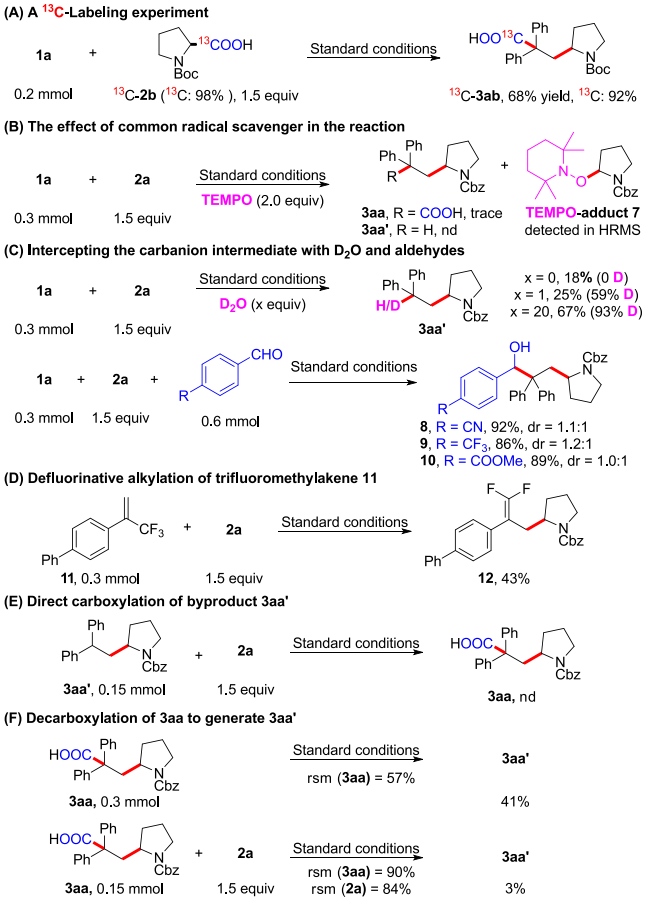
To gain further insight into the mechanistic nature of this transformation, we performed a series of control experiments (Scheme 2). A facile carbocarboxylation of **1a** with [^{13}C]-**2b** gave [^{13}C]-**3ab** with 92% ^{13}C incorporation, providing strong evidence that the carboxyl group in the desired product **3ab** came from the starting material **2b** (Scheme 2A). When we tested the effect of 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) in our system, we found that the formation of both **3aa** and **3aa′** were significantly inhibited, and we detected the α-amino radical−TEMPO adduct **7** by HRMS, indicating that radicals might be involved (Scheme 2B). When D_2O was added in the reaction mixture, up to 93% deuterium incorporation at the benzylic position of **3aa′** was observed (Scheme 2C). Furthermore, benzaldehydes could be applied as electrophiles under our standard conditions to deliver the desired products **8**−**10** in good yields (Scheme 2C). Both cases suggest the formation of a benzylic carbanion intermediate. Moreover, these results were consistent with the radical/polar crossover defluorinative alkylation of

Scheme 1. Sunlight-Driven Reaction, Gram-Scale Reaction, and Product Derivatizations



[a]**1a** (0.3 mmol), **2a** (0.45 mmol), Ir[dF(CF$_3$)(ppy)]$_2$(dtbbpy)·PF$_6$ (0.5 mol %), CsF (0.6 mmol), DMA (3.0 mL), N_2 atmosphere, natural sunlight irradiation, 30 °C ∼ 35 °C, 8 h (10:00−18:00).

Scheme 2. Control Experiments



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trifluoromethylalkenes **11** with **2a** to form the *gem*-difluoroalkene **12** (Scheme 2D).[24] The possibility that **3aa′** might be the intermediate to give the desired product **3aa** was excluded, as no **3aa** was observed when **3aa′** was applied as the starting material under the standard conditions (Scheme 2E).

Since the visible-light-driven decarboxylation of phenylacetic acids has been reported by several groups,[25] we wondered whether our products were stable under the reaction conditions. In order to test this, we subjected **3aa** to the standard conditions and found that **3aa** underwent decarboxylation in the absence of **2a** to give **3aa′** in 41% isolated yield (Scheme 2F). This decarboxylation was significantly inhibited, however, in the presence of **2a** and only afforded **3aa′** in 3% yield along with up to 90% recovery of starting material (rsm) **3aa** (Scheme 2F), which might arise from a competitive decarboxylation. Kinetic experiments also confirmed the formation of **3aa** and decomposition of **3aa** to **3aa′** under the standard reaction conditions (Figure 3).

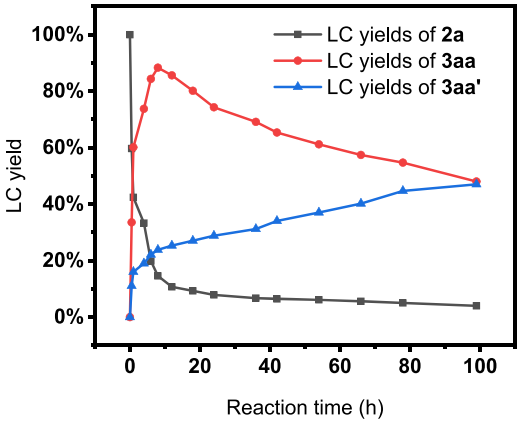

Figure 3. Kinetic experiments.

