

Cite this: *Chem. Sci.*, 2020, **11**, 11936

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 18th August 2020  
Accepted 5th October 2020

DOI: 10.1039/d0sc04548a

rsc.li/chemical-science

## Carbonate-promoted C–H carboxylation of electron-rich heteroarenes†

Tyler M. Porter and Matthew W. Kanan \*

C–H carboxylation is an attractive transformation for both streamlining synthesis and valorizing CO<sub>2</sub>. The high bond strength and very low acidity of most C–H bonds, as well as the low reactivity of CO<sub>2</sub>, present fundamental challenges for this chemistry. Conventional methods for carboxylation of electron-rich heteroarenes require very strong organic bases to effect C–H deprotonation. Here we show that alkali carbonates (M<sub>2</sub>CO<sub>3</sub>) dispersed in mesoporous TiO<sub>2</sub> supports (M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>) effect CO<sub>3</sub><sup>2–</sup>-promoted C–H carboxylation of thiophene- and indole-based heteroarenes in gas–solid reactions at 200–320 °C. M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> materials are strong bases in this temperature regime, which enables deprotonation of very weakly acidic bonds in these substrates to generate reactive carbanions. In addition, we show that M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> enables C3 carboxylation of indole substrates via an apparent electrophilic aromatic substitution mechanism. No carboxylations take place when M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> is replaced with un-supported M<sub>2</sub>CO<sub>3</sub>, demonstrating the critical role of carbonate dispersion and disruption of the M<sub>2</sub>CO<sub>3</sub> lattice. After carboxylation, treatment of the support-bound carboxylate products with dimethyl carbonate affords isolable esters and the M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> material can be regenerated upon heating under vacuum. Our results provide the basis for a closed cycle for the esterification of heteroarenes with CO<sub>2</sub> and dimethyl carbonate.

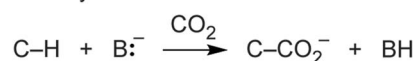
## Introduction

C–H carboxylation (Scheme 1) is a compelling alternative to conventional syntheses of carboxylic acids that utilize oxidative transformations or more functionalized substrates and has attracted attention as a way to expand the use of CO<sub>2</sub> in chemical production.<sup>1–3</sup> However, carboxylation faces the challenge of overcoming the low reactivity of C–H bonds and CO<sub>2</sub>, and it lacks the large intrinsic driving force of other C–H functionalizations such as oxidation or amination. The insertion of CO<sub>2</sub> into C–H bonds to form a carboxylic acid is actually endergonic on account of the small Δ*H* and negative Δ*S*, while C–H carboxylation is exergonic (depending on base strength) because of the driving force from deprotonation. Increased interest in this transformation over the last several years has led to a number of methods that encompass both acid–base<sup>2,4–9</sup> (ionic) and radical mechanisms<sup>2,10–14</sup> for C–H activation. Despite these recent advances, most methods for C–H carboxylation under conventional, solution-phase conditions require highly reactive, resource-intensive reagents to activate C–H bonds. As such, the development of alternatives that use benign,

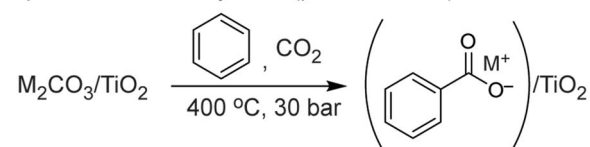
regenerable reagents is critical to create opportunities for scalable CO<sub>2</sub> utilization.

The carboxylation of aromatic substrates is of particular interest for the synthesis of a wide variety of both fine and commodity chemicals.<sup>2,15–19</sup> Because of the high bond

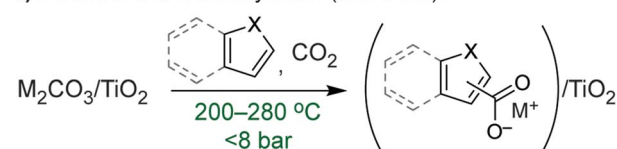
## a) C–H Carboxylation



## b) Benzene Carboxylation (previous work):



## c) Heteroarene Carboxylation (this work):



**Scheme 1** (a) General scheme for base-promoted C–H carboxylation; (b) C–H carboxylation of benzene using dispersed alkali carbonates (M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>); (c) C–H carboxylation of heteroarenes using M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>.

Department of Chemistry, Stanford University, Stanford, California 94305, USA.  
E-mail: mkanan@stanford.edu

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc04548a

dissociation enthalpy (BDE) of aromatic C–H bonds, acid–base (ionic) activation of the substrate has been the most commonly employed strategy. For some substrates, deprotonation of an X–H bond (X = heteroatom) generates a nucleophilic intermediate that undergoes C–H carboxylation *via* an electrophilic aromatic substitution (EAS) mechanism. The classic example is the Kolbe–Schmidt reaction used for aspirin synthesis, in which phenol is transformed into salicylate by reaction with hydroxide and CO<sub>2</sub>.<sup>20</sup> While the carboxylation of indoles and pyrroles has been achieved similarly,<sup>6,8,21</sup> these reactions have required the use of superstoichiometric LiO<sup>t</sup>Bu to deprotonate the N–H bonds.

