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Visible-Light Photoredox-Catalyzed Remote Difunctionalizing Carboxylation of Unactivated Alkenes with CO_2

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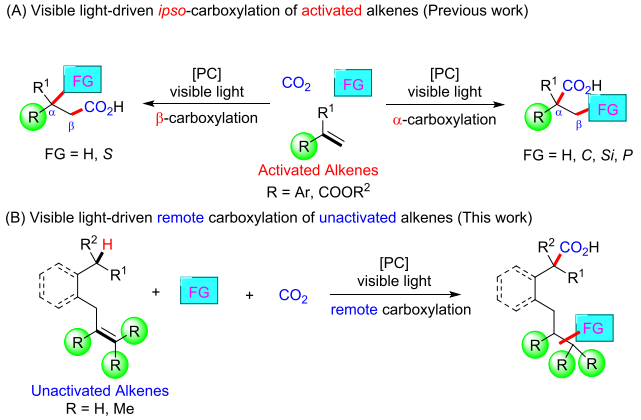
Abstract: Catalytic difunctionalization of alkenes is a powerful and efficient tool to synthesize complex molecules from simple starting materials. Remote difunctionalization of unactivated alkenes is more challenging but highly attractive tactic to install two functional groups across long distances. Herein, we report the first remote difunctionalization of alkenes with CO_2. This visible-light photoredox catalysis strategy provides a facile method to synthesize a series of carboxylic acids, such as non-natural α-amino acids, bearing valuable fluorine- or phosphorus-containing functional groups. Moreover, this versatile protocol shows mild reaction conditions, broad substrate scope, and good functional group tolerance. Based on DFT calculations, the observed reaction starts via radical addition to an unactivated alkene to smoothly form a new carbon radical. The following 1,5-hydrogen atom transfer process, which is considered to be the rate-limiting step, generates a more stable benzylic radical. In contrast to previous reports of direct coupling or single-electron oxidation of such radical species, experimental and computational studies suggest the reduction of the benzylic radicals by an Ir(II) species generates the corresponding benzylic carbanions as the key intermediates, which further undergo nucleophilic attack with CO_2 to generate carboxylates. Following this mechanistic study, diverse electrophiles, including aldehydes, ketones and benzylic bromides, are also applicable in such transformation, demonstrating a general strategy for redox-neutral remote difunctionalization of unactivated alkenes.

Introduction

Carbon dioxide (CO_2) is a promising one-carbon (C1) source in chemical synthesis because of its abundance, availability, low toxicity, and recyclability.[1] Carboxylations with CO_2 are fascinating processes to construct important carboxylic acids with high atom- and step-economy.[2] Recently, due to significant developments in photochemistry,[3] light-driven carboxylations using CO_2,[4,5] especially those employing visible light,[5] have attracted growing attention. Many groups have made great contributions to this field and have developed varied strategies to generate functionalized carboxylic acids with CO_2. The visible light-driven carboxylation of alkenes with CO_2, in particular, has attracted great attention due to the wide availability of a diversity of alkenes (Scheme 1A). For example, Iwasawa[5e,5s] and König[5n] both realized regioselective hydrocarboxylations of alkenes via visible-light photoredox and transition metal dual catalysis. Martin,[5h] Wu,[5r] Li[5z] and our group[5j,5x] have developed different visible light-driven difunctionalizing carboxylations of alkenes. These previously reported methods, however, are limited to activated alkenes, including styrenes and acrylates. In contrast, visible light-driven carboxylation of unactivated alkenes still remains an unresolved challenge in this field.

Catalytic difunctionalization of alkenes is an important tool to generate highly functionalized skeletons.[6] The 1,2-difunctionalization of alkenes has been investigated extensively, resulting in diverse tools to generate complex molecules with functional groups added across double bonds. With increased interest in remote C–H functionalization,[7] chemists have been recently investigating different strategies for the migrating difunctionalization of alkenes to generate valuable compounds with functional groups added over long relative distances.[8,9] Compared to chain-walking reactions of alkenes catalyzed by metal hydride species,[8] the strategy of radical-mediated remote functionalization of alkenes[9] demonstrates significant advantages such as mild reaction conditions, good regioselectivity, and applicability to a broader scope of substrates, including those in which pathways for chain-walking might be blocked. This process combines radical attack to alkenes, hydrogen atom transfer (HAT) and remote C–H functionalization. In this process, to the best of our knowledge, the newly generated radicals via HAT undergo either single electron oxidation to an electrophilic carbocation[9c,9d,9f,9h] or directly couple with reaction partners.[9e,9g] Another possibility involving the reduction of the radical intermediate to a carbanion and subsequent nucleophilic attack on an expectant electrophile

has never been reported for the remote functionalization of alkenes. Herein, we report the first remote difunctionalization of unactivated alkenes with CO_2 via visible-light photoredox catalysis (Scheme 1B). In addition to CO_2, diverse electrophiles, including aldehydes, ketones and benzylic bromides, are also applicable in this process.



