Photocarboxylation of Benzylic C–H Bonds

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Supporting Information

ABSTRACT: The carboxylation of sp³-hybridized C–H bonds with CO₂ is a challenging transformation. Herein, we report a visible-light-mediated carboxylation of benzylic C–H bonds with CO₂ into 2-arylpionic acids under metal-free conditions. Photo-oxidized trisopropylsilanethiol was used as the hydrogen atom transfer catalyst to afford a benzylic radical that accepts an electron from the reduced form of 2,3,4,6-tetra(9H-carbazol-9-yl)-5-(1-phenylethyl)benzonitrile generated in situ. The resulting benzylic carbonion reacts with CO₂ to generate the corresponding carboxylic acid after protonation. The reaction proceeded without the addition of any sacrificial electron donor, electron acceptor or stoichiometric additives. Moderate to good yields of the desired products were obtained in a broad substrate scope. Several drugs were successfully synthesized using the novel strategy.

Environmental concerns and the quest for chemical energy storage have boosted the search for new applications of carbon dioxide (CO₂) beyond its current use for the production of industrial chemicals. Obviously, utilization of CO₂ would provide an ideal, but challenging renewable one-carbon (C1) building block in organic synthesis. In particular, one of these intriguing transformations of CO₂ is the carboxylation of carbon nucleophiles, offering a straightforward access to carboxylic acid derivatives. Compared to using prefunctionalized starting materials, direct activation of C–H bonds and subsequent carboxylation represents an attractive and promising strategy for such CO₂ reactions as the number of steps to the target molecules is reduced, resulting in lower cost and less waste. Due to their inherent acidity, carboxylation of sp C–H bonds with CO₂ is well developed via C–Cu or C–Ag intermediates in the presence of a suitable base. Likewise, sp²–C–H bonds were carboxylated with CO₂ via deprotonation of heterocycles with low pKa values for subsequent Au or Cu metalation, or via the coordination with a directing-group to generate C–Rh or C–Pd intermediates.

Although significant progress has been made for sp and sp³ C–H bonds, direct carboxylation of sp³ C–H bonds with CO₂ remains to be less explored. Murakami and co-workers initially reported the direct carboxylation of benzylic sp³ C–H bonds by using ortho-carbonyl directing groups, which can be excited with UV light (Scheme 1, eq 1). Later, they disclosed the carboxylation of an allylic C–H bond of simple alkenes catalyzed by a ketone and a copper complex under UV irradiation and high temperature. However, catalyst turnover numbers were low (Scheme 1, eq 2). Jamison and co-workers employed a photoredox strategy to realize carboxylation of α-amino sp³ C–H bonds through the cross-coupling between an α-amino radical and a radical anion CO₂, affording an excellent approach to the synthesis of α-amino acids (Scheme 1, eq 3). Notably, UV irradiation was necessary for the above presented systems and some require the addition of stoichiometric amounts of additives. To the best of our knowledge, visible-light-mediated direct carboxylation of sp³ C–H bonds has not been reported to date. Herein, we disclose a novel way for the carboxylation of benzylic sp³ C–H bonds with CO₂ under visible light irradiation and a catalytic amount of photosensitizer and hydrogen atom transfer (HAT) catalyst (Scheme 1, eq 4).

Recently, we reported the carboxylation of (pseudo)halides and the hydrocarboxylation of styrenes with CO₂ by dual visible-light-nickel catalysis. Considering the fact that an alkyl radical can be captured by a Ni⁰ intermediate, which has been proposed as an active species for carboxylation with CO₂, we envisioned a photoredox strategy involving hydrogen atom transfer (HAT) to realize C–H bond carboxylation with CO₂. We selected 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) and LNiB₃ (L = neocuproine) as the photosensitizer and catalyst, respectively. Trisopropylsilanethiol (HAT1) was added as the HAT catalyst and ethylbenzene was used as the model substrate, because the product structural motif is found in some bioactive molecules.