Apart from these special cases, carboxylation of (hetero)arene substrates *via* acid–base chemistry requires direct activation of the C–H bond to generate a reactive carbon-centered nucleophile. Within the last decade, several groups have demonstrated Brønsted-base-promoted carboxylation of (hetero)arenes in organic solvents at near ambient CO<sub>2</sub> pressure.<sup>4,6–9,21</sup> Hu *et al.* have shown that relatively acidic heteroarenes (pK<sub>a</sub> up to 28 in organic solvent) can be carboxylated using Cs<sub>2</sub>CO<sub>3</sub> as the base in refluxing DMF.<sup>4,7</sup> The carboxylation of electron-rich heteroarenes beyond this pK<sub>a</sub> threshold, however, has required much stronger bases. For example, the carboxylation of benzothiophene (pK<sub>a</sub> of 33 in THF) was not possible under these same conditions.<sup>4</sup> Recently, Kondo *et al.* have demonstrated the carboxylation of a diverse set of (benzo)thiophenes and (benzo)furans by reaction with excess LiO<sup>t</sup>Bu, CsF, and crown ether at 160 °C under a CO<sub>2</sub> atmosphere.<sup>9</sup> However, these conditions were not able to carboxylate protected indoles, such as 1-methylindole, whose C2 carbon has a pK<sub>a</sub> near 38. Carboxylation of electron rich heteroarenes functionalized with an amide directing group has been achieved using Ni catalysis with stoichiometric KO<sup>t</sup>Bu and Mn<sup>0</sup>.<sup>22</sup>

Arenes have pK<sub>a</sub>s that generally lie beyond what can be measured (pK<sub>a</sub> > 40). Researchers have developed methods to carboxylate arenes that are functionalized with a directing group by using a Rh or Pd species to catalyze C–H activation.<sup>23–25</sup> In addition to the directing group and catalyst, these methods also require a strong base (KO<sup>t</sup>Bu) or Lewis acid activator (AlMe(OMe)<sub>2</sub>) to engender reactivity. In the absence of a directing group, solution-phase arene C–H carboxylation requires an extremely strong base such as Schlosser's base,<sup>26</sup> or stoichiometric aluminum reagents.<sup>25,27</sup>

Apart from acid–base strategies, a very recent report by König *et al.* has described a photoredox method to carboxylate of (hetero)arenes under mild conditions in which the substrate is activated by one-electron photoreduction and Cs<sub>2</sub>CO<sub>3</sub> serves as the stoichiometric base.<sup>28</sup> This method affords moderate to high yields across a variety of substrates, although it is presently incompatible with some classes of (hetero)arene substrates and uses relatively high loadings of a photocatalyst requiring multi-step synthesis.

We previously showed that simple alkali carbonates (M<sub>2</sub>CO<sub>3</sub>) can promote C–H carboxylation of very weakly acidic substrates in solvent-free, alkali salt media at elevated temperature.<sup>29–32</sup> This transformation is particularly useful for converting a monocarboxylate substrate into a dicarboxylate product,

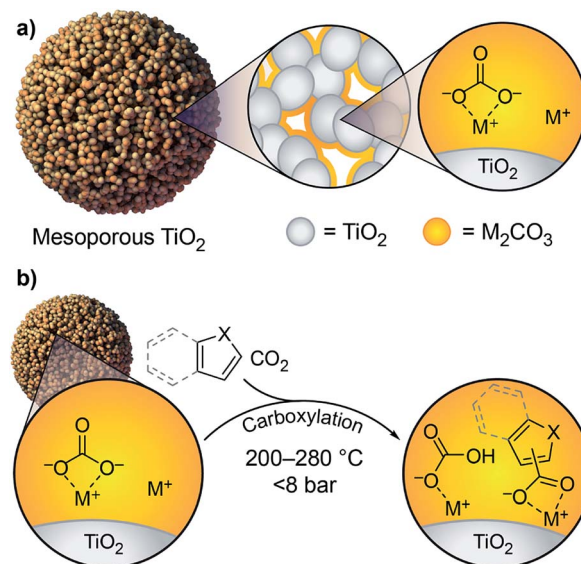


Fig. 1 (a) Schematic view of M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> showing the M<sub>2</sub>CO<sub>3</sub> dispersed over the mesoporous TiO<sub>2</sub> surface; (b) heteroarene C–H carboxylation promoted by M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>. Note that MHCO<sub>3</sub> is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv. M<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, and CO<sub>2</sub>.

