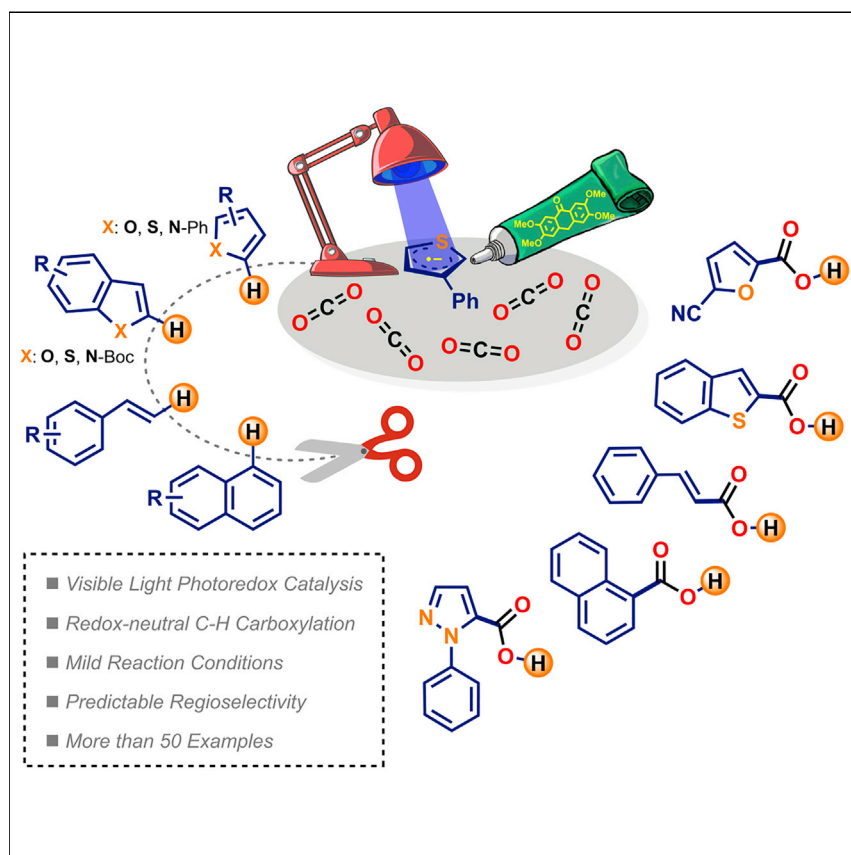


## Article

Redox-Neutral Photocatalytic C–H  
Carboxylation of Arenes and Styrenes  
with CO<sub>2</sub>

The redox-neutral, photocatalyzed insertion of CO<sub>2</sub> into C(sp<sup>2</sup>)-H bonds of (hetero)arenes and styrenes with a blue LED light is demonstrated. Our approach presents a novel, straightforward, and an atom-efficient alternative to the current carboxylation approaches and paves the way to develop further applications to use CO<sub>2</sub> in chemical synthesis. Characterized by a broad substrate scope, this methodology provides a new avenue for the valorization of common arenes and styrenes and holds a promise for future applications in the late-stage functionalization.

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## HIGHLIGHTS

Redox-neutral insertion of CO<sub>2</sub> into C–H bonds

Visible-light photoredox catalysis characterized by mild and metal-free conditions

Broad substrate scope for aromatic carboxylations including a gram-scale example

Substrate reactivity and regioselectivity can be assessed based on DFT calculations



Article

# Redox-Neutral Photocatalytic C–H Carboxylation of Arenes and Styrenes with CO<sub>2</sub>

Matthias Schmalzbauer,<sup>1,4</sup> Thomas D. Svejstrup,<sup>2,4</sup> Florian Fricke,<sup>1</sup> Peter Brandt,<sup>2</sup> Magnus J. Johansson,<sup>2,3</sup> Giulia Bergonzini,<sup>2,\*</sup> and Burkhard König<sup>1,5,\*</sup>

## SUMMARY

Carbon dioxide (CO<sub>2</sub>) is an attractive one-carbon (C1) building block in terms of sustainability and abundance. However, its low reactivity limits applications in organic synthesis as typically high-energy reagents are required to drive transformations. Here, we present a redox-neutral C–H carboxylation of arenes and styrenes using a photocatalytic approach. Upon blue-light excitation, the anthrolate anion photocatalyst is able to reduce many aromatic compounds to their corresponding radical anions, which react with CO<sub>2</sub> to afford carboxylic acids. High-throughput screening and computational analysis suggest that a correct balance between electron affinity and nucleophilicity of substrates is essential. This novel methodology enables the carboxylation of numerous aromatic compounds, including many that are not tolerated in classical carboxylation chemistry. Over 50 examples of C–H functionalizations using CO<sub>2</sub> or ketones illustrate a broad applicability. The method opens new opportunities for the valorization of common arenes and may find application in late-stage C–H carboxylation.

## INTRODUCTION

Photosynthesis, the most important photobiological process on our planet, allows photoautotrophs to store energy in the form of chemical bonds by absorbing sunlight. Driven by that energy, carbon dioxide (CO<sub>2</sub>) is captured from the atmosphere and serves as a carbon feedstock for the organisms to build up sugars and biomass in the Calvin cycle.<sup>1</sup>

The electrochemical and catalytic dihydrogen reductions of CO<sub>2</sub> have been developed in the field of renewable energy storage.<sup>2–4</sup> However, the use of CO<sub>2</sub> as a C1 building block in organic synthesis has received far less attention, despite resembling the principle of biological carbon fixing process the most.<sup>5</sup> The high thermodynamic stability and kinetic inertness of CO<sub>2</sub> require the use of stoichiometric amounts of reactive reaction partners, such as Grignard reagents or organolithium compounds for chemical conversion.<sup>6</sup> Aiming for a better efficiency and an increased atom economy, a variety of catalytic carboxylation methods have been developed. These processes make use of the readily available aryl bromides, which undergo carboxylation with CO<sub>2</sub> in the presence of catalytic Pd(OAc)<sub>2</sub>, as reported by Martín and Correa.<sup>7</sup> Daugulis showed that Cu(I) catalyzes the carboxylation of aryl iodides.<sup>8</sup> Tsuji and co-workers applied NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> to carboxylate more inert aryl and vinyl chlorides under 1 atm CO<sub>2</sub> at room temperature.<sup>9</sup> The reaction scope was extended to sulfonates,<sup>10</sup> ester derivatives,<sup>11,12</sup> allylic alcohols,<sup>13</sup> benzylic ammonium salts,<sup>14</sup> arylsulfonium salts,<sup>15</sup> and unsaturated hydrocarbons.<sup>16–20</sup>

## The Bigger Picture

CO<sub>2</sub> is a highly abundant and sustainable carbon source that serves as a feedstock for the biosynthesis of organisms. However, it is also considered a greenhouse gas, therefore, the fixation of CO<sub>2</sub> in synthetic processes is of great environmental value. In the field of renewable energy storage and conversion of CO<sub>2</sub> into solar fuels, large strides have been made into effective catalytic reductions. However, the need for a stoichiometric reductant is a significant disadvantage for the use of CO<sub>2</sub> as a C1 synthon in synthesis, limiting its use. A mild, direct, redox-neutral, and transition-metal-free insertion of CO<sub>2</sub> into a C–H bond, as reported here, accomplishes highest energy and atom economy, avoiding pre-functionalization. Using a new mechanistic manifold, the methodology presents a straightforward, sustainable, and atom-efficient alternative to current approaches and paves the way to develop novel applications of CO<sub>2</sub> in chemical synthesis.

However, all these systems require stoichiometric reducing reagents based on Et<sub>2</sub>Zn, AlMe<sub>3</sub>, Mn, and Zn powders or prefunctionalized starting materials.<sup>21</sup> Electrical current may also be used to drive reductive carboxylation chemistry. Buckley and co-workers reported the regioselective hydrocarboxylation of styrenes using a non-sacrificial electrode system.<sup>22</sup> Ackermann et al. showed that allyl chlorides derived from cinnamyl chloride are carboxylated in the presence of a cobalt catalyst.<sup>23</sup> Concomitantly, difunctionalizations of alkenes via radical addition and subsequent reduction were reported affording thio-,<sup>24</sup> carbo-,<sup>25–27</sup> phosphono-,<sup>28</sup> or silylcarboxylation<sup>27</sup> products.