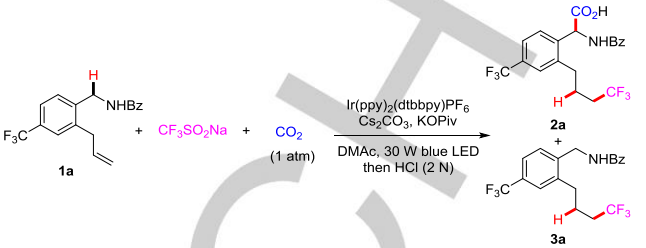
Scheme 1. Visible light-driven carboxylations of alkenes with CO_2.

It is well known that α-amino acids are valuable synthetic building blocks for peptides and they are widely used as components of active drug molecules.[10] Moreover, due to the effects on the metabolic stability, lipophilicity, and biopotency induced by fluorine atoms, the introduction of fluorine-containing groups on amino acids has beneficial effects in drug design and peptide modification.[11] Therefore, at the early stage of this project, we hoped to synthesize fluorine-containing α-amino acids via remote difunctionalization of alkenes. We envisioned that the addition of fluorine-containing carbon radicals to the unactivated alkene would generate new carbon radicals, which then might undergo selective 1,5-HAT to give benzylic radicals. Reduction to the corresponding benzylic carbanions and nucleophilic attack on CO_2 was expected to lead to generation of the desired fluorine-containing α-amino acids. This hypothesis, however, faced several challenges, including the low reactivity of unactivated alkenes as well as chemo- and regio-selectivity issues arising from competitive monofunctionalization and other side reactions.

Results and Discussion

On the basis of our hypothesis, we began our investigations on the remote difunctionalizing carboxylation with substrate **1a** with Langlois reagent (CF_3SO_2Na, E_{ox} = +1.05 V vs SCE in MeCN)[12] and CO_2 (1 atm) under visible-light irradiation at room temperature. After systematically screening the reaction parameters, the desired product **2a** was obtained in 77% yield in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ (E_{red} [Ir^{III}/Ir^{II}] = -1.51 V vs SCE in MeCN)[13] as photocatalyst (PC) as well as the mixture of Cs_2CO_3 and KOPiv as base (Table 1, entry 1). The hydrotrifluoromethylation byproduct **3a** was detected, which presumably arose via competing protonation. Control experiments revealed that the light, PC and CO_2 were all essential for the transformation (entries 2-4). It should be noted that the desired product **2a** also could be obtained in 14% yield under N_2 atmosphere (1 atm), which might because Cs_2CO_3 acts as the source of CO_2 (entry 4).[5i] Both KOPiv and Cs_2CO_3 played an important role in the reaction, as lower yields of **2a** were obtained in the absence of either (entries 5-7). A lower yield also was obtained when reducing the amount of PC or shortening the reaction time (entries 8-9). Additionally, the employment of other solvents and/or PCs resulted in lower yields (entries 10-11)

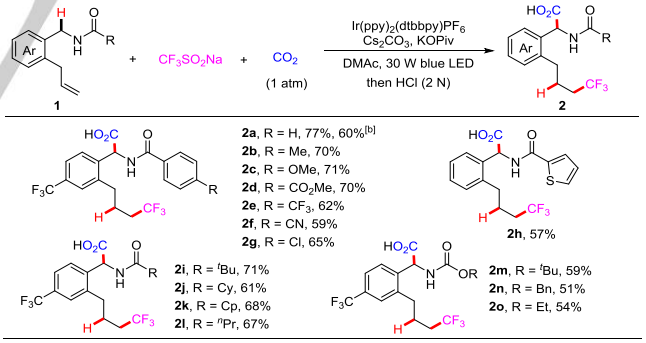
Table 1. Reaction conditions screening.[a]