where the substrate enables the formation of a molten reaction medium.<sup>33</sup> More recently, we demonstrated that M<sub>2</sub>CO<sub>3</sub> dispersed into mesoporous TiO<sub>2</sub> (M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>, Fig. 1a) promotes the carboxylation of benzene and other aromatic hydrocarbon C–H bonds in gas–solid reactions (Scheme 1b).<sup>34</sup> Dispersion in mesopores disrupts the bulk M<sub>2</sub>CO<sub>3</sub> crystal structure, creating an amorphous material that can attain superbase reactivity, even in the presence of CO<sub>2</sub>. This carbonate-promoted C–H carboxylation of aromatic hydrocarbons takes place at moderate pressures and temperatures of ~400 °C. In this study, we begin to assess the generality and selectivity of this strategy using electron-rich heteroarenes, which have somewhat more acidic C–H bonds. We show that gas–solid carbonate-promoted C–H carboxylation occurs at substantially lower temperatures for these substrates and that selective reactions are possible in the presence of multiple C–H bonds (Scheme 1c, Fig. 1b). For thiophene substrates, the selectivity and mechanistic studies support a carboxylation pathway that proceeds *via* C–H deprotonation by the amorphous CO<sub>3</sub><sup>2–</sup>, as seen previously with arenes. For more nucleophilic indole substrates, however, carboxylation proceeds *via* electrophilic aromatic substitution, which provides a new pathway for CO<sub>2</sub> utilization enabled by dispersed carbonate materials.

## Results and discussion

### Acidity calculations

Thiophene- and indole-based heterocycles were selected as C–H carboxylation substrates to probe the effects of C–H acidity and  $\pi$ -nucleophilicity. The C–H acidities were evaluated by using density functional theory (DFT) to calculate the standard



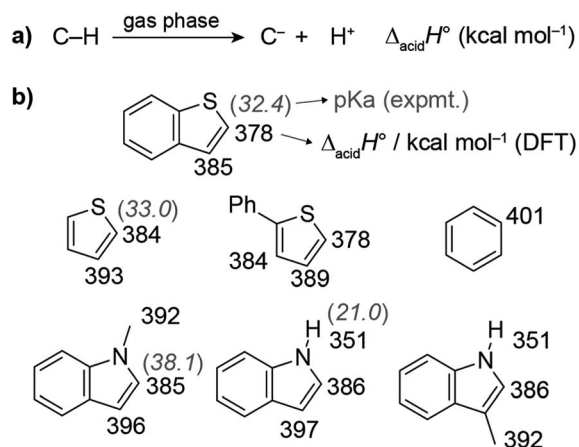


Fig. 2 (a) Schematic depiction of gas-phase heterolytic C–H bond dissociation. The standard enthalpy of this reaction is the gas phase acidity. (b) Calculated gas phase acidities and experimental  $pK_a$ s of the most acidic C–H bonds in the heteroarene substrates. Benzene is included as a reference point.

enthalpy change for heterolytic bond dissociation in the gas phase ( $\Delta_{\text{acid}}H^\circ$ , also known as the gas phase acidity) (Fig. 2 and S1†).<sup>35,36</sup>  $\Delta_{\text{acid}}H^\circ$  provides a way to compare the thermodynamics of deprotonation irrespective of whether the  $pK_a$  can be measured. Benzene, which reacts with dispersed carbonates at  $\sim 400^\circ\text{C}$ , has a  $\Delta_{\text{acid}}H^\circ$  of  $401 \text{ kcal mol}^{-1}$ ; its  $pK_a$  is too large to be measured but has been estimated to be  $>43$ .<sup>36</sup> The most acidic C–H bonds in each heterocycle were found to be more acidic (lower  $\Delta_{\text{acid}}H^\circ$ ) than benzene by  $15\text{--}23 \text{ kcal mol}^{-1}$ , while the separation between the two most acidic C–H bonds in each substrate was  $6\text{--}11 \text{ kcal mol}^{-1}$ . For comparison, the experimental  $pK_a$  values of benzothiophene (C2), thiophene (C2), and 1-methylindole (C2) are 32, 33, and 38 according to measurements performed in THF.<sup>36,37</sup> Additional DFT calculations to determine solution state  $pK_a$  values showed good agreement to these experimental values (Fig. S2†).