Non-catalytic C(sp<sup>2</sup>)-H carboxylations typically require stoichiometric amounts of either strong bases, such as NaH<sup>29</sup> or LiO<sup>t</sup>Bu,<sup>30,31</sup> or Lewis acids, like AlX<sub>3</sub> (X = Br, Cl),<sup>32–35</sup> Me<sub>2</sub>AlCl,<sup>36</sup> and EtAlCl<sub>2</sub><sup>37,38</sup> to activate CO<sub>2</sub>. Transition metal-catalyzed directed C(sp<sup>2</sup>)-H carboxylation reactions have been reported with Au,<sup>39</sup> Cu,<sup>39,40</sup> and Rh<sup>41</sup> complexes.<sup>42</sup> Moreover, direct carboxylation of non-activated C(sp<sup>2</sup>)-H was reported in molten alkali carbonate salts under elevated temperatures (>200°C) and high CO<sub>2</sub> pressure.<sup>43,44</sup>

More recently, photoredox catalysis has been applied in the field of carboxylation chemistry. Photocatalytic carboxylation of aryl-<sup>45,46</sup> and alkyl-halides<sup>46</sup> were the first transformations to be reported, followed by direct C–H carboxylation of alkynes<sup>47</sup> and styrenes.<sup>48,49</sup> These methods utilize a dual catalytic approach consisting of a photocatalyst and an *in-situ* generated low-valent transition metal complex enabled by an excess amount of a sacrificial electron donor. Visible-light mediated benzylic C–H carboxylation was recently reported by the use of 4CzIPN and an organo-silathiol hydrogen-atom-transfer (HAT) reagent, which allowed to generate carbanions.<sup>50</sup>

Direct UV-light excitation of polyaromatic hydrocarbons in the presence of sacrificial amines and CO<sub>2</sub> was reported to yield the corresponding carboxylic acids.<sup>51,52</sup> Jamison employed *p*-terphenyl, which forms a radical anion upon UV-light excitation in the presence of amines.<sup>53</sup> The *p*-terphenyl radical anion is capable of the kinetically slow one-electron reduction of CO<sub>2</sub> to its radical anion, which is used in the hydrocarboxylation of styrenes. Murakami and co-workers employed UV-excited xanthone as HAT reagent in combination with a Cu complex or a Ni catalyst to carboxylate allylic<sup>54</sup> and benzylic<sup>55</sup> C(sp<sup>3</sup>)-H, respectively.

However, despite the great progress achieved in thermal and photochemical carboxylation methods (Schemes 1 and S20), the efficient redox-neutral carboxylation of C(sp<sup>2</sup>)-H in arenes, heteroarenes and alkenes remains challenging. Here, we report a mechanistically different catalytic approach in which aromatic compounds are converted into their radical anions by a photoinduced single-electron transfer (SET) from a visible-light excited anthrolate anion. The generated nucleophilic arene radical anions react with CO<sub>2</sub> to provide (hetero)aromatic carboxylic and cinnamic acids.

## RESULTS AND DISCUSSION

Recently, we showed that upon photoexcitation, the anionic form of commercially available 9-anthrone and derivatives (Scheme S2) readily generate strong reductants capable of activating aryl chlorides.<sup>56</sup> While comparing the reported reduction potentials of various aromatic compounds, we noticed that many arenes lay within the range of the approximated excited state oxidation potential of the strongest

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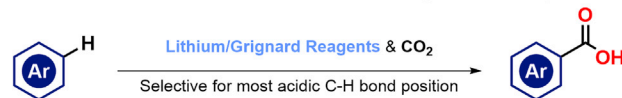
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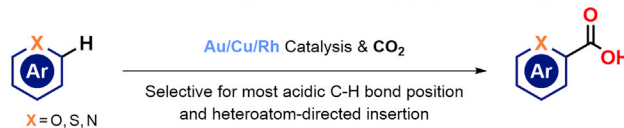
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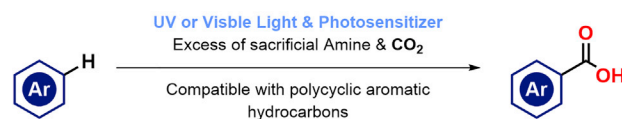
**A Base-Mediated Anion Formation & Subsequent Carboxylation**



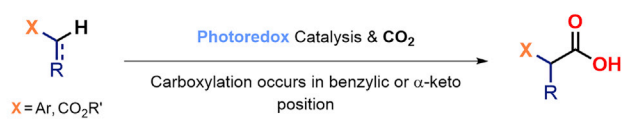
**B Transition Metal-Catalyzed Directed C(sp<sup>2</sup>)–H Carboxylation**



**C Reductive Carboxylation of Polycyclic Aromatic Radical Anions**



**D Photocatalyzed Carbanion Generation in Privileged Cores**

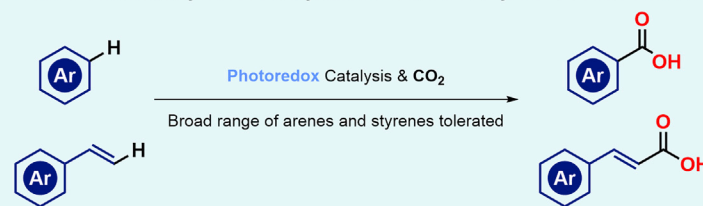


**This Work:**

**Redox-Neutral Photocatalyzed Carboxylation of Arene & Styrene Radical Anions**

>50 substrates including:

- Thiophenes
- Benzothiophenes
- Naphthalenes
- Furans
- Indoles
- Indazoles
- Pyrazoles
- Thiazoles
- Styrenes



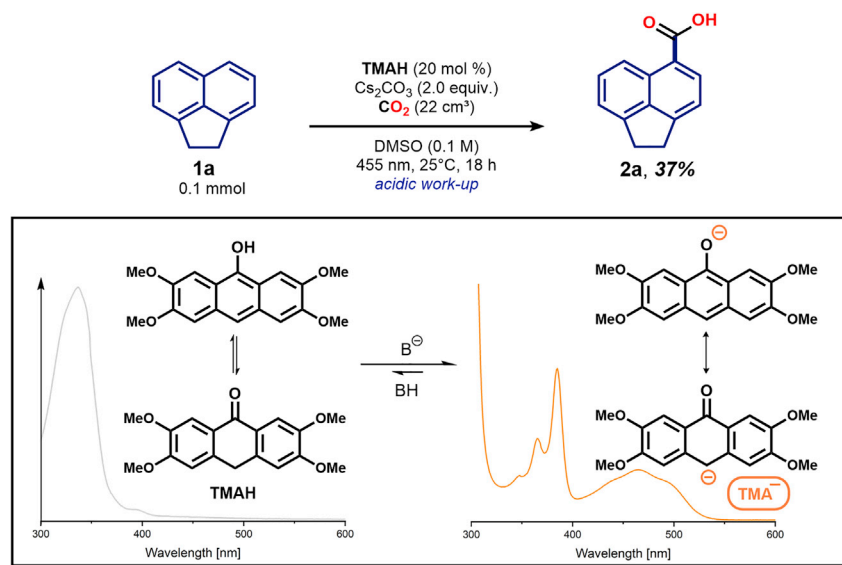
- Transition-metal-free
- No sacrificial reagents
- Mild reaction conditions
- Predictable regioselectivity

**Scheme 1. Overview of Different Strategies for the Direct C–H Carboxylation with CO<sub>2</sub>**

photo-reductant 2,3,6,7-tetramethoxyanthracen-9(10H)-one (TMAH) [ $E_{\text{ox}}(\text{TMA}^{\cdot-}/\text{TMA}^{-\cdot}) = -2.92$  V versus SCE] shown in that series. We thus envisioned a direct activation of arenes via radical anion formation, which may subsequently react with CO<sub>2</sub> to form aromatic carboxylic acids. Strong carbon nucleophiles (e.g., organolithium and -magnesium reagents)<sup>57–60</sup> or carbanions are well known to react with CO<sub>2</sub>. By contrast, aromatic radical anions formed in the presence of alkali metal have always been considered poor nucleophiles,<sup>61</sup> yet, still showed reactivity toward CO<sub>2</sub>.<sup>62,63</sup> With a strongly reducing photoredox catalyst in hand and inspired by early literature reports, we questioned if a similar reactivity of aromatic radical anions toward CO<sub>2</sub> can be obtained under much milder photocatalytic conditions.

**Initial Experiments and Optimization**

We chose acenaphthene (1a, Scheme 2) as a model substrate and applied the established combination of TMAH as the photocatalyst and cesium carbonate as the base. To our delight, after 18 h of irradiation with a blue LED light and an acidic work-up, the desired carboxylic acid 2a could be isolated in a 37% yield as a single regioisomer. Encouraged by this first result, we run an intensive screening of the reaction conditions (Table 1). During the optimization studies, we observed that the reaction outcome was dependent on the amount of Cs<sub>2</sub>CO<sub>3</sub>. The use of less than 3 equivalents of the base led to a significantly lower product yield (entry 2), while more equivalents of Cs<sub>2</sub>CO<sub>3</sub> reduced the yield (entry 3). A lower catalyst loading reduced the overall amount of base required, while the carboxylated product 2a was still obtained in a good yield (entry 4–5). Note that the base is not only necessary for the *in-situ* activation of the photocatalyst but also to trap the released proton upon re-aromatization and hence to maintain alkaline reaction conditions. K<sub>2</sub>CO<sub>3</sub>, although being scarcely soluble in DMSO, was also able to promote the carboxylation reaction and useful product yields were obtained in combination with crown-ether (entry 6). Monitoring the reaction progress over time (Figure S8) showed that the reaction was not complete after 6 h (entry 7). An overpressure of CO<sub>2</sub> was found to be beneficial for the reaction outcome (entries 8 and 9). The solubility of



**Scheme 2. (Top) Photocatalytic C–H Carboxylation of Acenaphthene 1a; (Bottom) Base-Promoted Formation of TMA<sup>−</sup> and the Influence on the Absorption Spectrum**

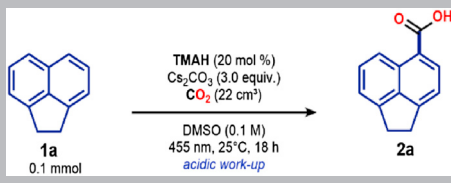
CO<sub>2</sub> was reported to be higher in DMF compared with DMSO, yet, a better yield was obtained in the latter (entry 10).<sup>64</sup> When using green light (535 nm), a reduced product yield was obtained (entry 11), which can be explained by both weaker catalyst absorption and LED radiant flux. Control experiments revealed that all reagents and light are crucial, as no product was detected in the absence of either photocatalyst, cesium carbonate, carbon dioxide, or light (entry 12–15).

