

Photocarboxylation of Benzylic C–H Bonds

Qing-Yuan Meng,^{1b} Tobias E. Schirmer, Anna Lucia Berger, Karsten Donabauer, and Burkhard König*^{1b}

Institute of Organic Chemistry, Faculty of Chemistry and Pharmacy, University of Regensburg, D-93040 Regensburg, Germany

Supporting Information

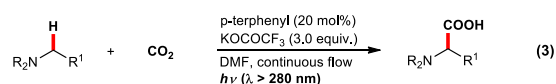
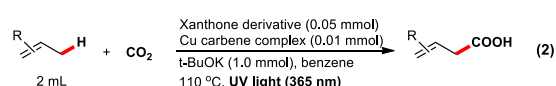
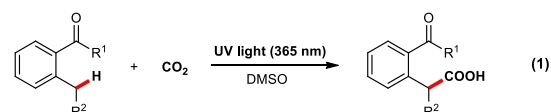
ABSTRACT: The carboxylation of sp^3 -hybridized C–H bonds with CO_2 is a challenging transformation. Herein, we report a visible-light-mediated carboxylation of benzylic C–H bonds with CO_2 into 2-arylpropionic acids under metal-free conditions. Photo-oxidized triisopropylsilanethiol was used as the 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)benzotrile generated *in situ*. The resulting benzylic carbanion reacts with CO_2 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 (CO_2) beyond its current use for the production of industrial chemicals. Obviously, utilization of CO_2 would provide an ideal, but challenging renewable one-carbon (C1) building block in organic synthesis.¹ In particular, one of these intriguing transformations of CO_2 is the carboxylation of carbon nucleophiles, offering a straightforward access to carboxylic acid derivatives.² Compared to using prefunctionalized starting materials, direct activation of C–H bonds and subsequent carboxylation represents an attractive and promising strategy for such CO_2 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 CO_2 is well developed via C–Cu or C–Ag intermediates in the presence of a suitable base.³ Likewise, sp^2 C–H bonds were carboxylated with CO_2 via deprotonation of heterocycles with low pK_a values for subsequent Au or Cu metalation,⁴ or via the coordination with a directing-group to generate C–Rh or C–Pd intermediates.^{5,6}

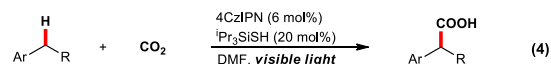
Although significant progress has been made for sp and sp^2 C–H bonds, direct carboxylation of sp^3 C–H bonds with CO_2 remains to be less explored.⁷ Murakami and co-workers initially reported the direct carboxylation of benzylic sp^3 C–H bonds by using *ortho*-carbonyl directing groups, which can be excited with UV light (Scheme 1, eq 1).^{7a} 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).^{7b} Jamison and co-workers employed a photoredox strategy to realize carbox-

Scheme 1. Direct Carboxylation of sp^3 C–H Bond with CO_2 by Photocatalysis

Previous works:



This work:



ylation of α -amino sp^3 C–H bonds through the cross-coupling between an α -amino radical and a radical anion $CO_2^{\bullet-}$, affording an excellent approach to the synthesis of α -amino acids (Scheme 1, eq 3).^{7c} 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 sp^3 C–H bonds has not been reported to date. Herein, we disclose a novel way for the carboxylation of benzylic sp^3 C–H bonds with CO_2 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 CO_2 by dual visible-light-nickel catalysis.⁸ Considering the fact that an alkyl radical can be captured by a Ni^0 species⁹ affording a Ni^I intermediate, which has been proposed as an active species for carboxylation with CO_2 ,¹⁰ we envisioned a photoredox strategy involving hydrogen atom transfer (HAT) to realize C–H bond carboxylation with CO_2 . We selected 2,4,5,6-tetra(carbazol-9-yl)isophthalonitrile (4CzIPN) and $LNiBr_2$ (L = neocuproine) as the photosensitizer and catalyst, respectively. Triisopropylsilanethiol (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,