### Carbonate-promoted C–H carboxylation reactions

C–H carboxylation reactions were performed in a sealed vessel containing  $\text{M}_2\text{CO}_3$  dispersed on  $\text{TiO}_2$  ( $\text{M}_2\text{CO}_3/\text{TiO}_2$ ,  $\text{M}^+ = \text{Cs}^+$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ), heterocycle substrate, and  $\text{CO}_2$  (see ESI† for detailed experimental procedures). In most cases, the substrate was placed within a glass culture tube in the reactor to ensure that only volatilized substrate would be able to react with the  $\text{M}_2\text{CO}_3/\text{TiO}_2$  material (Fig. S3†). The products were isolated by aqueous extraction from the  $\text{TiO}_2$  support and quantified by  $^1\text{H}$  NMR (Fig. S4–S9†). In all cases, control experiments using  $\text{M}_2\text{CO}_3$  without the  $\text{TiO}_2$  support showed no reactivity, whereas  $\text{M}_2\text{CO}_3/\text{TiO}_2$  promoted C–H carboxylation in varying degrees depending on the identity of  $\text{M}^+$ . Additional control experiments showed minimal reactivity with the mesoporous  $\text{TiO}_2$  support alone.

We first assessed the temperature dependence of C–H carboxylation under a common set of conditions using  $1.5 \text{ mmol}$  substrate, a  $\text{CO}_2$  loading corresponding to  $4\text{--}5 \text{ bar}$  at the reaction temperature, and a reaction time of  $3 \text{ h}$  (Fig. 3 and S10†). The

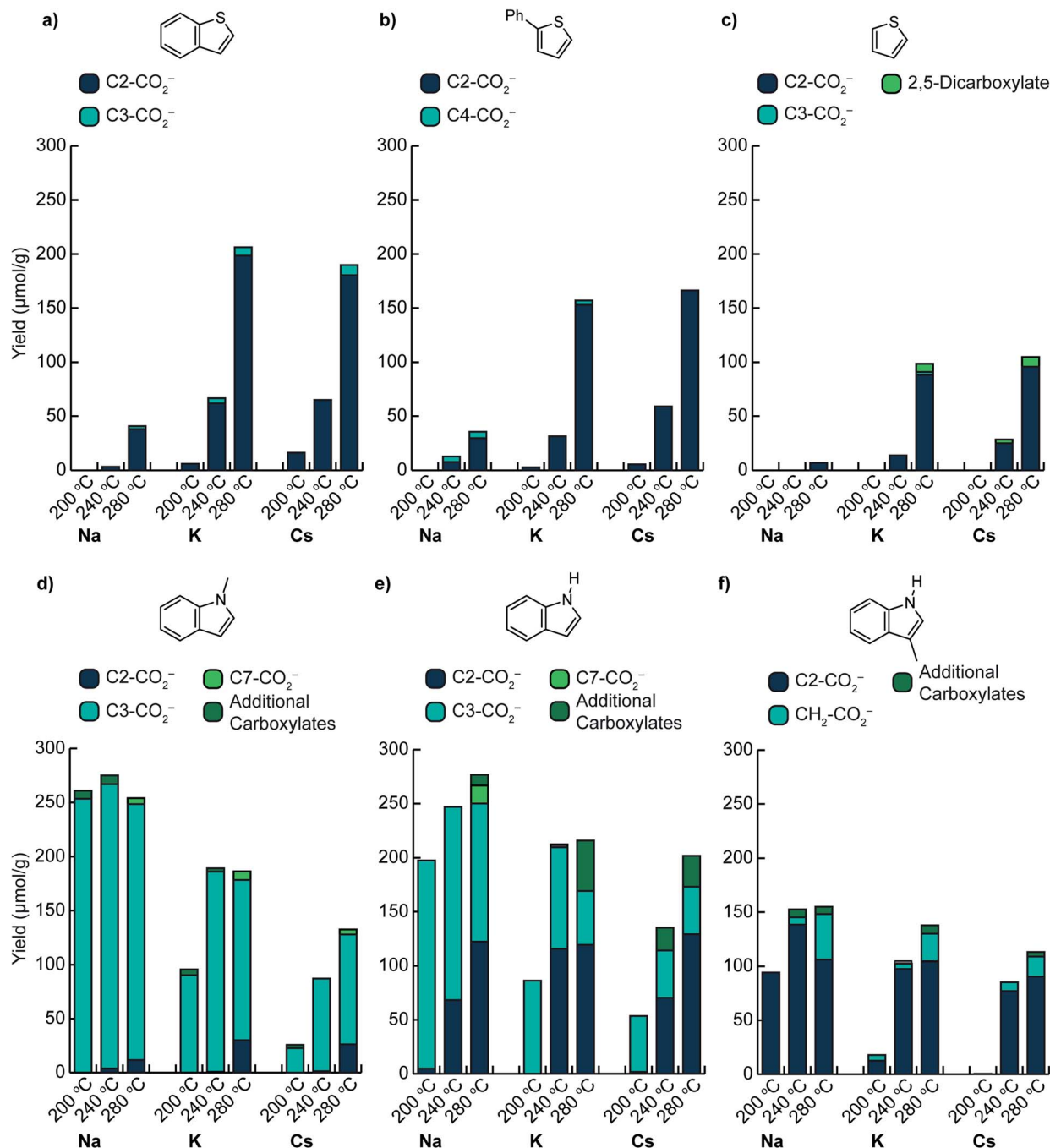
relatively low substrate loading corresponded to a maximum pressure of  $\sim 2.5 \text{ bar}$  at the highest temperature evaluated ( $320^\circ\text{C}$ ). Thus, the overall pressure of the reactor at temperature was  $<8 \text{ bar}$  for all of the reactions in this temperature screen. For benzothiophene (Fig. 3a), the onset of carboxylation reactivity was observed at  $200^\circ\text{C}$ . Optimal results were seen at  $280^\circ\text{C}$ , where  $190 \mu\text{mol}$  of benzothiophene carboxylation product was obtained per gram of  $\text{TiO}_2$  ( $190 \mu\text{mol g}^{-1} \text{ TiO}_2$ ) with a  $20 : 1$  ratio of 2-carboxylate to 3-carboxylate isomers for  $\text{Cs}_2\text{CO}_3/\text{TiO}_2$ . Using  $\text{K}_2\text{CO}_3/\text{TiO}_2$ ,  $207 \mu\text{mol g}^{-1} \text{ TiO}_2$  of benzothiophene carboxylate product was obtained with a  $25 : 1$  product ratio (Fig. 3a). While both the yield and selectivity declined at higher temperatures, the carboxylation selectivity followed the C–H acidities, consistent with a mechanism gated by C–H deprotonation (see below). In contrast to  $\text{Cs}^+$  and  $\text{K}^+$ , much lower reactivity was observed with  $\text{Na}_2\text{CO}_3/\text{TiO}_2$ , suggesting that this material is a weaker base in gas–solid reactions.