### Substrate Scope of the Carboxylation Reaction

With the optimized reaction conditions in hand (*cf* Table 1), we explored the scope of this novel transformation. Naphthalene derivatives were investigated, as their reported potentials are in a feasible range (−2.49 up to −2.65 V versus SCE)<sup>65</sup> for reduction by the photocatalyst (Scheme 3). We were pleased to see that unsubstituted as well as substituted naphthalene derivatives were converted to the corresponding aromatic carboxylic acids (**2b–2g**) and could be isolated in useful yields. The regioselectivity of the reaction was found to be affected by strong electron-donating groups (−OMe **2c**, −NMe<sub>2</sub> **2d**) in the C1-position, giving selectively 5-naphthoic acids as single regioisomers. In contrast, the directing effect of electronically neutral substituents (−Me, **2e**) was minor and led to a mixture of 4- and 5-naphthoic acids. Remarkably, carboxylation in the C8-position was not observed. Notably, unprotected hydroxyl groups (**2f** and **2g**) were tolerated. Utilizing 1-naphthol (**1f**) led to the formation of two regioisomers of the corresponding acid in 2- and 4-positions. 2,7-Dihydroxynaphthalene (**1g**) reacted smoothly under our reaction conditions to yield the corresponding 1-naphthoic acid **2g** as a single regioisomer. Quinoline (**1h**), isoquinoline or quinazoline, although quenching the photoexcited state of the catalyst, failed to yield any product (see Figure S12A).

Pleasingly, many other heteroaromatic compounds were suitable substrates for our carboxylation method (Scheme 4). Thiophenes, bearing electron-deficient (**3a–3d**, **3f**, **3i–3k**) and -neutral (**3e**, **3g–3h**, **3l–3n**) substituents smoothly converted into the corresponding thiophenecarboxylic acids **4a–4n** in a good to excellent yield. Remarkably, a broad range of functional groups, including ketones, esters,

**Table 1. Optimized Reaction Conditions and Effects upon Deviation**



Entry	Deviations from Optimized Conditions	Yield 2a (%) <sup>a</sup>
1	None	68 <sup>b</sup>
2	Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	37 <sup>b</sup>
3	Cs <sub>2</sub> CO <sub>3</sub> (4 equiv)	59
4	TMAH (5 mol %), Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	54
5	TMAH (10 mol %), Cs <sub>2</sub> CO <sub>3</sub> (2 equiv)	60
6 <sup>c</sup>	TMAH (10 mol %), K <sub>2</sub> CO <sub>3</sub> instead of Cs <sub>2</sub> CO <sub>3</sub> , 18-crown-6	47
7	6 h instead of 18 h	44
8	no CO <sub>2</sub> pressure (1 atm)	37
9	11 cm <sup>3</sup> CO <sub>2</sub> instead of 22 cm <sup>3</sup>	48
10	DMF instead of DMSO	35
11 <sup>d</sup>	535 nm instead of 455 nm	29
12	no TMAH	n.d.
13	no Cs <sub>2</sub> CO <sub>3</sub>	n.d.
14	N <sub>2</sub> (1 atm) instead of CO <sub>2</sub>	n.d.
15 <sup>e</sup>	no light	n.d.

Optimized reaction conditions: **1a** (0.1 mmol), **TMAH** (20 mol %) and Cs<sub>2</sub>CO<sub>3</sub> (0.3 mmol) were added to a 5 mL crimp top vial equipped with a stirring bar. The vial was sealed, evacuated and backfilled with CO<sub>2</sub> (5×). Degassed, anhydrous DMSO (1 mL) was added via syringe. The septum was further sealed with Parafilm® and gaseous CO<sub>2</sub> (22 cm<sup>3</sup>) was added to the headspace via syringe. While stirring, the reaction was irradiated from the bottom side (blue LED, 455 ± 15 nm) and constant temperature was maintained by an aluminum cooling block and a water-cooling circuit. For the complete optimization table, please see [Table S1](#); Information. n.d., not detected.

<sup>a</sup>Product yield was determined after acidic work-up by crude <sup>1</sup>H-NMR with an internal standard.

<sup>b</sup>Combined isolated yield of four reactions.

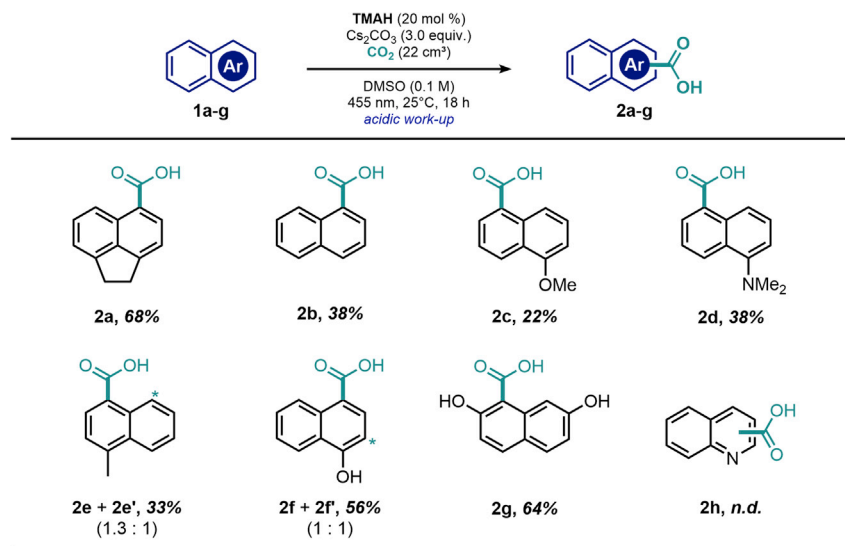
<sup>c</sup>Crown ether 18-crown-6 (1 equiv) was added to the reaction.

<sup>d</sup>Radiant flux is lowered by a factor of eight compared with 455 nm LED (see [Supplemental Information](#)).

<sup>e</sup>Reaction mixture was stirred in the dark.

amides, –CH<sub>2</sub>CO<sub>2</sub>Me, –CH<sub>2</sub>CN, phenyl-, trimethylsilyl- and nitrile were tolerated. However, unfunctionalized thiophene could not be activated by the photocatalyst (see [Figure S11B](#)). Due to the mild nature of this reaction, we were pleased to see that regioselectivity was maintained even with substrates containing acidic C–H (**4c**, **4j**) or active methylene groups (**4g–4h**). This is in contrast to the reported base-promoted methods that are usually selective for the most acidic positions of the substrates and that fail in the presence of sensitive functionalities. Our procedure allowed for the conversion of methyl thiophene-2-carboxylate to 5-(methoxycarbonyl)thiophene-2-carboxylic acid (**4a**) in one step, providing a much shorter route than by using other reported methods (Scheme 5Ai).<sup>66</sup> Moreover, our method allowed the synthesis of 5-carboxy-2-acetylthiophene (**4c**), an important building block for the synthesis of the alpha and beta dual receptor blocker arotinolol,<sup>67</sup> in one step from 1-(thiophen-2-yl)ethan-1-one (**3c**). This is significantly shorter than the well-established synthetic routes (Scheme 5Aii).<sup>68</sup> Remarkably, we also found





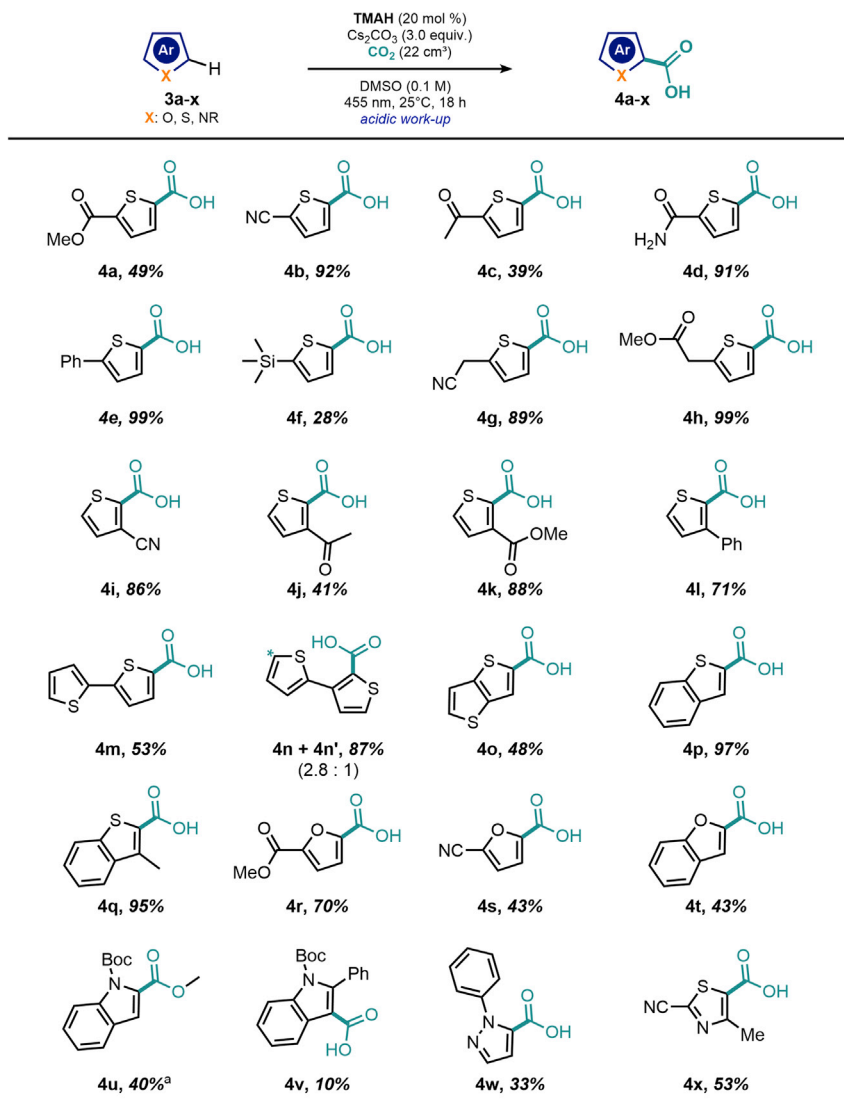
**Scheme 3. Substrate Scope for the Carboxylation of Naphthalene Derivatives**

n.d., product was not detected.