Entry	Variations	**2a** (%)[b]	**3a** (%)[b]
1	**none**	**81 (77)**	**13**
2	no light	N.D.	N.D.
3	no $Ir(ppy)_2(dtbbpy)PF_6$	N.D.	N.D.
4	N_2 instead of CO_2	14	69
5	no KOPiv	71	18
6	no Cs_2CO_3	60	30
7	no KOPiv and Cs_2CO_3	50	14
8	$Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %)	76	14
9	12 h	67	24
10	DMF instead of DMAc	65	23
11	4CzIPN as PC	64	14

[a] Reaction conditions: **1a** (0.2 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol %), CF_3SO_2Na (2.5 equiv), Cs_2CO_3 (1.3 equiv), KOPiv (1 equiv), DMAc (0.1 M), irradiation with 30 W blue LEDs at room temperature (22 - 25 °C) under CO_2 (1 atm) for 24 h. [b] ^1H NMR yields using CH_2Br_2 as an internal standard and isolated yields in parentheses. Bz = Benzoyl. N.D. = Not detected. DMAc = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, 4CzIPN = 2,4,5,6-tetrakis(carbazol-9-yl)-1,3-dicyanobenzene.

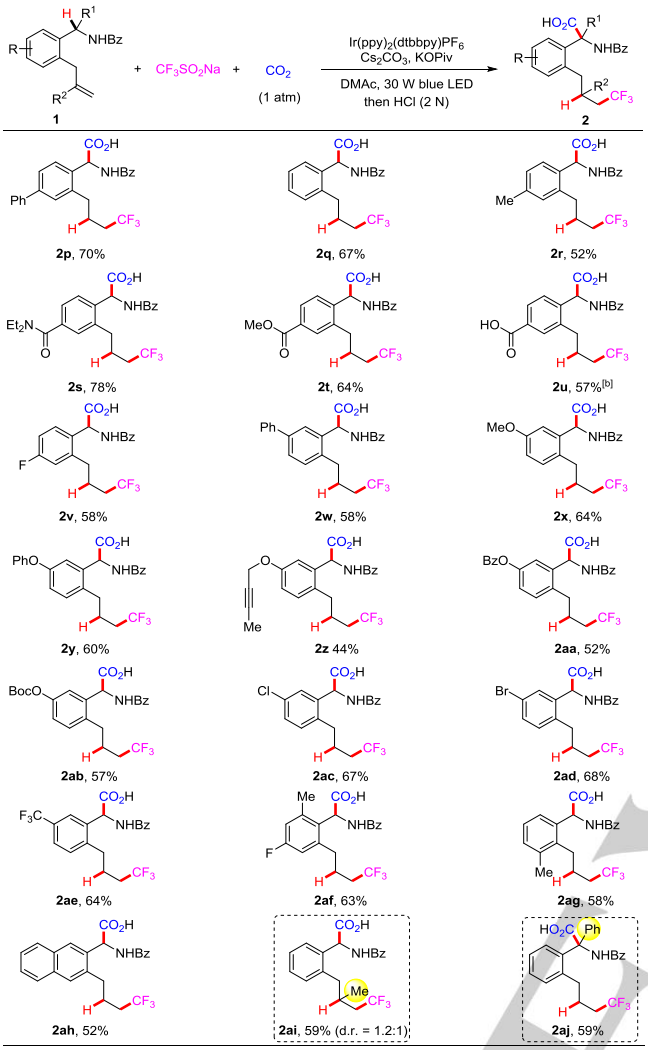
Table 2. Substrates with different amide motifs.[a]



[a] Standard reaction conditions (Table 1, entry 1) with yields of isolated products. [b]: 5.0 mmol scale. Cy = cyclohexyl, Cp = cyclopropyl.

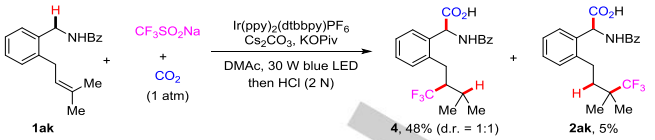
With the optimal reaction conditions in hand (Table 1, entry 1), we then investigated substrates with different amide motifs, which provided CF_3-containing non-natural α-amino acids in moderate-to-good isolated yields (57-77%, Table 2). Moreover, both electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) were tolerated at the *para*-position of the aryl amides moieties (**1a**-**1g**). In addition to aryl amides, amides substrates bearing heteroarenes, such as thiophene (**1h**), alkyl groups (**1i**-**1l**), and carbamates (**1m**-**1o**) also worked well under the standard conditions. Importantly, a 5 mmol scale reaction of **1a** was carried out to afford **2a** in 60% yield.