Comparison of benzothiophene carboxylation with our previous results for benzene carboxylation further highlights the effect of C–H acidity on carboxylation. Whereas  $>200 \mu\text{mol g}^{-1} \text{ TiO}_2$  of carboxylate products were obtained for benzothiophene at  $280^\circ\text{C}$  and  $<8 \text{ bar}$  total pressure, the maximum yields for benzene carboxylation using the same  $\text{M}_2\text{CO}_3/\text{TiO}_2$  materials were  $\sim 100 \mu\text{mol g}^{-1} \text{ TiO}_2$  at  $420\text{--}440^\circ\text{C}$  and  $\sim 30 \text{ bar}$  total pressure. Thus, reducing the C–H bond acidity ( $\Delta_{\text{acid}}H^\circ$ ) by  $23 \text{ kcal mol}^{-1}$  enables higher yielding carboxylation reactions under substantially milder conditions ( $100^\circ\text{C}$  lower temperature,  $1/3$  the total pressure). Furthermore, the benzothiophene results also demonstrate that a  $7 \text{ kcal mol}^{-1}$  separation in C–H acidity (C2 vs. C3 position) is sufficient for selective C–H carboxylation.

Because of its high boiling point ( $221^\circ\text{C}$ ), the vapor pressure of benzothiophene is expected to reach its saturation pressure at  $T \leq 240^\circ\text{C}$  under the conditions used for the data in Fig. 3a (see Table S1† for saturation vapor pressures calculated using the Clausius–Clapeyron equation). As a result, the vapor pressure of benzothiophene varies by  $\sim 5\times$  over the  $200\text{--}320^\circ\text{C}$  range examined. To deconvolute temperature dependence from substrate pressure dependence, a series of carboxylation reactions were performed at  $280^\circ\text{C}$  for  $3 \text{ h}$  using different amounts of benzothiophene corresponding to calculated pressures ranging from  $0.5 \text{ bar}$  to  $3.5 \text{ bar}$ , which is approximately the saturation pressure at  $280^\circ\text{C}$ . The total benzothiophene carboxylate yield showed a modest variation from  $150 \mu\text{mol g}^{-1} \text{ TiO}_2$  to  $210 \mu\text{mol g}^{-1} \text{ TiO}_2$  over this range (Fig. S17†). Thus, the temperature dependence of the benzothiophene carboxylation yield in Fig. 3a is primarily a result of the temperature effect on the rate constant.