Supporting Information

Scheme 1. Direct Carboxylation of sp³ C–H Bond with CO₂ by Photocatalysis

Previous works:

![Scheme 1. Direct Carboxylation of sp³ C–H Bond with CO₂ by Photocatalysis](https://pubs.acs.org/doi/abs/10.1021/jacs.9b05360)

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such as Ibuprofen, Naproxen and Flurbiprofen. Although an initial attempt did not yield the desired product, encouragingly we found that 2-phenylpropionic acid was formed in the absence of LNiBr2 (L = neocuproine), albeit in low yield (Table 1, entry 1). Next, different HAT catalysts were investigated, where (3-mercaptopropyl)trimethoxysilane (HAT6) showed comparable catalytic efficiency to HAT1, while other HAT catalysts were not effective (Table 1, entries 1–9). Solvent screening revealed that dimethylformamide (DMF) was the best choice for the formation of 2-phenylpropionic acid (Table S1, entries 1–4). Increasing the amount of photosensitizer slightly promoted the conversion of the starting material, as well as the generation of the final product (Table 1, entries 10–15), while a further increase proved to be not beneficial (Table 1, entry 16). In comparison with 4CzIPN, no better results were obtained when Ir photosensitizers or other derivatives of 4CzIPN were examined (Table S1, entries 5–11). To our delight, lowering the reaction temperature increased the yield to 40% (Table 1, entry 17).

Importantly, 48% yield of product was generated when high power blue light-emitting diodes (LEDs) were used (Table 1, entry 18). Further experiments were conducted to examine the influence of the CO2 pressure. Improved yields were obtained when the reaction vial was pressurized to 4 atm of CO2 by injection (Table 1, entries 19–22). Finally, control experiments in the absence of HAT1, 4CzIPN and light, respectively, gave no detectable products, confirming that each component is essential to the success of this transformation (Table 1, entries 23–25).

With the optimized reaction conditions in hand, we then examined the carboxylation of other benzylic C–H bonds using our catalytic system. As shown in Table 2, a variety of 2-arylpropionic acids with moderate to higher yields was obtained. Compared to para-substituted starting materials, the same substrates at meta- or ortho-position gave higher yields of the desired products (2b–2f). It is noteworthy that 4CzIPN (Ered = −1.21 V vs SCE)11 should be replaced by 3DPAFIPN (Ered = −1.59 V vs SCE)12 when 4-ethyltoluene was used as the substrate, which can be explained by an increased reduction potential of the benzylic radical due to the methyl group in para-position (2d). Similarly, we employed 3DPA2FBN (Ered = −1.92 V vs SCE)12 as the photosensitizer for the carboxylation of 4-ethylanisole (2f). A range of functional groups including fluoro (2g), chloro (2h), amide (2i), ester (2j) and acetal (2k) are tolerated, providing the basis for subsequent conversion of the corresponding products into more complex compounds. Particularly, substrates bearing 2-phenyl, 4-phenyl or 4-pyrazolyl react with CO2 effectively and afford carboxylic acids in good to excellent yields (2l, 2m and 2n). However, aldehydes and ketones and substrates containing bromo or iodo substituents are not compatible with the present protocol (Table S2). The reaction gave comparable product yields regardless of the alkyl chain length (2o, 2p and 2q).

In the presence of more than one benzylic C–H site within the substrate, monocarboxylated acids were formed exclusively, where reactions using bibenzyl and 9,10-dihydroanthracene performed better than reactions employing acenaphthene and 9,10-dihydronaphthanthrene (2r, 2s, 2t and 2u). The carboxylation at the benzylic position of heteroarenes also proceeded well: 42% yield of 2-(thiophen-2-yl)propanoic acid were isolated by using 3DPAFIPN as the photosensitizer, while 4CzIPN promoted the carboxylation of 2-ethylbenzofuran to give 85% yield of 2-(benzofuran-2-yl)propanoic acid (2v and 2w). Furthermore, we examined the carboxylation of saturated oxygen heterocycles. It is obvious that chromane showed higher efficiency than 2,3-dihydrobenzofuran (2x and 2y). Finally, we applied our protocol to synthesize several drugs that contain the structure of 2-phenylpropionic acid. Gratifyingly, Fenoprofen and Flurbiprofen were obtained in 53% and 76% yields, respectively (2aa and 2ab). For the substrate 1-ethyl-4-isobutylbenzene, the highly selective formation of Ilubprofen was observed; we attribute this