Table 3. Substrates with different allyl arene motifs.[a]



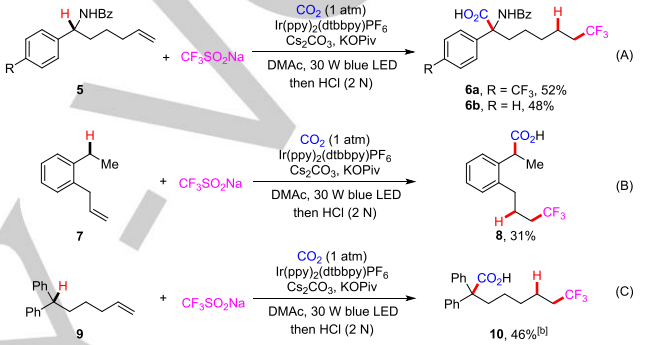
[a] Standard reaction conditions (Table 1, entry 1) with yields of isolated products. [b] Cs_2CO_3 (2.3 equiv). Boc = *tert*-butoxycarbonyl. d.r. = diastereoselectivity ratio.

We further explored the substrates with different allyl arene motifs (Table 3). As expected, a broad range of benzylic amides bearing diverse functional groups on the central arene component, including amides (**1s**), esters (**1t**, **1aa**), halides (**1v**, **1ac-1af**), alkynes (**1z**), and carbonates (**1ab**), delivered the corresponding products in moderate-to-good yields (44-78%). This reaction was not hampered by *ortho* (**1af**, **1ag**) or *meta* substitutions (**1w**-**1ae**) on the central benzene ring. The substrates bearing disubstitution on the arene core (**1af**) or naphthalene (**1ah**) also were suitable. It is noteworthy that the geminal-disubstituted alkene **1ai** was also reactive, providing the expected difunctionalization product **2ai** in 59% yield. Furthermore, the reaction of substrate **1aj** also was smooth and generated the corresponding α,α-diaryl amino acid **2aj**. To our surprise, the tri-substituted unactivated alkene motifs (**1ak**) also was compatible to give **4** as the major product via 1,6-HAT process, which might arise from easier radical attack of alkene at the less steric hindrance and generation of more stable tertiary carbon radical (Scheme 2).

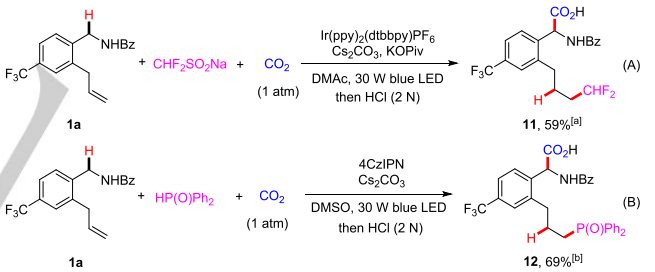


Scheme 2. The reaction of **1ak** bearing challenging tri-substituted unactivated alkene under standard reaction conditions (Table 1, entry 1).

It should be noted that our reaction conditions also were suitable for other structures containing an unactivated alkene an a benzylic hydrogen (Scheme 3). For example, substrates **5** underwent the reaction smoothly to give products **6** with satisfactory yields (48%-52%, Scheme 3A). In addition to the synthesis of non-natural α-amino acids, the strategy was also amenable to the remote carboxylation of 1-allyl-2-ethylbenzene (**7**) and hex-5-ene-1,1-diyldibenzene (**9**) to afford the corresponding carboxylic acids in relatively lower yields (Scheme 3B and 3C).



Scheme 3. Other substrates bearing unactivated alkenes.[a] [a] Standard reaction conditions (Table 1, entry 1) with yields of isolated products. [b] KOPiv (1.5 equiv).

