

Communication

Subscriber access provided by UNIVERSITY OF TOLEDO LIBRARIES

Photocarboxylation of Benzylic C-H bonds

Qing-yuan Meng, Tobias E. Schirmer, Anna Lucia Berger, Karsten Donabauer, and Burkhard König J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.9b05360 • Publication Date (Web): 07 Jul 2019 Downloaded from http://pubs.acs.org on July 7, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Photocarboxylation of Benzylic C-H bonds

Qing-Yuan Meng, Tobias E. Schirmer, Anna Lucia Berger, Karsten Donabauer and Burkhard König*

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

Supporting Information Placeholder

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-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 2.3.4.6tetra(9H-carbazol-9-yl)-5-(1-phenylethyl)benzonitrile

(4CzPEBN) generated in situ. The resulting benzylic carbanion 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 vields 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.1 In particular, one of these intriguing transformations of CO2 is the carboxylation of carbon nucleophiles, offering a straightforward access to derivatives.² Compared to carboxylic acid using prefunctionalized starting materials, direct activation of C-H bonds and subsequent carboxylation represent 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.³ Likewise sp² C-H bonds were carboxylated with CO₂ via deprotonation of heterocycles with low pKa values for subsequent Au or Cu metalation,⁴ or via the coordination with a directing-group to generate C-Rh or C-Pd intermediates.56

Although significant progress has been made for sp and sp² C-H bonds, direct carboxylation of sp³ C-H bonds with CO₂ remains to be less explored.7 Murakami and coworkers 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, equation 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, equation 2).7b Jamison and coworkers employed a photoredox strategy to realize

carboxylation of α -amino sp³ C-H bonds through the crosscoupling 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, equation 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 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, equation 4). Scheme 1. Direct carboxylation of sp³ C-H bond with CO₂





DMF. visible light

Recently, we reported the carboxylation of (pseudo)halides and the hydrocarboxylation of styrenes with CO₂ by dual visible-light-nickel catalysis.8 Considering the fact that an alkyl radical can be captured by a Ni⁰ species⁹ affording a Ni^I intermediate, which has been proposed as an active species for carboxylation with CO₂¹⁰ we envisioned a photoredox strategy involving hydrogen atom transfer (HAT) to realize C-H bond carboxylation with CO₂. We selected 2,4,5,6tetra(carbazol-9-yl)isophthalonitrile (4CzIPN) and LNiBr₂ (L neocuproine) as the photosensitizer and catalyst, respectively. Triisopropylsilanethiol (HAT1) was added as the HAT catalyst and ethyl benzene was used as model substrate, because the product structural motif is found in some bioactive molecules, such as Ibuprofen, Naproxen and Flurbiprofen. Although an initial attempt did not yield the desired product,

ACS Paragon Plus Environment

58

59

60

Table 1.	Optimization	of conditions
----------	--------------	---------------

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60

	Ĺ	H + 1a	CO₂Ca	4CzIPN	co 2a	он
-	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	НАТЗ	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
	11e	HAT1	2 mol%	balloon	29	20
	12e	HAT1	3 mol%	balloon	35	23
	13e	HAT1	4 mol%	balloon	43	27
	14 ^e	HAT1	5 mol%	balloon	45	31
	15e	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

^a Reaction conditions: Unless otherwise noted, all reactions were carried out with ethyl benzene (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. ^b GC-FID conversion using 1,3,5-trimethoxybenzene as an internal standard. ^c ¹H NMR yield using 1,3,5-trimethoxybenzene as an internal standard and yield of isolated product is given in parentheses. ^d When 0.04 mmol LNiBr₂ (L = neocuproine) was added, no desired product was observed. ^e 0.04 mmol ⁱPr₃SiSH was added. ^f The reaction was carried out at 0°C. ^g High power blue LEDs was used. ^h The reaction was carried out in the dark.



encouragingly we found that 2-phenylpropionic acid was formed in the absence of $LNiBr_2$ (L = 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 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 LEDs were used (Table 1, entries 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 was essential to the success of this transformation (Table 1, entries 23-25).