### Table 1. Optimization of Conditions

| Entry | Catalyst | Amount of 4CzIPN | CO2 | Conversion (%) | Yield (%) |
|-------|----------|-----------------|-----|---------------|----------|
| 1<sup>ac</sup> | HAT1 | 1 mol % | balloon | 18 | 11 |
| 2 | HAT2 | 1 mol % | balloon | 0 | 0 |
| 3 | HAT3 | 1 mol % | balloon | 0 | 0 |
| 4 | HAT4 | 1 mol % | balloon | 3 | 1 |
| 5 | HAT5 | 1 mol % | balloon | 0 | 0 |
| 6 | HAT6 | 1 mol % | balloon | 13 | 6 |
| 7 | HAT7 | 1 mol % | balloon | 0 | 0 |
| 8 | HAT8 | 1 mol % | balloon | 0 | 0 |
| 9 | HAT9 | 1 mol % | balloon | 0 | 0 |
| 10 | HAT10 | 1 mol % | balloon | 18 | 14 |
| 11 | HAT11 | 2 mol % | balloon | 29 | 20 |
| 12 | HAT12 | 3 mol % | balloon | 35 | 23 |
| 13 | HAT13 | 4 mol % | balloon | 43 | 27 |
| 14 | HAT14 | 5 mol % | balloon | 45 | 31 |
| 15 | HAT15 | 6 mol % | balloon | 48 | 32 |
| 16 | HAT16 | 7 mol % | balloon | 49 | 30 |
| 17 | HAT17 | 6 mol % | balloon | 59 | 40 |
| 18<sup>ac</sup> | HAT18 | 6 mol % | balloon | 89 | 48 |
| 19<sup>ac</sup> | HAT19 | 6 mol % | 2 atm | 90 | 52 |
| 20<sup>ac</sup> | HAT20 | 6 mol % | 3 atm | 91 | 54 |
| 21<sup>ac</sup> | HAT21 | 6 mol % | 4 atm | 92 | 57 (53) |
| 22<sup>ac</sup> | HAT22 | 6 mol % | 5 atm | 92 | 57 |
| 23<sup>c</sup> | – | 6 mol % | 4 atm | 0 | 0 |
| 24<sup>ac</sup> | HAT24 | – | 4 atm | 0 | 0 |
| 25<sup>ac</sup> | HAT25 | 6 mol % | 4 atm | 0 | 0 |

<sup>a</sup>Reaction conditions: Unless otherwise noted, all reactions were carried out with ethylbenzene (0.2 mmol), 4CzIPN, thiol catalyst (0.02 mmol) in DMF (2 mL), irradiation with blue LEDs at 25 °C under CO2 atmosphere for 24 h. <sup>ac</sup>Gas chromatography–flame ionization detector conversion using 1,3,5-trimethoxysilane as an internal standard. <sup>ace</sup>When nuclear magnetic resonance yield using 1,3,5-trimethoxysilane as an internal standard; yield of isolated product is given in parentheses.

<sup>b</sup>When 0.04 mmol LNiBr2 (L = neocuproine) was added, no desired product was observed. <sup>c</sup>High power blue LEDs were used. 2The reaction was carried out at 0 °C. 2The reaction was carried out in the dark.
To obtain mechanistic insights, we initially carried out radical inhibition experiments. No product was formed when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene was added to the reaction, suggesting the presence of radical intermediates during the process (Scheme S1). When d7-DMF or 1m-d2 was used, there was no H/D scrambling within the product, as well as in the recycled starting material, which indicates that hydrogen atoms of DMF do not take part in the reaction and the deprotonation of the starting material is irreversible (Scheme 2, eqs 1 and 2).

Moreover, a kinetic isotope effect was observed in the intramolecular and intermolecular competition experiments, demonstrating that the C−H bond cleavage is involved in the rate-determining step (Scheme 2, eqs 3 and 4).

To investigate the photocatalytic decarboxylation for benzylation of aliphatic aldehydes, we found that one cyano (CN) group of 4CzIPN was substituted by a benzyl (Bn) moiety to generate 3-benzyl-2,4,5,6-tetra(9H-carbazol-9-yl)benzonitrile (4CzBnBN), which was proposed as the main active catalyst for carbanion generation. Similarly, when ethylbenzene was used as the starting material, the formation of 2,3,4,6-tetra(9H-carbazol-9-yl)-5-(1-phenylethyl)benzonitrile (4CzPEBN) was detected. Considering the above-mentioned observations, a catalytic cycle for the carboxylation of benzylic C−H bonds is proposed. The reductive quenching of the visible-light excited 4CzPEBN* (E1/2(P+/P* ) = +1.19 V vs SCE, Figure S1 and S2) by triisopropylsilanethiol (E1/2ox = +0.28 V vs SCE) via single electron transfer gives rise to a thiol radical cation R-SH+ (R = iPr3Si) together with the reduced form of the photosensitizer, i.e., 4CzPEBN−. Subsequently, R-SH+ is deprotonated to yield an electrophilic thiyl radical R-S (BDE(S-H) = 88.2 kcal·mol−1), which further abstracts a hydrogen atom from the benzylic position of ethylbenzene (BDE(C-H) = 85.4 kcal·mol−1) to close the organocatalytic cycle and produce a benzylic radical. The previously formed 4CzPEBN− (E1/2(P/P−) = −1.69 V vs SCE, Figure S1) should be able to reduce the benzylic radical (E1/2red = −1.60 V vs SCE for the phenylethyl radical) to accomplish the photoredox catalytic cycle and afford the carbanion of ethylbenzene. It is well-known that this anion can be readily captured by CO2, generating the final product after protonation. Overall, CO2 formally inserts into the benzylic