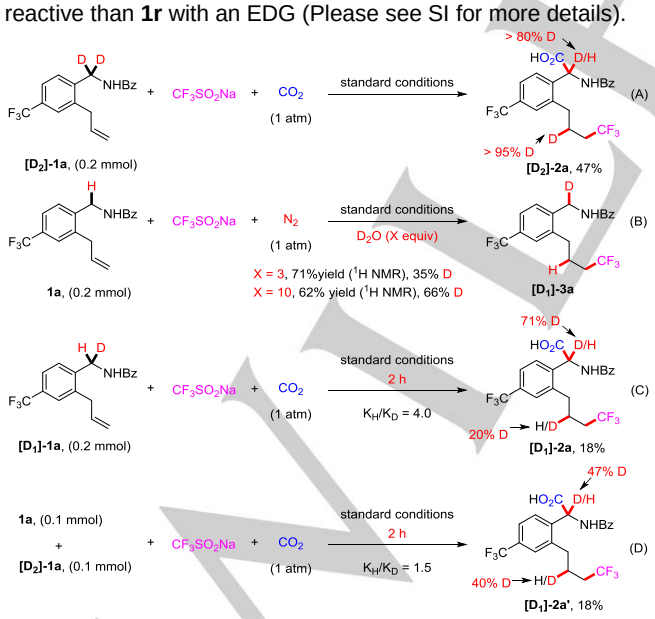


Scheme 4. Different radical precursors. [a] **1a** (0.2 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (4 mol %), CHF_2SO_2Na (2.5 equiv), Cs_2CO_3 (1.3 equiv), KOPiv (1 equiv), DMAc (0.1 M), irradiation with 30 W blue LEDs at room temperature under CO_2 (1 atm) for 48 h. [b] **1a** (0.2 mmol, 1 equiv), 4CzIPN (2 mol %), $HP(O)Ph_2$ (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMSO (0.1 M), irradiation with 30 W blue LEDs at room temperature under CO_2 (1 atm) for 24 h.

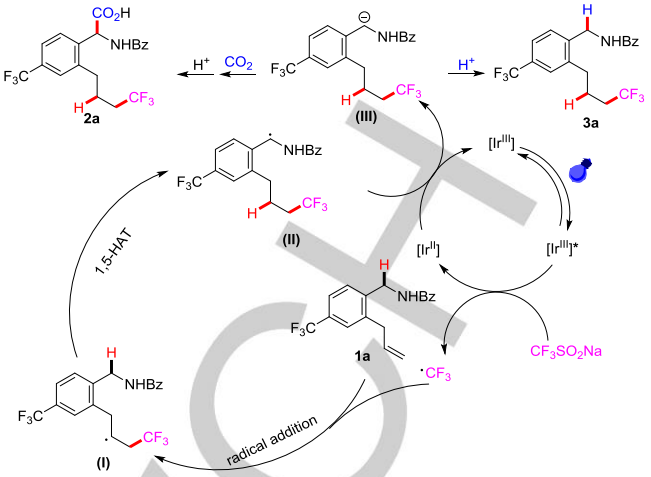
Encouraged by the high reactivity of this transformation, we wondered whether other radical precursors could also be applied in the remote difunctionalizing carboxylation. As shown in Scheme 4, we found that related difluoromethyl-containing α-amino acids are easily accessible when using CHF_2SO_2Na as the radical precursor under similar reaction conditions (Scheme 4A). In addition to carbon-centered radicals, heteroatom-based radicals were also examined. Considering the high value of widely existing phosphorus-containing compounds,[14] we tested $HP(O)Ph_2$ as a radical precursor and successfully synthesized the corresponding phosphorus-containing α-amino acids by using 4CzIPN as the photocatalyst (Scheme 4B). Taken together, the results demonstrate the potential of this methodology to construct functionalized α-amino acids.

To further explore the potential application of our transformation, the derivatizations of product **1a** were performed (Please see the supporting information (SI) for more details). Firstly, the protecting benzoyl group could be removed easily to generate the uniquely functionalized phenylglycine **13** in excellent yield (96%). Moreover, the trifluomethyl-containing dipeptide **14** and the thio-oxazolidine derivative **16** were easily obtained from **2a** in good yields. The success of these experiments indicates the great potential of the methodology to rapidly construct unique peptides for biological and pharmaceutical evaluation.

To gain more insight into this new transformation, we conducted various control experiments (Please see SI for more details). When we tested the effect of radical scavengers, including 2,2,6,6-tetramethyl-1-piperdiny-l-oxy (TEMPO) and diphenyldiselenide (PhSeSePh), to the standard reaction conditions, we found that only a trace amount or even no desired product was detected (Please see SI for more details), suggesting that radical intermediates might be involved. We then subjected the deuterated substrate **[D$_2$]-1a** to the reaction conditions and obtained the **[D$_2$]-2a** with more than 95% of deuteration at the position β to the CF_3 group, suggesting that a 1,5-deuterium atom transfer process occurred (Scheme 5A). Partial H/D exchange at the position α to the carboxylic acid in **[D$_2$]-2a** also was observed, which might arise from high acidity of this C−D/H bond. Additional isotope-labeling studies under a nitrogen atmosphere suggested that an α-amino benzylic anion was formed as an intermediate, which can be quenched with D_2O to afford **[D$_1$]-3a** (Scheme 5B). Moreover, kinetic isotopic effects (KIE, H vs. D) of 4.0 and 1.5 were obtained for the intra- and inter-molecular competition experiments, respectively (Scheme 5C and 5D), which indicated that the 1,5-HAT process might be involved in the rate-determining step. Finally, we performed an intermolecular competition experiment, which revealed that the substrate **1a** with an EWG was slightly more reactive than **1r** with an EDG (Please see SI for more details).