Phenylthiophene reacted in a very similar manner to benzothiophene. The onset of carboxylation was observed at  $200^\circ\text{C}$  with very high selectivity for the 5-phenylthiophene-2-carboxylate isomer (derived from the most acidic C–H bond) observed up to  $280^\circ\text{C}$ . Comparable yields were observed for  $\text{Cs}_2\text{CO}_3/\text{TiO}_2$  and  $\text{K}_2\text{CO}_3/\text{TiO}_2$ , while substantially lower yields were seen for  $\text{Na}_2\text{CO}_3/\text{TiO}_2$  (Fig. 3b). The carboxylate yield varied by  $\sim 50\%$  over a 7-fold variation in phenylthiophene pressure ( $0.5\text{--}3.5 \text{ bar}$ ) at  $320^\circ\text{C}$  (Fig. S17†). The similarity in the





**Fig. 3** Summary of C–H carboxylation for heteroarenes using  $M_2CO_3/TiO_2$  and  $CO_2$  at various temperatures ((a) benzothiophene, (b) 2-phenylthiophene, (c) thiophene, (d) 1-methylindole, (e) indole, (f) 3-methylindole). Reactions were performed using glass culture tubes to separate un-vaporized organics from the  $M_2CO_3/TiO_2$  materials. Conditions: 250 mg  $M_2CO_3/TiO_2$ , 1.5 mmol heterocycle, 2.5 bar  $CO_2$  at 298 K, 3 h reaction time.

temperature- and pressure-dependent yields for both benzothiophene and phenylthiophene is reflected in their nearly identical  $\Delta_{acid}H^\circ$  values for their two most acidic C–H bonds, suggesting that the same mechanism is operative for both substrates. Notably, although separating the substrate with a culture tube in the reactor ensures that it can only interact with the  $M_2CO_3$  *via* the gas phase, the carboxylation reactions with low-volatility substrates like benzothiophene and

phenylthiophene proceed in comparable or better yield when the two are combined directly (Fig. S11†).

In contrast to the heterocycle pressure dependence, increasing  $CO_2$  pressures were found to significantly inhibit C–H carboxylation for both substrates (Fig. S18†). The  $CO_2$  pressure dependence was evaluated for benzothiophene and phenylthiophene at 280 °C and 320 °C, respectively. Interestingly, inspection of the culture tubes for both substrates post-reaction revealed increasing amounts of un-vaporized



heterocycle with increasing CO<sub>2</sub> partial pressure (Fig. S18†). While the calculated saturation pressures indicate that all of the 1.5 mmol of substrate should be vaporized at these temperatures, this observation suggests that CO<sub>2</sub> dissolves in the substrate upon melting and lowers its vapor pressure substantially. An additional contributing factor may be that higher CO<sub>2</sub> pressure results in the formation of polycarbonate species (e.g. C<sub>2</sub>O<sub>5</sub><sup>2-</sup>) on the M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> material, which are weaker bases than CO<sub>3</sub><sup>2-</sup>, thereby reducing the rate of C–H deprotonation.

C–H carboxylation was also possible with thiophene itself. In the temperature screen performed with 1.5 mmol substrate (Fig. 3c), all of the thiophene is expected to be volatilized over the 200–320 °C range because of its relatively low boiling point (84 °C). The corresponding thiophene pressures range from 2–2.5 bar. In contrast to benzothiophene and phenylthiophene, no thiophene carboxylates were observed at 200 °C, which is consistent with the 6 kcal mol<sup>−1</sup> higher Δ<sub>acid</sub>H° for its C(2)–H bond (Fig. 2). The formation of thiophene-2-carboxylate was observed beginning at 240 °C, with optimal results at 280 °C, where 96 μmol g<sup>−1</sup> TiO<sub>2</sub> was formed along with 9 μmol g<sup>−1</sup> TiO<sub>2</sub> thiophene-2,5-dicarboxylate when using Cs<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>. Comparable yields were obtained with K<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>, while Na<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> was much less effective. The observation of thiophene-2,5-dicarboxylate indicates that the initially formed monocarboxylate product undergoes a second C–H carboxylation on the support. In addition to the thiophene carboxylates, ~25 μmol g<sup>−1</sup> TiO<sub>2</sub> of propionate was produced across the temperature range of 240–320 °C (Table S12†). This product arises from an unknown decomposition pathway starting from thiophene or a thiophene carboxylate. The yield of thiophene carboxylates was improved by increasing the thiophene pressure to 5 bar, with a comparable proportion of propionate byproduct

(Fig. S17†). In contrast to benzothiophene and phenylthiophene, essentially no CO<sub>2</sub> pressure dependence was observed for thiophene at 280 °C. Given the much higher volatility of thiophene, CO<sub>2</sub> has a negligible effect on its vapor pressure at this temperature.