Table 2. Scope of Carboxylation of Benzylic C−H bond with CO2

| Reaction | Product | Yield (%) |
|----------|---------|-----------|
| 2a | COOH | 53% yield |
| 2b, o-Me | COOH | 72% yield |
| 2e, m-Me | COOH | 61% yield |
| 2f, o-MeO | COOH | 52% yield |
| 2g | COOH | 51% yield |
| 2h | COOH | 49% yield |
| 2i | COOH | 49% yield |
| 2j | COOH | 56% yield |
| 2k | COOH | 64% yield |
| 2l | COOH | 89% yield |
| 2m, o-Me | COOH | 76% yield |
| 2n, m-Me | COOH | 85% yield |
| 2o, o-MeO | COOH | 55% yield |
| 2p, o-Me | COOH | 53% yield |
| 2q, o-Me | COOH | 50% yield |
| 2r, o-Me | COOH | 67% yield |
| 2s, o-Me | COOH | 77% yield |
| 2t, o-Me | COOH | 43% yield |
| 2u, o-Me | COOH | 43% yield |
| 2v, o-Me | COOH | 42% yield |
| 2w, o-Me | COOH | 65% yield |
| 2x, o-Me | COOH | 35% yield |
| 2y, o-Me | COOH | 81% yield |

All reactions were carried out with ethylbenzene derivatives (0.2 mmol), Pr3SiSH (0.04 mmol), 4CzIPN (0.012 mmol), and 4 atm of CO2 in anhydrous DMF (2 mL), irradiation with blue LEDs at 0 °C for 24 h. 4CzIPN was replaced by 3DPAFIPN. 4CzIPN was replaced by 3DPA2FBN. 3DPAFIPN: 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile. 3DPA2FBN: 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile.
C–H bond without the addition of any sacrificial reagent (Scheme 3).

Scheme 3. Plausible Reaction Mechanism

To summarize, we have designed a novel and atom-economic strategy for the carboxylation of C–H bonds with CO$_2$. An unprecedented visible-light-mediated benzylic C–H bond carboxylation was achieved via the synergistic merger of photoredox and organocatalysis. It is noteworthy that this reaction proceeds smoothly without adding any metal reagent, sacrificial electron donor, electron acceptor or stoichiometric additive, affording the desired carboxylic acids in moderate to excellent yields with a broad substrate scope. Particularly, our protocol is applicable to the synthesis of several drugs, such as Fenoprofen, Flurbiprofen and Naproxen. Further studies aiming to achieve other types of C–H bond carboxylation by this strategy are currently under investigation.

ASSOCIATED CONTENT

† Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05360.

Experimental procedures, methods and product characterization (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Braunstein, P.; Matt, D.; Nobel, D. Reactions of carbon dioxide with carbon–carbon bond formation catalyzed by transition-metal complexes. Chem. Rev. 1988, 88, 747–794. (b) Sakakura, T.; Choi, J.-C.; Yasuda, H. Transformation of Carbon Dioxide. Chem. Rev. 2007, 107, 2365. (c) Sakakura, T.; Kohno, K. The synthesis of organic carbonates from carbon dioxide. Chem. Commun. 2009, 1312. (d) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. Using carbon dioxide as a building block in organic synthesis. Nat. Commun. 2015, 6, 5933. (e) Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin, R. Transition-Metal-Catalyzed Carboxylation Reactions with Carbon Dioxide. Angew. Chem., Int. Ed. 2018, 57, 15948. (f) Wang, L.; Sun, W.; Liu, C. Recent Advances in Homogeneous Carboxylation Using CO$_2$ as CO Surrogate. Chin. J. Chem. 2018, 36, 353. (g) Zhang, Z.; Ye, J.-H.; Wu, D.-S.; Zhou, Y.-Q.; Yu, D.-G. Synthesis of Oxazolidin-2-ones from Unsaturated Amines with CO$_2$ by Using Homogeneous Catalysis. Chem. - Asian J. 2018, 13, 2292.