that 3-substituted thiophenes were exclusively carboxylated in the 2-position (4i–4l), which highlights the excellent regioselectivity of this reaction. In comparison, a previous literature report on the lithiation of 3-phenylthiophene (3l) and subsequent carboxylation led to a mixture of 4l and 4l' (Scheme 5B).<sup>69</sup> Perfect regioselectivity was also observed for the photocatalyzed carboxylation of 1-phenylpyrazole, where only 4w was obtained. In this case, due to the chelating effect of nitrogen, the use of organometallic reagents leads to product mixtures (*n*-BuLi)<sup>70</sup> or to an inverse regioselectivity (EtMgBr)<sup>71</sup> (Scheme 5C).

This photocatalyzed carboxylation method could also be extended to benzothiophenes (4p–4q), furans (4r–4s), benzofuran 4t, Boc-protected indoles (4u–4v) and thiocarbazole 4x. Non-protected 1*H*-indoles, however, were carboxylated at the nitrogen atom, as reported in literature.<sup>30</sup> Modifying the conditions during the reaction work-up of 4r allowed the formation of either 2,5-furandicarboxylic acid (FDCA) or dimethyl 2,5-furandicarboxylate (DMFDC, see Scheme S5), which is noteworthy. Both are important monomers for the manufacture of polyesters derived from biomass, including polyethylene furandicarboxylate (PEF), a potential large-scale substitute for fossil-based polyethylene terephthalate (PET).<sup>72,73</sup> Lignocellulose is converted into furfural on an industrial scale<sup>74</sup> and catalytic follow-up procedures have been reported to yield methyl furoate quantitatively.<sup>75,76</sup> Starting from methyl furan-2-carboxylate 3r, our procedure offers a new one-step synthetic route to form lignocellulose-derived monomers.

Remarkably, all examined heterocycles were carboxylated at the five-membered ring in  $\alpha$ -position (except 4v, where the  $\alpha$ -position is blocked) to the heteroatom. Contrarily, hydroxybenzothiophene 6a or condensed heterocycles, such as indazoles (6b–6c) and pyrazolo[1,5-*a*]pyridine (6d), showed exclusive selectivity for the six-membered ring (Scheme 6A). With mild carboxylation conditions in hand, we postulated that this methodology could be applied for the late-stage functionalization of biologically active molecules. To this end, a Boc-protected thiophene analog of propranolol, a well-established beta blocker bearing a free hydroxyl group in the side chain, was subjected to our reaction conditions.



**Scheme 4. Substrate Scope for the Carboxylation of 5-Membered (Hetero)arenes**

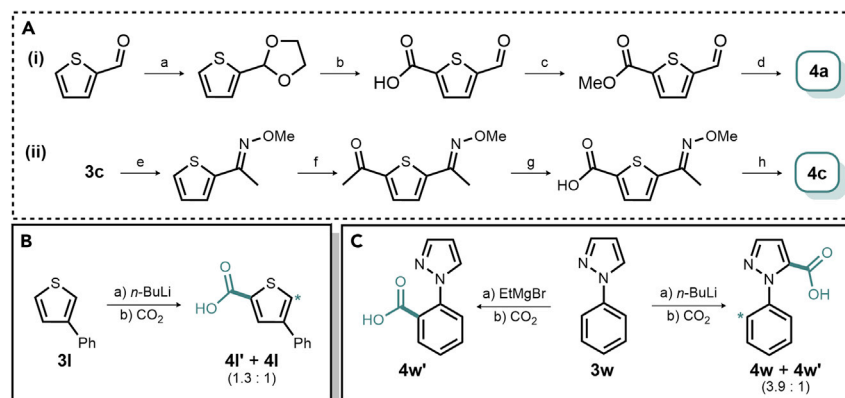
<sup>a</sup>Overall yield: methyl iodide was added to the crude mixture and the compound was isolated as methyl ester **4u**.

Pleasantly, regioselective carboxylation was successfully achieved to provide **6e**, albeit in modest yield.

To demonstrate the scalability of our reaction, we repeated the synthesis of **4b** on a gram-scale. 2-Cyanothiophene **3b** was reacted in a custom-built glass reactor (see Figure S2) with a reduced amount of both TMAH (5 mol %) and cesium carbonate (1.5 equiv) in DMSO (Scheme 6B). Remarkably, as working with CO<sub>2</sub> overpressure was not possible with this reaction vessel, a gentle stream of CO<sub>2</sub> was sufficient to obtain the product in a good yield.

We then questioned whether our photocatalytic system could be further utilized for the direct carboxylation of other stabilized sp<sup>2</sup>-hybridized carbon atoms. To this end, we examined styrene derivatives (Scheme 7) and we were delighted to see





**Scheme 5. Commonly Applied Synthetic Routes to Obtain Products 4a and 4c and the Issues Associated with Regioselectivity in Organometallic Carboxylation**

(A) Reported four-step synthesis for compound **4a** (Ai)<sup>66</sup> and **4c** (Aii)<sup>68</sup>; conditions: (a) ethane-1,2-diol, Al<sub>2</sub>O<sub>3</sub>, CCl<sub>4</sub>,  $\Delta$ , 48 h; (b) *n*-BuLi, THF,  $-78^{\circ}\text{C}$ , then CO<sub>2</sub> followed by H<sub>2</sub>SO<sub>4</sub> (10%); (c) MeI, Na<sub>2</sub>CO<sub>3</sub>, DMF,  $20^{\circ}\text{C}$ , 48 h; (d) Jones reagent; (e) MeONH<sub>2</sub>·HCl, Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, MeOH, AcOH (pH 5),  $\Delta$ , 3 h; (f) ZnCl<sub>2</sub>, CHCl<sub>3</sub>, Ac<sub>2</sub>O,  $100^{\circ}\text{C}$ , 12 h, RT, aq. HCl (20%) (g) MeOH, aq. NaOCl (5.5%),  $70^{\circ}\text{C}$ , 4 h, RT, HCl conc.; (h) aq. HCl,  $65^{\circ}\text{C}$ , 12 h.

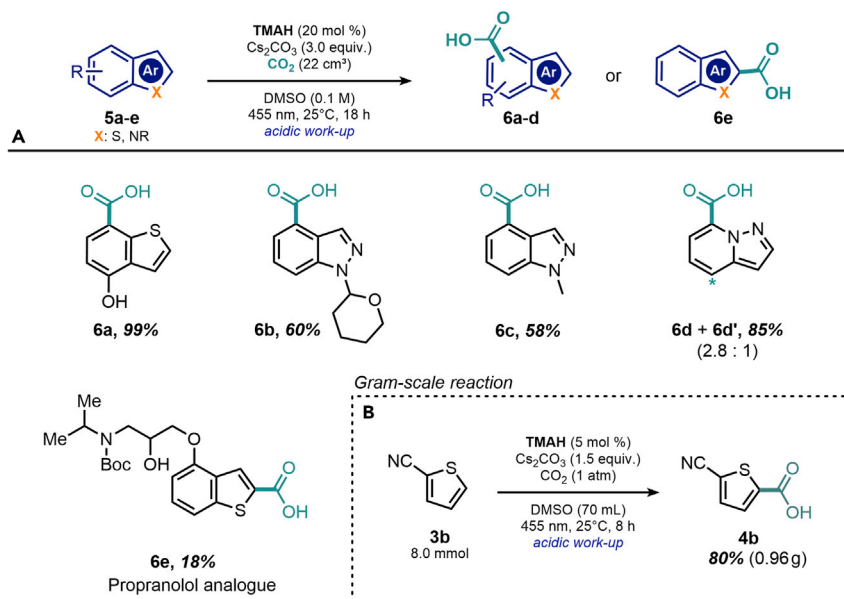
(B) *n*-BuLi promoted carboxylation of **3I** leads to a mixture of regioisomers.