In order to explain the competitive decarboxylation, we further tested the Stern−Volmer analysis with **2a** and **3aa** in the presence of CsF. As shown in Figure 4, the luminescence of

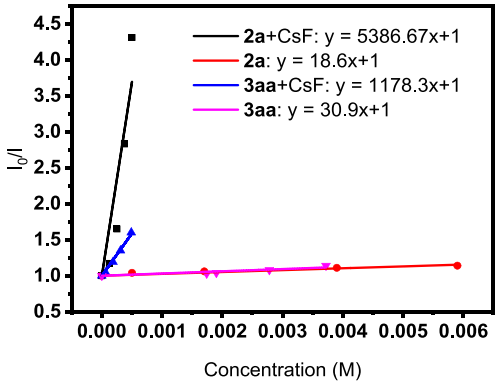

Figure 4. Stern−Volmer analysis with **2a** and **3aa** in the presence or absence of CsF under N_2.

$Ir[dF(CF_3)(ppy)]_2(dtbbpy)\cdot PF_6$ at λ_{max} = 470 nm was readily quenched by both **2a** and **3aa** in the presence of CsF (Figure 4). The quenching rate of **3aa** is much slower than that of **2a** in the presence of CsF, which might be the key factor for the more facile decarboxylation of **2a** over **3aa** under the reaction conditions. The poor quenching by either **2a** or **3aa** in the absence of CsF indicated the important role of CsF as the base to deprotonate carboxylic acids to carboxylates, which then could readily undergo SET with the excited photocatalyst.

On the these mechanistic studies and previous investigations,[26,27] we propose the mechanism as shown in Figure 5 for

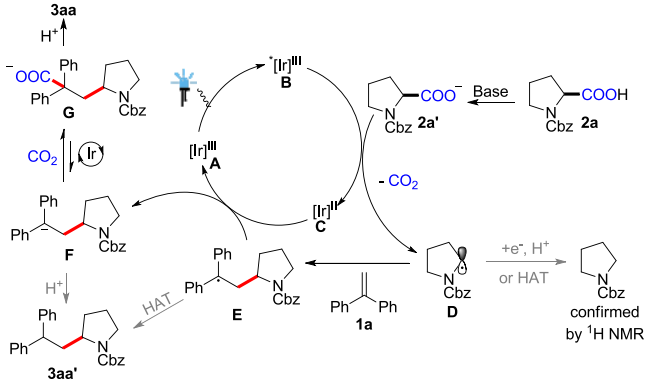

Figure 5. Possible mechanism.

the transformation. With the reaction of **1a** and **2a** as an example, initial SET between the photoexcited [Ir^{III}] and the carboxylate **2a′**, formed *in situ* upon deprotonation of **2a** in the presence of a base, generates the α-amino radical **D** and CO_2. Radical addition of **D** to **1a** produces the more stable benzylic radical **E**, which undergoes SET reduction with the reduced [Ir^{II}] photocatalyst to give the benzylic carbanion **F**. Further nucleophilic attack into the *in situ* generated CO_2 furnishes carboxylate **G**, which undergoes protonation during workup to afford the desired product **3aa**. Although the carboxylation of **F** is reversible, the irreversible decarboxylation of **2a'** and slower decarboxylation of **G** might explain this conversion.

CONCLUSION

In summary, we disclosed a novel strategy using carboxylic acids, including diverse α-amino acids, peptides, and alkyl carboxylic acids, as bifunctional reagents in the redox-neutral carbocarboxylation of activated alkenes via visible-light photoredox catalysis. In comparison with traditional carboxylations of alkenes under at least 1 atm of CO_2, this strategy resolves the challenge in carboxylation with *in situ* generated CO_2, which is released as the byproduct via catalytic decarboxylation and thus is in low concentration. By using this method, we could prepare a variety of valuable but difficult to access γ-aminobutyric acids from inexpensive and readily available α-amino acids with broad substrate scope. Moreover, this method makes it easy to modify residues in peptides and introduce a GABA functionality into complex molecules, including the terpenoids isobornyl, menthol, cholesterol, and ergosterol. Moreover, the reaction can be performed under sunlight irradiation, it is readily amenable to gram-scale production, and diverse product derivations are also realized. Mechanistic studies indicate that a benzylic carbanion is generated catalytically and acts as the key intermediate to react with the *in situ* generated CO_2. Further application of this new strategy in other GTRA processes is underway in our laboratory.

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J. Am. Chem. Soc. 2021, 143, 2812−2821

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11896.

Detailed experimental procedures, spectral data, and analytical data (PDF)

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Notes

The authors declare the following competing financial interest(s): A Chinese Patent on this work has been applied with the number 202011267379.4.

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