(2) (a) Huang, K.; Sun, C.-L.; Shi, Z.-J. Transition-metal-catalyzed C-C bond formation through the fixation of carbon dioxide. Chem. Soc. Rev. 2011, 40, 2435. (b) Martin, R.; Klei, A. W. Myth or Reality? Fixation of Carbon Dioxide into Complex Organic Matter under Mild Conditions. ChemSusChem 2011, 4, 1259. (c) Tsuji, Y.; Fujihara, T. Carbon dioxide as a carbon source in organic transformation: carbon-carbon bond forming reactions by transition-metal catalysts. Chem. Commun. 2012, 48, 9956. (d) Börjesson, M.; Moragas, T.; Gallego, D.; Martin, R. Metal-Catalyzed Carboxylation of Organic (Pseudo)-halides with CO$_2$. ACS Catal. 2016, 6, 6739. (e) Cao, Y.; He, X.; Wang, N.; Li, H.-R.; He, L.-N. Photochemical and Electrochemical Carbon Dioxide Utilization with Organic Compounds. Chin. J. Chem. 2018, 36, 644. (f) Yeung, C. S. Photoredox Catalysis as a Strategy for CO$_2$ Incorporation: Direct Access to Carboxylic Acids from a Renewable Feedstock. Angew. Chem., Int. Ed. 2019, 58, 5492.

(3) (a) Yu, D. Y.; Zhang, Y. G. Copper- and copper-N-heterocyclic carbene-catalyzed C-H activating carboxylation of terminal alkynes with CO$_2$ at ambient conditions. Proc. Natl. Acad. Sci. U. S. A. 2010, 107, 20144. (b) Zhang, X.; Zhang, W.-Z.; Ren, X.; Zhang, L.-L.; Lu, X.-B. Ligand-Free Ag(I)-Catalyzed Carboxylation of Terminal Alkynes with CO$_2$. Org. Lett. 2011, 13, 2402.

(4) (a) Boogaerts, I. I. F.; Nolan, S. P. Carboxylation of C-H Bonds Using N-Heterocyclic Carbene Gold(I) Complexes. J. Am. Chem. Soc. 2010, 132, 8858. (b) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. Carboxylation of N-H-C-H Bonds Using N-Heterocyclic Carbene Copper(I) Complexes. Angew. Chem., Int. Ed. 2010, 49, 8674.

(5) (a) Mizuno, H.; Takaya, J.; Iwasawa, N. Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO$_2$ via Chelation-Assisted C-H Bond Activation. J. Am. Chem. Soc. 2011, 133, 1251. (b) Sasano, K.; Takaya, J.; Iwasawa, N. Palladium(I)-Catalyzed Direct Carboxylation of Alkenyl C-H Bonds with CO$_2$. J. Am. Chem. Soc. 2013, 135, 10954. (c) Suga, T.; Mizuno, H.; Takaya, J.; Iwasawa, N. Palladium(I)-Catalyzed Direct Carboxylation of Alkenyl C-H Bonds with CO$_2$. J. Am. Chem. Soc. 2013, 135, 10954. (d) Suga, T.; Mizuno, H.; Takaya, J.; Iwasawa, N. Palladium(I)-Catalyzed Direct Carboxylation of Alkenyl C-H Bonds with CO$_2$. J. Am. Chem. Soc. 2013, 135, 10954.

(6) (a) Song, L.; Tao, G.-M.; Zhou, W.-J.; Ye, J.-H.; Zhang, Z.; Tian, X.-Y.; Li, J.; Yu, D.-G. Pd-catalyzed carboxylation of aryl C-H bonds in benzenes with CO$_2$. Org. Chem. Front. 2018, 5, 2086. (e) Song, L.; Zhou, L.; Zhang, Z.; Ye, J.-H.; Yan, S.-S.; Han, J.-L.; Yin, Z.-B.; Lan, Y.; Yu, D.-G. Catalytic Lactonization of Unactivated Aryl C-H Bonds with CO$_2$. J. Chem. Soc. Perkin Trans. 1 2018, 20, 3776. (f) Fu, L.; Li, S.; Cai, Z.; Ding, Y.; Guo, X.-Q.; Zhou, L.-P.; Yuan, D.; Sun, Q.-F.; Li, G. Ligand-enabled site-selectivity in a versatile rhodium(II)-catalysed aryl C-H carboxylation with CO$_2$. Nat. Catal. 2018, 1, 469.