We next investigated the effects of increasing the nucleophilicity of the heterocycle by switching from thiophene to indole substrates.<sup>38</sup> To avoid the complication of an acidic N–H bond, we first evaluated 1-methylindole. The most acidic C–H position of this substrate is C(2)–H, whose Δ<sub>acid</sub>H° (384 kcal mol<sup>−1</sup>) is very close to the C(2)–H bond of thiophene (Fig. 2). The most nucleophilic position, however, is C3,<sup>39</sup> which has a much less acidic C–H bond (Δ<sub>acid</sub>H° of C(3)–H is 11 kcal mol<sup>−1</sup> higher than C(2)–H). Surprisingly, C–H carboxylation occurred readily at 200 °C with a strong preference for the C3 position (Fig. 3d). Moreover, the yield *increased* substantially as the alkali cation size was decreased, resulting in the highest yields for reactions using Na<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub>. Optimal results were obtained using Na<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> at 200 °C, with a yield of 250 μmol g<sup>−1</sup> TiO<sub>2</sub> for the C3-carboxylate (Fig. 3d and S8†). At higher temperatures (*T* > 240 °C) the C2-carboxylate was observed as an additional minor product. The selective formation of the C3 carboxylate is consistent with an EAS mechanism in which C–C bond formation precedes C–H deprotonation. Further support was found in the kinetic isotope effect for C–H carboxylation and DFT calculations (see below). Previously reported methods have achieved selective C3 carboxylation of 1-methylindole with CO<sub>2</sub>, but have required the use of stoichiometric organoaluminum reagents.<sup>25,40,41</sup> Na<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> provides a benign and much less resource-intensive alternative.

Selective C3 carboxylation was also observed with indole at 200 °C using M<sub>2</sub>CO<sub>3</sub>/TiO<sub>2</sub> (Fig. 3e). The M<sub>2</sub>CO<sub>3</sub> dependence followed the same trend as for 1-methylindole, with optimal

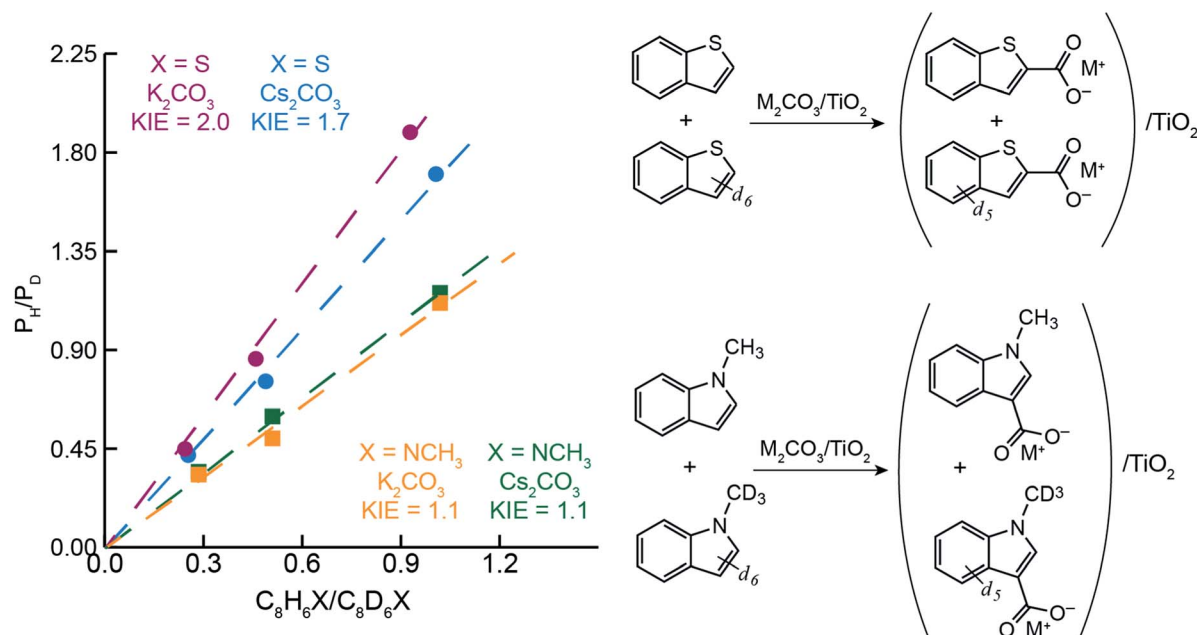


Fig. 4 Ratio of protiated to deuterated products obtained from CO<sub>3</sub><sup>2-</sup>-promoted C–H carboxylation vs. the ratio of C<sub>8</sub>H<sub>6</sub>X to C<sub>8</sub>D<sub>6</sub>X (where X = S, NCH<sub>3</sub>, or NCD<sub>3</sub>) at 260 °C and 0.5 h for benzothiophene (top-right) and 200 °C and 1.5 h for methylindole (bottom-right).