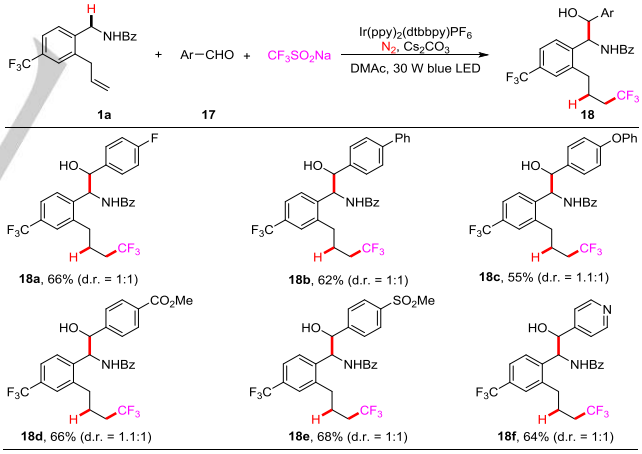
Scheme 5. Control experiments.



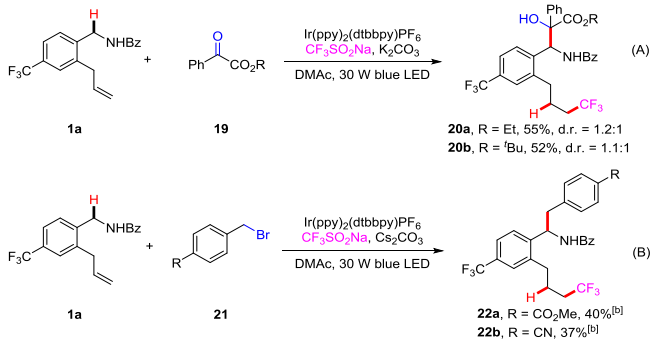
Scheme 6. Plausible mechanism.

Based on the control experiments and previous studies,[5] a plausible mechanism for the overall transformation is proposed and outlined in Scheme 6. First, the photo-excited Ir(III)-photocatalyst is reductively quenched by CF_3SO_2Na to deliver a CF_3 radical and an Ir(II) species. The CF_3 radical then undergoes radical addition to the C=C bond to produce a new carbon-centered radical (**I**). A rate-determining 1,5-HAT process in a remote and site-selective manner then occurs to afford the more stable benzylic radical **II**, which can be reduced by the Ir(II) species to both afford the α-amino benzylic anionic species **III** and regenerate the requisite Ir(III)-photocatalyst. The subsequent nucleophilic attack to CO_2 and following protonation can provide the observed carboxylic acids. Meanwhile, the direct protonation of **III** would lead to the formation of byproduct **3a**.

Table 4. Difunctionalization with aryl aldehydes.[a]



[a] All reactions were carried out with **1a** (0.2 mmol, 1 equiv), ArCHO (1.5 equiv), CF_3SO_2Na (2.5 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol %), Cs_2CO_3 (1.1 equiv), 1 atm of N_2 in anhydrous DMAc (0.1 M), irradiation with 30 W blue LEDs at room temperature (22 - 25 °C) for 24 h, yields of isolated products.



Scheme 7. Difunctionalization with other electrophiles.[a] [a] **1a** (0.2 mmol), **19** (3 equiv), CF_3SO_2Na (2.5 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol %), K_2CO_3 (2 equiv), DMAc (0.1 M), irradiation with 30 W blue LEDs at room temperature under N_2 (1 atm) for 24 h. [b] **21** (3 equiv), Cs_2CO_3 (2 equiv).