(C) Organometallic methods for carboxylation of 1-phenylpyrazole. Due to the chelating effect of nitrogen, the use of organometallic reagents causes a mixture of regioisomers (*n*-BuLi) or leads to an inversion of regioselectivity (EtMgBr) yielding benzoic acid **4w'** as single product.

that under the presented redox-neutral conditions, only the corresponding *trans*-cinnamic acids were obtained. Our protocol thus provides a complementary method to previous net-reductive approaches where excess of sacrificial reductant or electrical current yielded hydrocarboxylated products.<sup>22,48,53</sup> Despite the limitations posed by competing polymerization reactions, a variety of vinyl benzenes could be converted into *trans*-cinnamic acid derivatives **8b–8I** (Scheme 7), which find applications in the food industry, material science,<sup>77</sup> and cosmetics.<sup>78</sup> While styrene derivatives bearing electron-donating substituents (**7d–7f**, **7h**) reacted smoothly, the reaction with the electron-poor 4-(trifluoromethyl)styrene resulted in low product yield. 4-Cyanostyrene (**7n**) or methyl-4-vinylbenzoate (**7o**) were not suitable substrates under these conditions. As the electron transfer from the excited photocatalyst to an electron-poor styrene is thermodynamically favored, we postulated that electron-withdrawing groups stabilize the negative charge and reduce the nucleophilicity of the corresponding radical anion. When using  $\alpha$ -methylstyrene, we observed the formation of 3-aryl-3-butenic acid **8m** in favor of the thermodynamically more stable  $\alpha,\beta$ -unsaturated acid **8m'**.<sup>38</sup>

### Mechanistic Insights

We propose a photoinduced SET from the excited TMA<sup>−\*</sup> to the substrate as the first step. The excited photocatalyst TMA<sup>−\*</sup> is strongly emissive and its luminescence decay follows first-order kinetics (see Figures S4A, S4B, and S5). In the presence of chosen (hetero)arenes (cf Scheme 4) as well as styrenes (cf Scheme 7) we observed a decrease in the luminescence lifetime of TMA<sup>−\*</sup>. Based on the obtained data, a Stern-Volmer plot was derived (see Figures S11A and S11B). The luminescence lifetime of TMA<sup>−\*</sup> in a CO<sub>2</sub>-saturated solution of DMSO remains almost unchanged, indicating that CO<sub>2</sub> is not reduced by the photocatalyst. Reduction of CO<sub>2</sub> by SET to achieve carbon-bond formation has been reported, but it requires reagents such as *p*-terphenyl radical anion.<sup>53,79</sup> Although a direct reduction of CO<sub>2</sub> ( $-2.21$  V versus SCE in DMF)<sup>80</sup> by TMA<sup>−\*</sup> is thermodynamically feasible, we assume



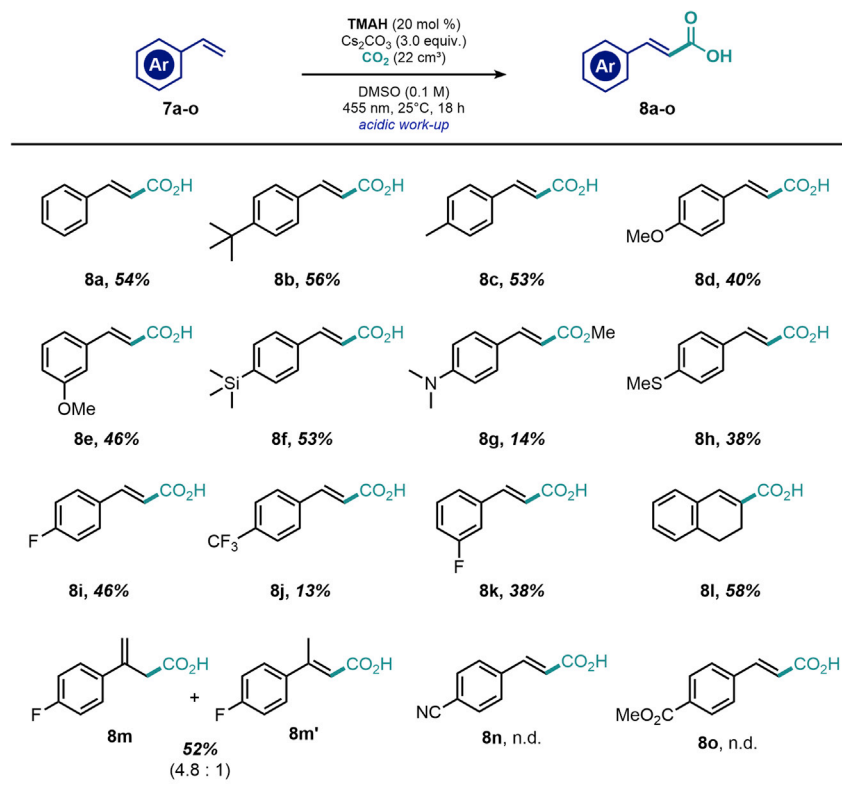
**Scheme 6. Substrate Scope for the Carboxylation of Heteroarenes with Non-classical Regioselectivity, Late Stage Carboxylation, and Gram Scale Carboxylation of 3b**

(A) Substrate scope for the carboxylation of (hetero)arenes on the six-membered ring and example of late-stage functionalization.

(B) Reaction conditions for the gram-scale carboxylation of 3b.

a kinetic barrier preventing the formation of the bent CO<sub>2</sub> radical anion within the excited state lifetime of TMA<sup>•-</sup>. Thus, we ascertained that the productive pathway is dominated by the formation of an aromatic radical anion, which subsequently reacts with CO<sub>2</sub> via nucleophilic addition. In order to get further insight into the reaction mechanism, we tested other electrophiles than CO<sub>2</sub>. We decided to use ketones for this study, as single-electron reduction from the excited photocatalyst to the ketone would give a ketyl radical anion. In sharp contrast to the radical anion of CO<sub>2</sub>, ketyl radical anions are considered as electron-rich species acting as single-electron reductants rather than forming C–C bonds via radical reactions.<sup>81</sup> When benzo[*b*]thiophene (3p, Scheme 8) was reacted with acetone (9a), the corresponding tertiary alcohol adduct 9pa was formed in good yield. The luminescence lifetime of TMA<sup>•-</sup> remains unchanged upon titration with acetone (–2.84 V versus SCE in DMF)<sup>82</sup> and thus, the formation of a ketyl radical anion is unlikely (Figure S12B). Remarkably, similar transformations require very harsh reaction conditions (–78°C, excess of *n*-BuLi) and are not viable in a one-pot procedure.<sup>83</sup> Moderate yields of the resulting tertiary alcohol were also obtained using cyclic ketone 9b and non-conjugated enone 9c as electrophiles.

In addition, we performed deuterium-labeling experiments using D<sub>2</sub>O and <sup>4</sup>BuOD, respectively. Upon formation of the nucleophilic arene radical anion, we envisioned a fast acid-base reaction followed by deprotonation to yield a mixture of H and D in the substrate (see Scheme S3). However, as water in the reaction mixture was found to be detrimental and protic solvents were shown to inhibit the reaction (*cf* Table S1), only small amounts of incorporated deuterium were detected using benzothiophene 3q (Table S3). Based on the aforementioned results we propose the following reaction mechanism for the photocatalytic C–H carboxylation of (hetero)arenes (Scheme 9). In the presence of a base, the pre-catalyst TMAH is chemically activated

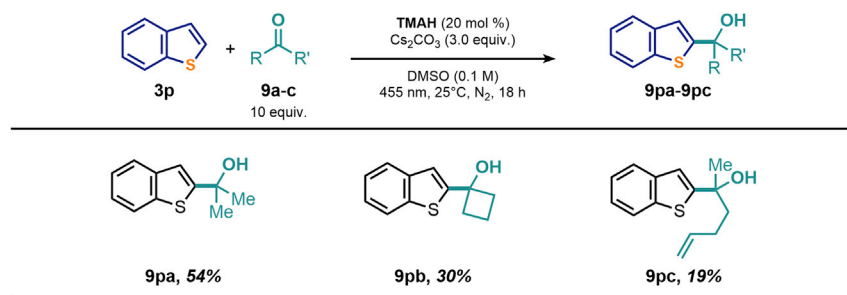


### Scheme 7. Substrate Scope for the Carboxylation of Styrene Derivatives

<sup>a</sup>Overall yield: methyl iodide was added to the crude mixture and the compound was isolated as the methyl ester **8g**.

by deprotonation to form an anionic species  $\text{TMA}^-$ , indicated by the solution color change. Upon irradiation with visible light (455 nm) a strongly reducing excited anion  $\text{TMA}^{-*}$  is formed. The excited state is then quenched by the arene **I** via PET to afford the radical of the photocatalyst  $\text{TMA}^\cdot$  and the electron-rich radical anion of the arene (**II**). The screening calculations show that the regioselectivity is correlated with the Mulliken spin population as illustrated for the benzothiophene radical anion (**II**, Scheme 9). While this would indicate that the reaction is radical in character, the spin population is also strongly correlated with both the atomic change in charge upon the single-electron reduction and the f-NN-HOMO parameter of the radical. Whereas the rate of a nucleophilic attack is dependent on the charge of the nucleophilic atom, the Mulliken spin population is poorly correlated with the Mulliken charges and the regioselectivity is not well predicted by the Mulliken charges of the radical anion *per se*. In the bond-forming step,  $\text{CO}_2$  is attacked by **II** to generate a radical carboxylate **III** as an intermediate. We assume that **III** is deprotonated immediately in the presence of base (**IV**). Similar radical species have been reported to cause an enormous increase in CH acidity in order to gain resonance energy upon deprotonation.<sup>84,85</sup> The resulting radical dianion **IV** is expected to be a sufficiently strong reductant [ $E^0(\text{TMA}^\cdot/\text{TMA}^-) = -0.51$  V versus SCE] to close the catalytic cycle via SET and to recapture the active catalyst  $\text{TMA}^-$ .