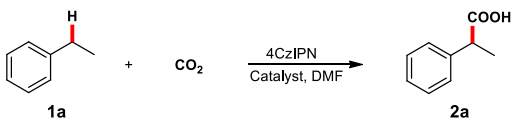
Received: May 19, 2019

Published: July 8, 2019

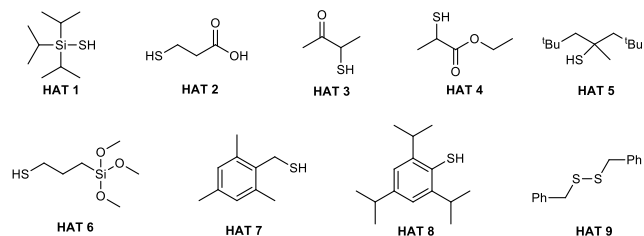
such as Ibuprofen, Naproxen and Flurbiprofen. Although an initial attempt did not yield the desired product, encouragingly we found that 2-phenylpropionic acid was formed in the absence of LNiBr_2 ($\text{L} = \text{neocuproine}$), albeit in low yield (Table 1, entry 1). Next, different thio HAT catalysts 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 CO_2 pressure. Improved yields were obtained when the reaction vial was pressurized to 4 atm of CO_2 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).

Table 1. Optimization of Conditions^a

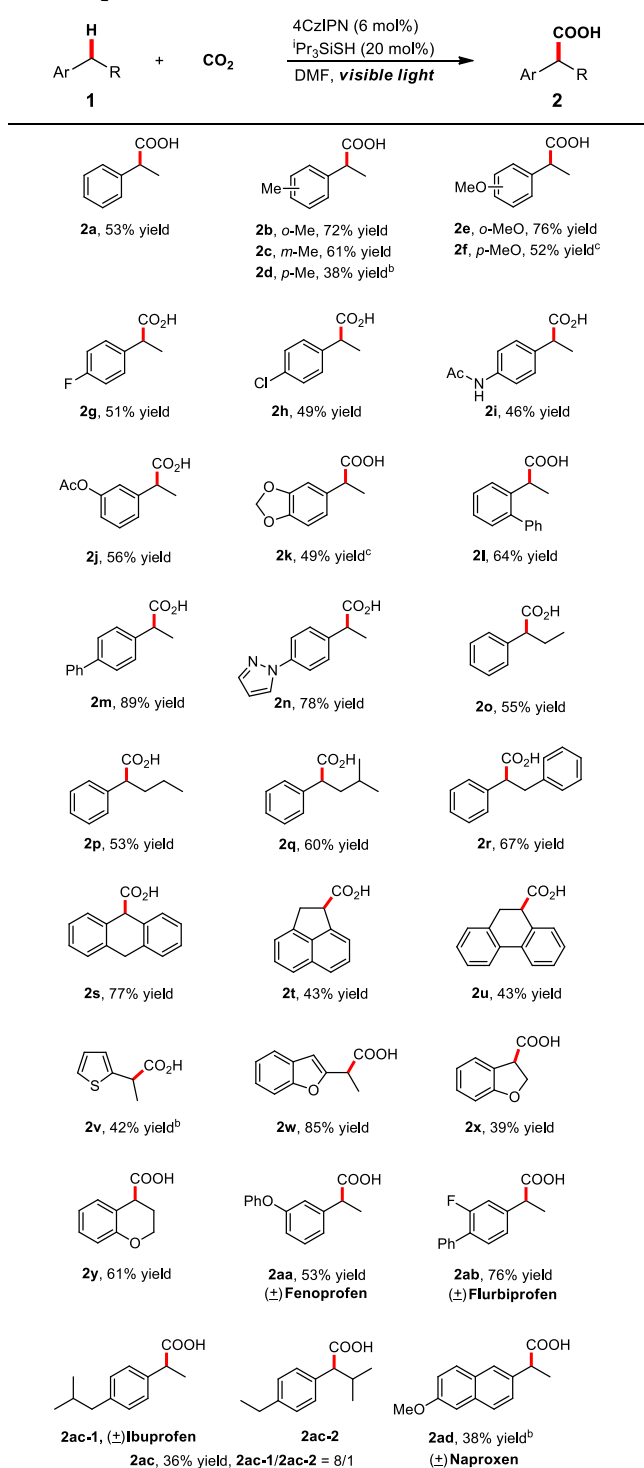


Entry	Catalyst	Amount of 4CzIPN	CO_2	Conversion (%) ^b	Yield (%) ^c
1 ^d	HAT1	1 mol %	balloon	18	11
2	HAT2	1 mol %	balloon	0	0
3	HAT3	1 mol %	balloon	0	0
4	HAT4	1 mol %	balloon	3	1
5	HAT5	1 mol %	balloon	0	0
6	HAT6	1 mol %	balloon	13	6
7	HAT7	1 mol %	balloon	0	0
8	HAT8	1 mol %	balloon	0	0
9	HAT9	1 mol %	balloon	0	0
10 ^e	HAT1	1 mol %	balloon	18	14
11 ^e	HAT1	2 mol %	balloon	29	20
12 ^e	HAT1	3 mol %	balloon	35	23
13 ^e	HAT1	4 mol %	balloon	43	27
14 ^e	HAT1	5 mol %	balloon	45	31
15 ^e	HAT1	6 mol %	balloon	48	32
16 ^e	HAT1	7 mol %	balloon	49	30
17 ^{e,f}	HAT1	6 mol %	balloon	59	40
18 ^{e,f,g}	HAT1	6 mol %	balloon	89	48
19 ^{e,f,g}	HAT1	6 mol %	2 atm.	90	52
20 ^{e,f,g}	HAT1	6 mol %	3 atm.	91	54
21 ^{e,f,g}	HAT1	6 mol %	4 atm.	92	57 (53)
22 ^{e,f,g}	HAT1	6 mol %	5 atm.	92	57
23 ^{f,g}	–	6 mol %	4 atm.	0	0
24 ^{e,f,g}	HAT1	–	4 atm.	0	0
25 ^{e,f,h}	HAT1	6 mol %	4 atm.	0	0