Based on our proposed formation of α-amino benzylic carbanion **III** as a key intermediate under our reaction conditions, we considered whether this remote difunctionalization could be suitable for other electrophiles beyond CO_2. To our delight, after slightly modifying the reaction conditions, we demonstrated that aryl aldehydes could be employed as electrophiles in a three-component coupling protocol (Table 4). As illustrated, substrates bearing either EDGs or EWGs (**17a-17f**) took part in this reaction to deliver the corresponding 1,2-amino alcohols in moderate-to-good yields (55-68%) without any significant diastereoselectivity. A diverse range of functional groups, such as fluoro (**17a**), phenoxyl (**17c**), ester (**17d**), sulfonyl (**17e**), and pyridyl (**17f**), were well tolerated. In addition to aryl aldehydes, aromatic ketoesters (**19**) also were appropriate coupling partners in this reaction, affording β-amino acids **20** in moderate yields (52-55%, Scheme 7A) and trace diastereoselectivity. Moreover, benzyl bromides **21** also delivered corresponding products **22** in relatively lower yields under the modified reaction conditions (37-40%, Scheme 7B). Successful implementation of these reactions suggests that this strategy would be useful for achieving various other remote difunctionalizations of alkenes.

In order to validate the proposed reaction mechanism, we conducted density functional theory (DFT) calculations at the M06-2X/def2-TZVP/SMD(DMAc)/B3LYP/def2-SVP level of theory.[15] As shown in Figure 1, the trifluoromethylsulfinate (**CP1**) can undergo single-electron transfer (SET) with the excited Ir(III)-photocatalyst to deliver a CF_3SO_2 radical (**CP2**). Cleavage of the C–S bond then would readily generate trifluoromethyl radical (**CP3**) with release of a gaseous SO_2 molecule. Three possible pathways were duly considered in the reaction between CF_3 radical (**CP3**) and substrate **1a**, including radical addition to the C=C bond (black line), hydrogen atom abstraction of the benzylic C−H (blue line), and radical type substitution with the arene (red line). DFT calculations determined that the activation free energy of radical addition to the C=C bond via transition state **TS1** was only 8.6 kcal/mol, which was much lower than that found for the other two processes via transition state **TS4** or **TS5**. This radical addition will generate a new C–C covalent bond in alkyl radical species **I**, which is an irreversible exergonic process (29.8 kcal/mol). The alkyl radical **I** can undergo a 1,5-HAT process via transition state **TS2** with an energy barrier of 12.7 kcal/mol to generate a stabilized benzylic radical **II**. Then the radical **II** can be reduced by Ir(II) to the benzylic carbanion **III** in an event that was calculated to be exergonic by 12.5 kcal/mol. Subsequently, an intermolecular nucleophilic attack of **III** to CO_2 will take place via transition state **TS3** and a free energy barrier of only 3.4 kcal/mol to form carboxylate species **CP4**. In this process, the 1,5-HAT is considered to be the rate-limiting step with an energy barrier of only 12.7 kcal/mol. The computational predictions are consistent with the experimentally observed KIE values of 4.0 and 1.5 (Scheme 5C and 5D).

To evaluate the influence of different substitutions on the reactivity, we further examined the 1,5-HAT process of two other substrates. As shown in Figure S1b and S1c, the calculated free energy barriers of 1,5-HAT for *ortho*-allylethylbenzene **23** and amide **24** were 15.1 and 24.3 kcal/mol, respectively. Both of these values are higher than that calculated for alkyl radical species **I** (12.7 kcal/mol). These results revealed that the stabilization of the carbon-centered radical was contributed by both amino group and the conjugative phenyl ring, the latter of which is considered to be the dominant factor.