During the exploration of the substrate scope, we found that several aromatic compounds that quench the excited state of the photocatalyst did not undergo carboxylation (see Figure S12A). While some functional groups are understandably not tolerated under our reaction conditions, such as aromatic halides (these may undergo fast



**Scheme 8. Mechanistic Investigations: Probing the Possibility of other Electrophiles as Viable Candidates for Reactivity with Aromatic Radical Anions**

mesolytic bond-cleavage to form aryl radicals) or highly electrophilic moieties, we were surprised that only certain radical anions were reacting with CO<sub>2</sub>. In order to determine the required electronic characteristics for reactivity and to improve our insight regarding functional group tolerance, high-throughput screening (HTS) of various arenes containing a large array of functionalities and differing in complexity was carried out (see [Figure S9](#)). The analysis of the HTS outcome indicates that aldehydes, halides (with the exception of fluorine), aliphatic amines, 6-membered nitrogen heterocycles, and nitro groups are not compatible with the reaction conditions. Beyond functional group interference, calculations indicate that the applicability of our methodology is related to the arene electron affinity and the nucleophilicity of the resulting radical anion. Arenes may be able to accept an electron with ease, but the radical anion formed may not be nucleophilic enough to add to CO<sub>2</sub>. Conversely, some aromatic radical anions may be highly nucleophilic, but their formation may be beyond the reductive capabilities of the photocatalyst or a functional group present may be reduced instead. The estimated electron affinities of the arenes, and the Mulliken spin population and charges for the arene radical anions were derived from DFT calculations. The importance of a correct balance of electron affinity of the arene and the nucleophilicity of the aromatic radical anion for a successful reaction is illustrated in [Figures S13–S17 \(Supplemental Information\)](#). Additionally, DFT calculations also showed that the regioselectivity is generally well predicted by comparing the Mulliken spin population for the aromatic carbons of calculated substrate radical anions (see [Scheme S4](#)).

## Conclusion

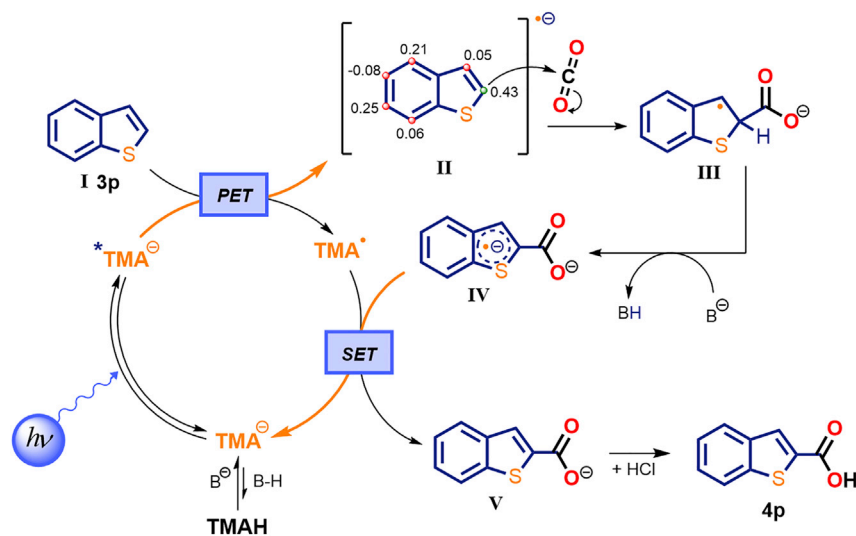
We have developed a mild, direct, redox-neutral, and transition-metal-free insertion of CO<sub>2</sub> into non-prefunctionalized C(sp<sup>2</sup>)-H bonds, leading to an efficient method for producing valuable aromatic carboxylic acids and *trans*-cinnamic acids in a single operation. A reaction performed on gram-scale demonstrated the scalability of this carboxylation method, while ketones could be used as alternative electrophiles to CO<sub>2</sub> yielding tertiary alcohols. The scope of the reaction can be predicted by DFT-estimated reduction potential of the substrates and nucleophilicity of the intermediate arene radical anions. These findings may open new opportunities for an atom-economic and energy-efficient use of CO<sub>2</sub> as a C<sub>1</sub> building block in the chemical processing of aromatic hydrocarbons, as well as for developing new photocatalytic late-stage functionalizations of drug-like compounds.

## EXPERIMENTAL PROCEDURES

### Resource Availability

#### Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Burkhard König ([burkhard.koenig@ur.de](mailto:burkhard.koenig@ur.de)).



**Scheme 9. Proposed Mechanism for the C–H Carboxylation of (Hetero)arenes Exemplified by the Carboxylation of Benzothiophene**

The numbers besides intermediate II indicate the calculated Mulliken spin population for each sp<sup>2</sup>-hybridized carbon atom.

#### Materials Availability

Unique and stable reagents generated in this study will be made available on request, but we may require a payment and/or a completed Materials Transfer Agreement if there is potential for commercial application.

#### Data and Code Availability

There is no dataset and code associated with the paper. Full experimental procedures are provided in the [Supplemental Information](#).

Images of the key spectral and analytical data of the compounds generated in this study are included in [Figures S1–S126](#) in the [Supplemental Information](#).

### SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.chempr.2020.08.022>.

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### AUTHOR CONTRIBUTIONS

M.S. developed the catalytic system, optimized the reaction, isolated the compounds 2a–2d, 4a–4f, 4i–4t, 4v–4w, 8a–8m, 9pa–9pc, designed and carried out

the gram-scale reaction and conducted all experiments to investigate the reaction mechanism. T.D.S. designed and performed the high-throughput-screening and isolated compounds 2f–2g, 4g–4h, 4u, 4x, 6a–6e. F.F. prepared compounds and isolated compound 2e. M.S. and T.D.S. wrote the manuscript and [Supplemental Information](#) with input from all of the authors. P.B. conducted the computational studies. M.J.J., G.B., and B.K. supervised the project.

## DECLARATION OF INTERESTS

T.D.S., P.B., M.J.J., and G.B. are employees and shareholders of AstraZeneca. The authors declare no competing interests.