^aReaction 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 CO_2 atmosphere for 24 h. ^bGas chromatography–flame ionization detector conversion using 1,3,5-trimethoxybenzene as an internal standard. ^c¹H nuclear magnetic resonance yield using 1,3,5-trimethoxybenzene as an internal standard; yield of isolated product is given in parentheses. ^dWhen 0.04 mmol LNiBr_2 ($\text{L} = \text{neocuproine}$) was added, no desired product was observed. ^e0.04 mmol $^3\text{Pr}_3\text{SiSH}$ was added. ^fThe reaction was carried out at 0 °C. ^gHigh power blue LEDs were used. ^hThe reaction was carried out in the dark.

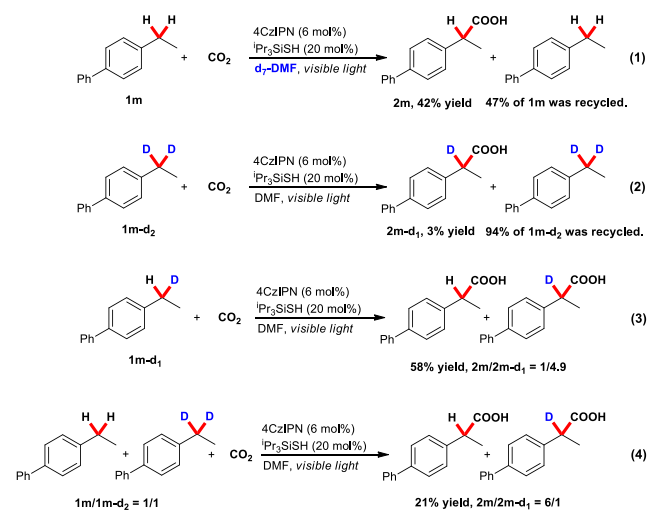
With the optimized reaction conditions in hand, we then explored the carboxylation of other benzylic C–H bonds using our catalytic system. As shown in Table 2, a variety of 2-arylpropionic acids with moderate to higher yields was obtained. Compared to *para*-substituted starting materials, the same substituents at *meta*- or *ortho*-position gave higher yields of the desired products (2b–2f). It is noteworthy that 4CzIPN ($E_{1/2}^{\text{red}} = -1.21 \text{ V vs SCE}$)¹¹ should be replaced by 3DPAFIPN ($E_{1/2}^{\text{red}} = -1.59 \text{ V vs SCE}$)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 ($E_{1/2}^{\text{red}} = -1.92 \text{ V vs SCE}$)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 CO_2 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-dihydroohenanthrene (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 Ibuprofen was observed; we attribute this

Table 2. Scope of Carboxylation of Benzylic C–H bond with CO₂^a

^aAll reactions were carried out with ethylbenzene derivatives (0.2 mmol), ⁱPr₃SiSH (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. ^b4CzIPN was replaced by 3DPAFIPN. ^c4CzIPN was replaced by 3DPA2FBN. 3DPAFIPN: 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile. 3DPA2FBN: 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile.

outcome to steric effects (**2ac**). In addition, using 3DPAFIPN promoted the generation of Naproxen in 38% yield (**2ad**).