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 2arylpropionic 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 $(E_{1/2}^{red} = -1.21 \text{ V } vs \text{ SCE})^{11}$ should be replaced by 3DPAFIPN $(E_{1/2}^{red} = -1.59 \text{ V } vs \text{ SCE})^{12}$ when 4-ethyltoluene was used as 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 $(E_{1/2}^{red} = -1.92 \text{ V vs SCE})^{12}$ 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 2phenyl, 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 (20, 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 9,10dihydroanthracene 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 2ethylbenzofuran to give 85% yield of 2-(benzofuran-2yl)propanoic acid (2v and 2w). Furthermore, we examined the carboxylation of saturated oxygen heterocycles. It is obvious that chromane showed higher efficiency than 2,3dihydrobenzofuran (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-4isobutylbenzene, the highly selective formation of Ibuprofen was observed and we attribute this 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

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60





^a All 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 $^{\circ}$ C for 24 h. ^b 4CzIPN was replaced by 3DPAFIPN. ^c 4CzIPN was replaced by 3DPAFIPN: 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile. 3DPA2FBN: 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile.

hydroxytoluene (BHT) 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, equations 1 and 2). Moreover, a kinetic isotope effect (KIE) 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, equations 3 and 4).¹³

Scheme 2. Deuterium-labelling experiments



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-9yl)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-(1phenylethyl)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 $4CzPEBN* (E_{1/2}(P^+/P^*) = +1.19 V vs SCE, Figure S1 and S2)$ by triisopropylsilanethiol ($E_{1/2}^{ox} = +0.28 \text{ V} \text{ vs SCE}$)¹⁵ via single electron transfer (SET) gives rise to a thiol radical cation R-SH^{•+} (R = $(i-Pr)_3Si$) together with the reduced form of the photosensitizer, *i.e.* 4CzPEBN^{•-}. Subsequently, R-SH^{•+} is deprotonated to yield an electrophilic thiyl radical R-S[•] $(BDE(S-H) = 88.2 \text{ kcal} \cdot \text{mol}^{-1})$,¹⁵ which further abstracts a hydrogen atom from the benzylic position of ethylbenzene $(BDE(C-H) = 85.4 \text{ kcal} \cdot \text{mol}^{-1})^{16}$ to close the organocatalytic cycle and produce a benzylic radical. The previously formed $4\text{CzPEBN}^{\bullet-}$ ($E_{1/2}(P/P^{\bullet-}) = -1.69 \text{ V vs SCE}$, Figure S1) should be able to reduce the benzylic radical ($E_{1/2}^{\text{red}} = -1.60 \text{ V} vs \text{ SCE}$ 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 CO_2 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







visible light

To summarize, we have designed a novel and atomeconomic 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

Experimental procedures, methods and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

burkhard.koenig@ur.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

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 GC-MS measurements, Regina Hoheisel (University of Regensburg) for her assistance in cyclic voltammetry measurements, Julia Zach (University of Regensburg) for her assistance in preparing high power LEDs setup.

REFERENCES

(1) (a) Braunstein, P.; Matt, D.; Nobel, D., Reactions of carbon dioxide with carbon-carbon bond formation catalyzed by transitionmetal 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 transitionmetal 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-Nheterocyclic carbene-catalyzed C-H activating carboxylation of terminal alkynes with CO₂ at ambient conditions. *Proc. Nat. 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 rhodiumcatalyzed 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 siteselectivity in a versatile rhodium(II)-catalysed aryl C-H carboxylation with CO₂. Nat. Catal. 2018, 1, 469.

(6) 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., EtAlCl₂/2,6-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.;

2

3

4

5

6

7

8

9

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60

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., 10 Synthesis of 2-aryloxy butenoates by copper-catalysed allylic C-H 11 carboxylation of allyl aryl ethers with carbon dioxide. Org. Biomol. 12 Chem. 2017, 15, 2370; (f) Michigami, K.; Mita, T.; Sato, Y., Cobalt-13 Catalyzed Allylic C(sp3)-H Carboxylation with CO2. J. Am. Chem. Soc. 2017, 139, 6094. 14

(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) D F McMillen, a.; 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 Intermolecular 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.