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## REFERENCES

- Hou, H.J.M., Najafpour, M.M., Moore, G.F., and Allakhverdiev, S.I. (2017). *Photosynthesis: Structures, Mechanisms, and Applications* (Springer International Publishing).
- Nitopi, S., Bertheussen, E., Scott, S.B., Liu, X., Engstfeld, A.K., Horch, S., Seger, B., Stephens, I.E.L., Chan, K., Hahn, C., et al. (2019). Progress and perspectives of electrochemical CO<sub>2</sub> reduction on copper in aqueous electrolyte. *Chem. Rev.* 119, 7610–7672.
- Küngas, R. (2020). Review— electrochemical CO<sub>2</sub> reduction for CO production: comparison of low- and high-temperature electrolysis technologies. *J. Electrochem. Soc.* 167, 044508.
- Nielsen, D.U., Hu, X.M., Daasbjerg, K., and Skrydstrup, T. (2018). Chemically and electrochemically catalysed conversion of CO<sub>2</sub> to CO with follow-up utilization to value-added chemicals. *Nat. Catal.* 1, 244–254.
- Liu, Q., Wu, L., Jackstell, R., and Beller, M. (2015). Using carbon dioxide as a building block in organic synthesis. *Nat. Commun.* 6, 5933.
- Correa, A., and Martín, R. (2009). Metal-catalyzed carboxylation of organometallic reagents with carbon dioxide. *Angew. Chem. Int. Ed. Engl.* 48, 6201–6204.
- Correa, A., and Martín, R. (2009). Palladium-catalyzed direct carboxylation of aryl bromides with carbon dioxide. *J. Am. Chem. Soc.* 131, 15974–15975.
- Tran-Vu, H., and Daugulis, O. (2013). Copper-catalyzed carboxylation of aryl iodides with carbon dioxide. *ACS Catal.* 3, 2417–2420.
- Fujihara, T., Nogi, K., Xu, T., Terao, J., and Tsuji, Y. (2012). Nickel-catalyzed carboxylation of aryl and vinyl chlorides employing carbon dioxide. *J. Am. Chem. Soc.* 134, 9106–9109.
- Liu, Y., Cornella, J., and Martin, R. (2014). Ni-catalyzed carboxylation of unactivated primary alkyl bromides and sulfonates with CO<sub>2</sub>. *J. Am. Chem. Soc.* 136, 11212–11215.
- Correa, A., León, T., and Martin, R. (2014). Ni-catalyzed carboxylation of C(sp<sup>2</sup>)- and C(sp<sup>3</sup>)-O bonds with CO<sub>2</sub>. *J. Am. Chem. Soc.* 136, 1062–1069.
- Moragas, T., Cornella, J., and Martin, R. (2014). Ligand-controlled regioselective Ni-catalyzed reductive carboxylation of allyl esters with CO<sub>2</sub>. *J. Am. Chem. Soc.* 136, 17702–17705.
- Mita, T., Higuchi, Y., and Sato, Y. (2015). Highly regioselective palladium-catalyzed carboxylation of allylic alcohols with CO<sub>2</sub>. *Chemistry* 21, 16391–16394.
- Moragas, T., Gaydou, M., and Martin, R. (2016). Nickel-catalyzed carboxylation of benzylic C–N bonds with CO<sub>2</sub>. *Angew. Chem. Int. Ed. Engl.* 55, 5053–5057.
- Yanagi, T., Somerville, R.J., Nogi, K., Martin, R., and Yorimitsu, H. (2020). Ni-catalyzed carboxylation of C(sp<sup>2</sup>)-S bonds with CO<sub>2</sub>: evidence for the multifaceted role of Zn. *ACS Catal.* 10, 2117–2123.
- Gaydou, M., Moragas, T., Juliá-Hernández, F., and Martin, R. (2017). Site-selective catalytic carboxylation of unsaturated hydrocarbons with CO<sub>2</sub> and water. *J. Am. Chem. Soc.* 139, 12161–12164.
- Michigami, K., Mita, T., and Sato, Y. (2017). Cobalt-catalyzed allylic C(sp<sup>3</sup>)-H carboxylation with CO<sub>2</sub>. *J. Am. Chem. Soc.* 139, 6094–6097.
- Williams, C.M., Johnson, J.B., and Rovis, T. (2008). Nickel-catalyzed reductive carboxylation of styrenes using CO<sub>2</sub>. *J. Am. Chem. Soc.* 130, 14936–14937.
- Tortajada, A., Ninokata, R., and Martin, R. (2018). Ni-catalyzed site-selective dicarboxylation of 1,3-dienes with CO<sub>2</sub>. *J. Am. Chem. Soc.* 140, 2050–2053.
- Huguet, N., Jevtovikj, I., Gordillo, A., Lejkowski, M.L., Lindner, R., Bru, M., Khalimon, A.Y., Rominger, F., Schunk, S.A., Hofmann, P., and Limbach, M. (2014). Nickel-catalyzed direct carboxylation of olefins with CO<sub>2</sub>: one-pot synthesis of  $\alpha,\beta$ -unsaturated carboxylic acid salts. *Chemistry* 20, 16858–16862.
- Yang, Y., and Lee, J.W. (2019). Toward ideal carbon dioxide functionalization. *Chem. Sci.* 10, 3905–3926.
- Alkayal, A., Tabas, V., Montanaro, S., Wright, I.A., Malkov, A.V., and Buckley, B.R. (2020). Harnessing applied potential: selective  $\beta$ -hydrocarboxylation of substituted olefins. *J. Am. Chem. Soc.* 142, 1780–1785.
- Ang, N.W.J., de Oliveira, J.C.A., and Ackermann, L. (2020). Electroreductive cobalt-catalyzed carboxylation: cross-electrophile electro-coupling with atmospheric CO<sub>2</sub>. *Angew. Chem. Int. Ed. Engl.* 59, 12842–12847.
- Ye, J.H., Miao, M., Huang, H., Yan, S.S., Yin, Z.B., Zhou, W.J., and Yu, D.G. (2017). Visible-light-driven iron-promoted thiocarboxylation of styrenes and acrylates with CO<sub>2</sub>. *Angew. Chem. Int. Ed. Engl.* 56, 15416–15420.
- Wang, H., Gao, Y., Zhou, C., and Li, G. (2020). Visible-light-driven reductive carboxylation of styrenes with CO<sub>2</sub> and aryl halides. *J. Am. Chem. Soc.* 142, 8122–8129.
- Yatham, V.R., Shen, Y., and Martin, R. (2017). Catalytic intermolecular dicarboxylation of styrenes with CO<sub>2</sub> and radical precursors. *Angew. Chem. Int. Ed. Engl.* 56, 10915–10919.
- Hou, J., Ee, A., Cao, H., Ong, H.W., Xu, J.H., and Wu, J. (2018). Visible-light-mediated metal-free difunctionalization of alkenes with CO<sub>2</sub> and silanes or C(sp<sup>3</sup>)-H alkanes. *Angew. Chem. Int. Ed. Engl.* 57, 17220–17224.
- Fu, Q., Bo, Z.Y., Ye, J.H., Ju, T., Huang, H., Liao, L.L., and Yu, D.G. (2019). Transition metal-free phosphonocarboxylation of alkenes with carbon dioxide via visible-light photoredox catalysis. *Nat. Commun.* 10, 3592.
- Luo, J., Preciado, S., Xie, P., and Larrosa, I. (2016). Carboxylation of phenols with CO<sub>2</sub> at atmospheric pressure. *Chemistry* 22, 6798–6802.
- Yoo, W.J., Capdevila, M.G., Du, X., and Kobayashi, S. (2012). Base-mediated carboxylation of unprotected indole