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 *d*₇-DMF or **1m-d**₂ 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).

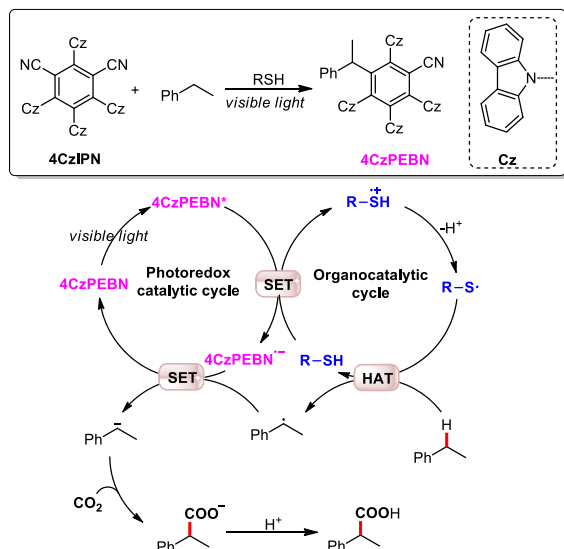
Scheme 2. Deuterium-Labeling Experiments

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).¹³

Investigating 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.¹⁴ 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* ($E_{1/2}(\text{P}^+/\text{P}^*) = +1.19 \text{ V vs SCE}$, Figure S1 and S2) by triisopropylsilanethiol ($E_{1/2}^{\text{ox}} = +0.28 \text{ V vs SCE}$)¹⁵ 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),¹⁵ which further abstracts a hydrogen atom from the benzylic position of ethylbenzene (BDE(C-H) = 85.4 kcal·mol⁻¹)¹⁶ to close the organocatalytic cycle and produce a benzylic radical. The previously formed 4CzPEBN^{•-} ($E_{1/2}(\text{P}/\text{P}^{\bullet-}) = -1.69 \text{ V vs SCE}$, Figure S1) should be able to reduce the benzylic radical ($E_{1/2}^{\text{red}} = -1.60 \text{ V vs SCE}$ for the phenylethyl radical)¹⁷ to accomplish the photoredox catalytic cycle and afford the carbanion of ethylbenzene. It is well-known that this anion can be readily captured by CO₂,¹⁸ generating the final product after protonation. Overall, CO₂ formally inserts into the benzylic

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 CO₂. 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 Fenopropfen, 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)

■ AUTHOR INFORMATION

Corresponding Author

*burkhard.koenig@ur.de

ORCID

Qing-Yuan Meng: 0000-0002-2611-4271

Burkhard König: 0000-0002-6131-4850

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the German Science Foundation (DFG; KO 1537/18-1) is acknowledged. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 741623). We thank Dr. Rudolf Vasold (University of Regensburg) for his

assistance in gas chromatography–mass spectrometry measurements, Regina Hoheisel (University of Regensburg) for her assistance in cyclic voltammetry measurements, Julia Zach (University of Regensburg) for her assistance in preparing the high power LED setup.