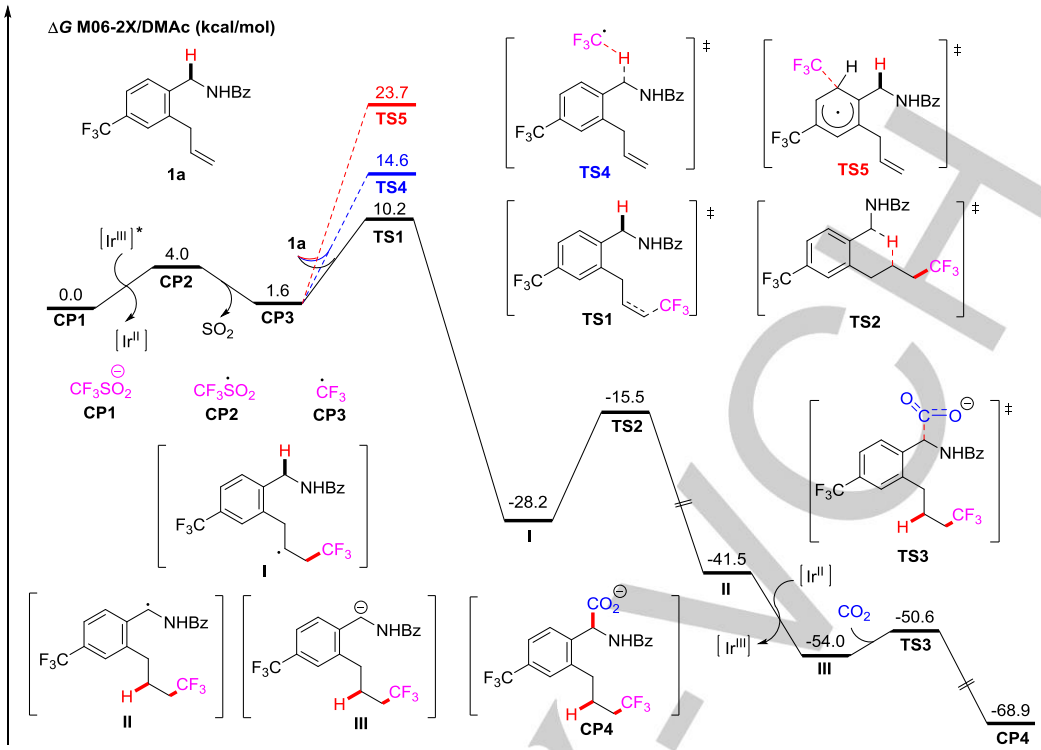


Figure 1. Free-energy profiles for the remote difunctionalizing carboxylation of unactivated alkenes. The values have been given in the unit of kcal/mol and represent the relative free energies calculated using the M06-2x method in DMAc solvent.

Conclusion

In summary, we have developed the first visible-light photoredox-catalyzed remote difunctionalization of unactivated alkenes with CO_2. In contrast to previous strategies via direct coupling or single-electron oxidation of radical intermediates generated from 1,5-HAT process, our experimental and computational investigations strongly indicate that our transformation involves the single electron reduction of the benzylic radicals to the corresponding carbanions, which further undergo nucleophilic attack on CO_2 to generate carboxylates. This strategy provides a facile method to synthesize a series of carboxylic acids, such as non-natural α-amino acids, bearing valuable fluorine- or phosphorus-containing functional groups, and it features mild reaction conditions, broad substrate scope, and good functional group tolerance. Moreover, this tactic can be extended to different electrophiles, including aldehydes, ketones, and benzylic bromides, allowing for the construction of multifunctional amino acids or alcohols. Further application of this strategy and biological activity testing for the novel small molecules that it generates are underway in our labs.

Acknowledgements

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Conflict of interest

The authors declare the following competing financial interest(s): A Chinese Patent on this work has been applied with the number 202010751742.3.

Keywords: visible-light photoredox catalysis · remote difunctionalization · unactivated alkene · carbon dioxide · α-amino acid

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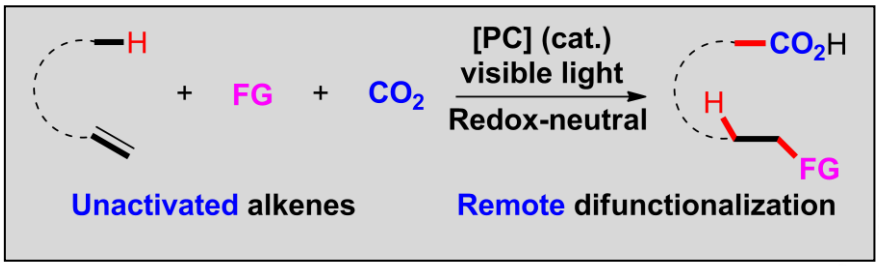
Visible-Light Photoredox-Catalyzed Remote Difunctionalizing Carboxylation of Unactivated Alkenes with CO_2



Herein, we report the first remote difunctionalization of unactivated alkenes with CO_2 via visible-light photoredox catalysis. Mechanistic studies indicate that 1,5-hydrogen atom transfer process is the rate-limiting step and reduction of radical intermediates generates the corresponding carbanions. Other electrophiles, including aldehydes, ketones and benzylic bromides, are also applicable in this process, demonstrating a general strategy for redox-neutral remote difunctionalization of unactivated alkenes.