- derivatives with carbon dioxide. *Org. Lett.* **14**, 5326–5329.
31. Shigeno, M., Hanasaka, K., Sasaki, K., Nozawa-Kumada, K., and Kondo, Y. (2019). Direct carboxylation of electron-rich heteroarenes promoted by LiO-tBu with CsF and (18)crown-6. *Chemistry* **25**, 3235–3239.
  32. Suzuki, Y., Hattori, T., Okuzawa, T., and Miyano, S. (2002). Lewis acid-mediated carboxylation of fused aromatic compounds with carbon dioxide. *Chem. Lett.* **31**, 102–103.
  33. Nemoto, K., Yoshida, H., Suzuki, Y., Morohashi, N., and Hattori, T. (2006). Beneficial effect of TMSCl in the Lewis acid-mediated carboxylation of aromatic compounds with carbon dioxide. *Chem. Lett.* **35**, 820–821.
  34. Nemoto, K., Yoshida, H., Egusa, N., Morohashi, N., and Hattori, T. (2010). Direct carboxylation of arenes and halobenzenes with CO<sub>2</sub> by the combined use of AlBr<sub>3</sub> and R<sub>3</sub>SiCl. *J. Org. Chem.* **75**, 7855–7862.
  35. Olah, G.A., Török, B., Joschek, J.P., Bucsi, I., Esteves, P.M., Rasul, G., and Surya Prakash, G.K. (2002). Efficient chemoselective carboxylation of aromatics to arylcarboxylic acids with a superelectrophilically activated carbon dioxide-Al<sub>2</sub>Cl<sub>6</sub>/Al system. *J. Am. Chem. Soc.* **124**, 11379–11391.
  36. Nemoto, K., Onozawa, S., Egusa, N., Morohashi, N., and Hattori, T. (2009). Carboxylation of indoles and pyrroles with CO<sub>2</sub> in the presence of dialkylaluminum halides. *Tetrahedron Lett.* **50**, 4512–4514.
  37. Nemoto, K., Onozawa, S., Konno, M., Morohashi, N., and Hattori, T. (2012). Direct carboxylation of thiophenes and benzothiophenes with the aid of EtAlCl<sub>2</sub>. *Bull. Chem. Soc. Jpn.* **85**, 369–371.
  38. Tanaka, S., Watanabe, K., Tanaka, Y., and Hattori, T. (2016). EtAlCl<sub>2</sub>/2,6-disubstituted pyridine-mediated carboxylation of alkenes with carbon dioxide. *Org. Lett.* **18**, 2576–2579.
  39. Boogaerts, I.I.F., Fortman, G.C., Furst, M.R.L., Cazin, C.S.J., and Nolan, S.P. (2010). Carboxylation of N-H/C-H bonds using N-heterocyclic carbene copper(I) complexes. *Angew. Chem. Int. Ed. Engl.* **49**, 8674–8677.
  40. Zhang, L., Cheng, J., Ohishi, T., and Hou, Z. (2010). Copper-catalyzed direct carboxylation of C-H bonds with carbon dioxide. *Angew. Chem. Int. Ed. Engl.* **49**, 8670–8673.
  41. Suga, T., Mizuno, H., Takaya, J., and Iwasawa, N. (2014). Direct carboxylation of simple arenes with CO<sub>2</sub> through a rhodium-catalyzed C-H bond activation. *Chem. Commun. (Camb.)* **50**, 14360–14363.
  42. Hong, J., Li, M., Zhang, J., Sun, B., and Mo, F. (2019). C-H Bond carboxylation with carbon dioxide. *ChemSusChem* **12**, 6–39.
  43. Banerjee, A., Dick, G.R., Yoshino, T., and Kanan, M.W. (2016). Carbon dioxide utilization via carbonate-promoted C-H carboxylation. *Nature* **531**, 215–219.
  44. Kudo, K., Shima, M., Kume, Y., Ikoma, F., Mori, S., and Sugita, N. (1995). Carboxylation of cesium 2-naphthoate in the alkali metal molten salts of carbonate and formate with CO<sub>2</sub> under high pressure. *J. Jpn. Petrol. Inst.* **38**, 40–47.
  45. Shimomaki, K., Murata, K., Martin, R., and Iwasawa, N. (2017). Visible-light-driven carboxylation of aryl halides by the combined use of palladium and photoredox catalysts. *J. Am. Chem. Soc.* **139**, 9467–9470.
  46. Meng, Q.Y., Wang, S., and König, B. (2017). Carboxylation of aromatic and aliphatic bromides and triflates with CO<sub>2</sub> by dual visible-light-nickel catalysis. *Angew. Chem. Int. Ed. Engl.* **56**, 13426–13430.
  47. Hou, J., Ee, A., Feng, W., Xu, J.H., Zhao, Y., and Wu, J. (2018). Visible-light-driven alkyne hydro-/carbocarbonylation using CO<sub>2</sub> via iridium/cobalt dual catalysis for divergent heterocycle synthesis. *J. Am. Chem. Soc.* **140**, 5257–5263.
  48. Meng, Q.Y., Wang, S., Huff, G.S., and König, B. (2018). Ligand-controlled regioselective hydrocarboxylation of styrenes with CO<sub>2</sub> by combining visible light and nickel catalysis. *J. Am. Chem. Soc.* **140**, 3198–3201.
  49. Murata, K., Numasawa, N., Shimomaki, K., Takaya, J., and Iwasawa, N. (2017). Construction of a visible light-driven hydrocarboxylation cycle of alkenes by the combined use of Rh(I) and photoredox catalysts. *Chem. Commun. (Camb.)* **53**, 3098–3101.
  50. Meng, Q.Y., Schirmer, T.E., Berger, A.L., Donabauer, K., and König, B. (2019). Photocarboxylation of benzylic C–H Bonds. *J. Am. Chem. Soc.* **141**, 11393–11397.
  51. Tagaya, H., Onuki, M., Tomioka, Y., Wada, Y., Karasu, M., and Chiba, K. (1990). Photocarboxylation of naphthalene in the presence of carbon dioxide and an electron donor. *Bull. Chem. Soc. Jpn.* **63**, 3233–3237.
  52. Minabe, M., Isozumi, K., Kawai, K., and Yoshida, M. (1988). An observation on carboxylation of 4H-Cyclopenta[def]phenanthrene. *Bull. Chem. Soc. Jpn.* **61**, 2063–2066.
  53. Seo, H., Liu, A., and Jamison, T.F. (2017). Direct  $\beta$ -selective hydrocarboxylation of styrenes with CO<sub>2</sub> enabled by continuous flow photoredox catalysis. *J. Am. Chem. Soc.* **139**, 13969–13972.
  54. Ishida, N., Masuda, Y., Uemoto, S., and Murakami, M. (2016). A light/ketone/copper system for carboxylation of allylic C–H bonds of alkenes with CO<sub>2</sub>. *Chemistry* **22**, 6524–6527.
  55. Ishida, N., Masuda, Y., Imamura, Y., Yamazaki, K., and Murakami, M. (2019). Carboxylation of benzylic and aliphatic C-H bonds with CO<sub>2</sub> induced by light/ketone/nickel. *J. Am. Chem. Soc.* **141**, 19611–19615.
  56. Schmalzbauer, M., Ghosh, I., and König, B. (2019). Utilising excited state organic anions for photoredox catalysis: activation of (hetero)aryl chlorides by visible light-absorbing 9-anthrolate anions. *Faraday Discuss* **215**, 364–378.
  57. Mutule, I., and Suna, E. (2005). Arylzinc species by microwave assisted Grignard formation-transmetalation sequence: application in the Negishi coupling. *Tetrahedron* **61**, 11168–11176.
  58. Hussey, A.S. (1951). The carbonation of Grignard reagent solutions. *J. Am. Chem. Soc.* **73**, 1364–1365.
  59. Nagaki, A., Takahashi, Y., and Yoshida, J. (2014). Extremely fast gas/liquid reactions in flow microreactors: carboxylation of short-lived organolithiums. *Chemistry* **20**, 7931–7934.
  60. Polyzos, A., O'Brien, M., Petersen, T.P., Baxendale, I.R., and Ley, S.V. (2011). The continuous-flow synthesis of carboxylic acids using CO<sub>2</sub> in a tube-in-tube gas permeable membrane reactor. *Angew. Chem. Int. Ed. Engl.* **50**, 1190–1193.
  61. Holy, N.L. (1974). Reactions of the radical anions and dianions of aromatic hydrocarbons. *Chem. Rev.* **74**, 243–277.
  62. Schlenk, W., and Bergmann, E. (1928). Forschungen auf dem gebiete der alkaliorganischen Verbindungen. I. Über produkte der addition von alkalimetall an mehrfache kohlenstoff-kohlenstoff-bindungen. *Justus Liebigs Ann. Chem.* **463**, 1–97.
  63. Walker, J.F., and Scott, N.D. (1938). Sodium naphthalene. II. Preparation and properties of dihydronaphthalene dicarboxylic acids. *J. Am. Chem. Soc.* **60**, 951–955.
  64. Gennaro, A., Isse, A.A., and Vianello, E. (1990). Solubility and electrochemical determination of CO<sub>2</sub> in some dipolar aprotic solvents. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **289**, 203–215.
  65. Montalti, M., Credi, A., Prodi, L., and Gandolfi, M.T. (2006). *Handbook of Photochemistry*, Third Edition (CRC Press).
  66. Mahboobi, S., Dove, S., Sellmer, A., Winkler, M., Eichhorn, E., Pongratz, H., Ciossek, T., Baer, T., Maier, T., and Beckers, T. (2009). Design of chimeric histone deacetylase- and tyrosine kinase-inhibitors: a series of imatinib hybrids as potent inhibitors of wild-type and mutant BCR-ABL, PDGF-Rbeta, and histone deacetylases. *J. Med. Chem.* **52**, 2265–2279.
  67. Hara, Y., Sato, E., Miyagishi, A., Aisaka, A., and Hibino, T. (1978). Synthesis and  $\beta$ -adrenergic blocking action of a new thiazolythiopropylamine derivative. *J. Pharm. Sci.* **67**, 1334–1335.
  68. Liu, H.B., Tang, H., Yang, D., and Ji, Q. (2011). Synthesis of arotinolol hydrochloride. *Chin. J. Pharm.* **42**, 641–644.
  69. Gschwend, H.W., and Rodriguez, H.R. (1979). Heteroatom-facilitated lithiations. In *Organic Reactions* (John Wiley & Sons, Inc.), pp. 1–360.
  70. Alley, P.W., and Shirley, D.A. (1958). The metalation of 1-phenyl- and 1-methylpyrazole with n-butyllithium. *J. Am. Chem. Soc.* **80**, 6271–6274.
  71. Marxer, A., and Siegrist, M. (1974). Über die umsetzung von 1-phenylpyrazol mit äthylmagnesiumbromid. 8. Mitteilung über grignard-reaktionen [1]. *Helv. Chim. Acta* **57**, 1988–2000.
  72. Banella, M.B., Bonucci, J., Vannini, M., Marchese, P., Lorenzetti, C., and Celli, A. (2019). Insights into the synthesis of poly(ethylene 2,5-furandicarboxylate) from 2,5-furandicarboxylic acid: steps toward environmental and food safety excellence in packaging applications. *Ind. Eng. Chem. Res.* **58**, 8955–8962.

73. Sousa, A.F., Vilela, C., Fonseca, A.C., Matos, M., Freire, C.S.R., Gruter, G.M., Coelho, J.F.J., and Silvestre, A.J.D. (2015). Biobased polyesters and other polymers from 2,5-furandicarboxylic acid: a tribute to furan excellency. *Polym. Chem.* **6**, 5961–5983.
74. Lange, J.P., van der Heide, E., van Buijtenen, J., and Price, R. (2012). Furfural-promising platform for lignocellulosic biofuels. *ChemSusChem* **5**, 150–166.
75. Cho, A., Byun, S., Cho, J.H., and Kim, B.M. (2019). AuPd-Fe<sub>3</sub>O<sub>4</sub> nanoparticle-catalyzed synthesis of furan-2,5-dimethylcarboxylate from 5-hydroxymethylfurfural under mild conditions. *ChemSusChem* **12**, 2310–2317.
76. Zhou, H., Hong, S., Zhang, H., Chen, Y., Xu, H., Wang, X., Jiang, Z., Chen, S., and Liu, Y. (2019). Toward biomass-based single-atom catalysts and plastics: highly active single-atom Co on N-doped carbon for oxidative esterification of primary alcohols. *Appl. Catal. B* **256**, 117767.
77. Fonseca, A.C., Lima, M.S., Sousa, A.F., Silvestre, A.J., Coelho, J.F.J., and Serra, A.C. (2019). Cinnamic acid derivatives as promising building blocks for advanced polymers: synthesis, properties and applications. *Polym. Chem.* **10**, 1696–1723.
78. Gunia-Krzyżak, A., Słoczyńska, K., Popiół, J., Koczurkiewicz, P., Marona, H., and Pękala, E. (2018). Cinnamic acid derivatives in cosmetics: current use and future prospects. *Int. J. Cosmet. Sci.* **40**, 356–366.
79. Seo, H., Katcher, M.H., and Jamison, T.F. (2017). Photoredox activation of carbon dioxide for amino acid synthesis in continuous flow. *Nat. Chem.* **9**, 453–456.
80. Lamy, E., Nadjó, L., and Saveant, J.M. (1977). Standard potential and kinetic parameters of the electrochemical reduction of carbon dioxide in dimethylformamide. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **78**, 403–407.
81. Xia, Q., Dong, J., Song, H., and Wang, Q. (2019). Visible-light photocatalysis of the ketyl radical coupling reaction. *Chemistry* **25**, 2949–2961.
82. Fuchigami, T., Inagi, S., and Atobe, M., eds. Appendix B: tables of physical data. In *Fundamentals and Applications of Organic Electrochemistry* (John Wiley & Sons Ltd), pp. 217–222.
83. Raghu, M., Grover, J., and Ramasastry, S.S.V. (2016). Cyclopenta[b]annulation of heteroarenes by organocatalytic  $\gamma$ [C(sp<sup>3</sup>)-H] functionalization of yrones. *Chemistry* **22**, 18316–18321.
84. Zhang, B., Mück-Lichtenfeld, C., Daniliuc, C.G., and Studer, A. (2013). 6-Trifluoromethylphenanthridines through radical trifluoromethylation of isonitriles. *Angew. Chem. Int. Ed. Engl.* **52**, 10792–10795.
85. Walton, J.C. (2018). Enhanced proton loss from neutral free radicals: toward carbon-centered superacids. *J. Phys. Chem. A* **122**, 1422–1431.