■ 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. (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 Carbonylation Using CO₂ 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 CO₂ 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) Martín, R.; Kleij, 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 CO₂. *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 CO₂ 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 CO₂ at ambient conditions. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20184. (b) Zhang, X.; Zhang, W.-Z.; Ren, X.; Zhang, L.-L.; Lu, X.-B. Ligand-Free Ag(I)-Catalyzed Carboxylation of Terminal Alkynes with CO₂. *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 CO₂ via Chelation-Assisted C-H Bond Activation. *J. Am. Chem. Soc.* **2011**, *133*, 1251. (b) Sasano, K.; Takaya, J.; Iwasawa, N. Palladium(II)-Catalyzed Direct Carboxylation of Alkenyl C-H Bonds with CO₂. *J. Am. Chem. Soc.* **2013**, *135*, 10954. (c) Suga, T.; Mizuno, H.; Takaya, J.; Iwasawa, N. Direct carboxylation of simple arenes with CO₂ through a rhodium-catalyzed C-H bond activation. *Chem. Commun.* **2014**, *50*, 14360. (d) Song, L.; Cao, G.-M.; Zhou, W.-J.; Ye, J.-H.; Zhang, Z.; Tian, X.-Y.; Li, J.; Yu, D.-G. Pd-catalyzed carbonylation of aryl C-H bonds in benzamides with CO₂. *Org. Chem. Front.* **2018**, *5*, 2086. (e) Song, L.; Zhu, 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 CO₂: Experimental and Computational Investigation. *Org. Lett.* **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 CO₂. *Nat. Catal.* **2018**, *1*, 469.

- (6) For other selected examples, see: (a) Vechorkin, O.; Hirt, N.; Hu, X. Carbon Dioxide as the C1 Source for Direct C-H Functionalization of Aromatic Heterocycles. *Org. Lett.* **2010**, *12*, 3567. (b) Tanaka, S.; Watanabe, K.; Tanaka, Y.; Hattori, T. EtAlCl₃/2,6-Disubstituted Pyridine-Mediated Carboxylation of Alkenes with Carbon Dioxide. *Org. Lett.* **2016**, *18*, 2576. (c) Luo, J.; Preciado, S.; Xie, P.; Larrosa, I. Carboxylation of Phenols with CO₂ at Atmospheric Pressure. *Chem. - Eur. J.* **2016**, *22*, 6798. (d) Liu, Q.; Li, M.; Xiong, R.; Mo, F. Direct Carboxylation of the Diazo Group *ipso*-C(sp²)-H bond with Carbon Dioxide: Access to Unsymmetrical Diazomalonates and Derivatives. *Org. Lett.* **2017**, *19*, 6756. (e) Juhl, M.; Lee, J.-W. Umpolung Reactivity of Aldehydes toward Carbon Dioxide. *Angew. Chem., Int. Ed.* **2018**, *57*, 12318. (f) Shigeno, M.; Hanasaka, K.; Sasaki, K.; Nozawa-Kumada, K.; Kondo, Y. Direct Carboxylation of Electron-Rich Heteroarenes Promoted by LiO-tBu with CsF and [18]Crown-6. *Chem. - Eur. J.* **2019**, *25*, 3235.
- (7) (a) Masuda, Y.; Ishida, N.; Murakami, M. Light-Driven Carboxylation of *o*-Alkylphenyl Ketones with CO₂. *J. Am. Chem. Soc.* **2015**, *137*, 14063. (b) Ishida, N.; Masuda, Y.; Uemoto, S.; Murakami, M. A Light/Ketone/Copper System for Carboxylation of Allylic C-H Bonds of Alkenes with CO₂. *Chem. - Eur. J.* **2016**, *22*, 6524. (c) Seo, H.; Katcher, M. H.; Jamison, T. F. Photoredox activation of carbon dioxide for amino acid synthesis in continuous flow. *Nat. Chem.* **2017**, *9*, 453. (d) Gui, Y.-Y.; Zhou, W.-J.; Ye, J.-H.; Yu, D.-G. Photochemical Carboxylation of Activated C(sp³)-H Bonds with CO₂. *ChemSusChem* **2017**, *10*, 1337. (e) Ueno, A.; Takimoto, M.; Hou, Z. Synthesis of 2-aryloxy butenoates by copper-catalysed allylic C-H carboxylation of allyl aryl ethers with carbon dioxide. *Org. Biomol. Chem.* **2017**, *15*, 2370. (f) Michigami, K.; Mita, T.; Sato, Y. Cobalt-Catalyzed Allylic C(sp³)-H Carboxylation with CO₂. *J. Am. Chem. Soc.* **2017**, *139*, 6094.
- (8) (a) Meng, Q.-Y.; Wang, S.; König, B. Carboxylation of Aromatic and Aliphatic Bromides and Triflates with CO₂ by Dual Visible-Light-Nickel Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 13426. (b) Meng, Q.-Y.; Wang, S.; Huff, G. S.; König, B. Ligand-Controlled Regioselective Hydrocarboxylation of Styrenes with CO₂ by Combining Visible Light and Nickel Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 3198.
- (9) (a) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896. (b) Jouffroy, M.; Primer, D. N.; Molander, G. A. Base-Free Photoredox/Nickel Dual-Catalytic Cross-Coupling of Ammonium Alkylsilicates. *J. Am. Chem. Soc.* **2016**, *138*, 475. (c) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. Metallaphotoredox-catalysed sp³-sp³ cross-coupling of carboxylic acids with alkyl halides. *Nature* **2016**, *536*, 322. (d) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective sp³ C-H alkylation via polarity-match-based cross-coupling. *Nature* **2017**, *547*, 79.
- (10) (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. *J. Am. Chem. Soc.* **2012**, *134*, 9106. (b) León, T.; Correa, A.; Martin, R. Ni-Catalyzed Direct Carboxylation of Benzyl Halides with CO₂. *J. Am. Chem. Soc.* **2013**, *135*, 1221. (c) Correa, A.; León, T.; Martin, R. Ni-Catalyzed Carboxylation of C(sp²)- and C(sp³)-O Bonds with CO₂. *J. Am. Chem. Soc.* **2014**, *136*, 1062. (d) Charboneau, D. J.; Brudvig, G. W.; Hazari, N.; Lant, H. M. C.; Saydjari, A. K. Development of an Improved System for the Carboxylation of Aryl Halides through Mechanistic Studies. *ACS Catal.* **2019**, *9*, 3228.
- (11) (a) Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. Highly efficient organic light-emitting diodes from delayed fluorescence. *Nature* **2012**, *492*, 234. (b) Luo, J.; Zhang, J. Donor-Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic C(sp³)-C(sp²) Cross-Coupling. *ACS Catal.* **2016**, *6*, 873.
- (12) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353.
- (13) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.
- (14) Donabauer, K.; Maity, M.; Berger, A. L.; Huff, G. S.; Crespi, S.; König, B. Photocatalytic carbanion generation-benzylation of aliphatic aldehydes to secondary alcohols. *Chem. Sci.* **2019**, *10*, 5162.
- (15) Zhou, R.; Goh, Y. Y.; Liu, H.; Tao, H.; Li, L.; Wu, J. Visible-Light-Mediated Metal-Free Hydrosilylation of Alkenes through Selective Hydrogen Atom Transfer for Si-H Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16621.
- (16) (a) McMillen, D. F.; Golden, D. M. Hydrocarbon Bond Dissociation Energies. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. (b) Cuthbertson, J. D.; MacMillan, D. W. C. The direct arylation of allylic sp³ C-H bonds via organic and photoredox catalysis. *Nature* **2015**, *519*, 74.
- (17) (a) Wayner, D. D. M.; McPhee, D. J.; Griller, D. Oxidation and reduction potentials of transient free radicals. *J. Am. Chem. Soc.* **1988**, *110*, 132. (b) Sim, B. A.; Griller, D.; Wayner, D. D. M. Reduction potentials for substituted benzyl radicals: pKa values for the corresponding toluenes. *J. Am. Chem. Soc.* **1989**, *111*, 754.
- (18) (a) Yatham, V. R.; Shen, Y.; Martin, R. Catalytic Inter-molecular Dicarbofunctionalization of Styrenes with CO₂ and Radical Precursors. *Angew. Chem., Int. Ed.* **2017**, *56*, 10915. (b) Hou, J.; Ee, A.; Cao, H.; Ong, H.-W.; Xu, J.-H.; Wu, J. Visible-Light-Mediated Metal-Free Difunctionalization of Alkenes with CO₂ and Silanes or C(sp³)-H Alkanes. *Angew. Chem., Int. Ed.* **2018**, *57*, 17220. (c) Yoo, W.-J.; Kondo, J.; Rodríguez-Santamaría, J. A.; Nguyen, T. V. Q.; Kobayashi, S. Efficient Synthesis of α -Trifluoromethyl Carboxylic Acids and Esters through Fluorocarboxylation of gem-Difluoroalkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6772.