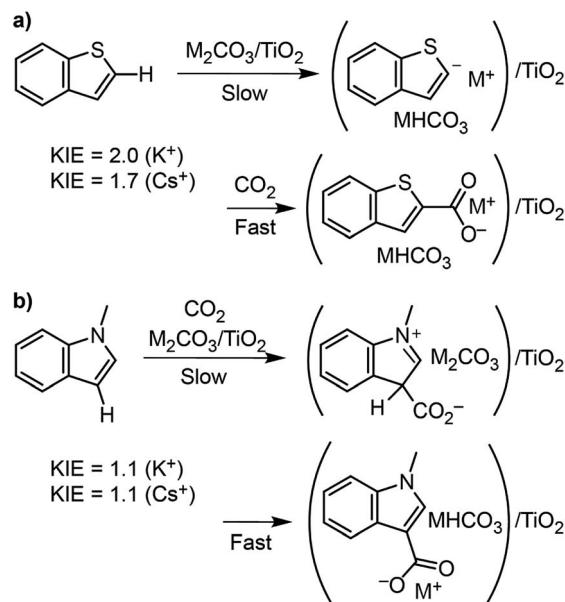
results obtained using  $\text{Na}_2\text{CO}_3/\text{TiO}_2$ . Because the N–H functionality on indole is much more acidic than the C–H bonds ( $\geq 35 \text{ kcal mol}^{-1}$  difference in  $\Delta_{\text{acid}}H^\circ$ ), it is likely that indole is rapidly deprotonated by  $\text{M}_2\text{CO}_3/\text{TiO}_2$  to form indolide, which can react reversibly with  $\text{CO}_2$  to form indole-1-carboxylate ( $\text{N}-\text{CO}_2^-$ ). Given the very low acidity of the C–H bond at C3 ( $\Delta_{\text{acid}}H^\circ = 397 \text{ kcal mol}^{-1}$ , Fig. 2), the selectivity for C3 carboxylation at  $200^\circ\text{C}$  is consistent with an EAS mechanism in which deprotonated indole is the reactive nucleophile.<sup>39</sup> Beyond  $200^\circ\text{C}$ , however, the reaction yielded a mixture of C3, C2, and C7 carboxylation products. At  $280^\circ\text{C}$ , C2 carboxylation accounted for 44–64% of the total carboxylation products depending on the choice of  $\text{M}_2\text{CO}_3$ . Substitution at C2 is commonly seen alongside C3 in solution-phase EAS reactions with indole.<sup>42</sup> Both methylindole and indole showed very similar pressure dependences on both heterocycle and  $\text{CO}_2$  partial pressure (Fig. S17 and S18†).

Finally, 3-methylindole (skatole) was evaluated to assess the effects of blocking carboxylation at C3. Carboxylation was observed at C2 with a similar temperature dependence as seen for C2 carboxylation of indole (Fig. 3f). Using  $\text{Na}_2\text{CO}_3/\text{TiO}_2$ ,  $94 \mu\text{mol g}^{-1} \text{TiO}_2$  of the C2-carboxylate was obtained at  $200^\circ\text{C}$ . Increasing the temperature to  $240^\circ\text{C}$  boosted the yield to  $138 \mu\text{mol g}^{-1} \text{TiO}_2$ , although minor amounts of additional carboxylates were observed at this temperature, including the product of methyl carboxylation. To our knowledge, C2 carboxylation of 3-methylindole with  $\text{CO}_2$  has not previously been achieved.

### Kinetic isotope effects and DFT calculations to probe C–H carboxylation mechanism

To better understand the differences in thiophene- vs. indole-based heteroarene C–H carboxylation, kinetic isotope effects (KIEs) were measured using intermolecular competition experiments.<sup>43</sup> C–H carboxylation reactions were performed for 1-methylindole ( $200^\circ\text{C}$ , 1.5 h) and benzothiophene ( $260^\circ\text{C}$ , 0.5 h) using various ratios of protiated and deuterated substrate (Fig. 4).<sup>34</sup> KIE values of 2.0 and 1.7 were observed for C2 carboxylation of benzothiophene using  $\text{K}_2\text{CO}_3/\text{TiO}_2$  and  $\text{Cs}_2\text{CO}_3/\text{TiO}_2$ , respectively. These values are consistent with a mechanism in which C–H deprotonation is slow and the resulting carbanion reacts rapidly with  $\text{CO}_2$  (Scheme 2) and does not support an EAS mechanism. In addition, previous studies of benzothiophene substitution with strong electrophiles have shown selective substitution at C3, indicating that this is the preferred position for EAS reactivity.<sup>39,44,45</sup> The KIE values for benzothiophene are similar to what we have previously observed for benzene C–H carboxylation using the same  $\text{M}_2\text{CO}_3/\text{TiO}_2$  materials,<sup>34</sup> as well as solid base-catalyzed reactions that feature rate-determining deprotonation.<sup>46</sup>

In contrast to benzothiophene, a KIE value of 1.1 was observed for C3 carboxylation of 1-methylindole, which is within NMR quantification error of 1.0. The disparity in KIE values for these two substrates indicates distinct mechanisms for their C–H carboxylation reactivity. The lack of a KIE for 1-methylindole is consistent with an EAS mechanism at  $200^\circ\text{C}$  in



**Scheme 2** Proposed C–H carboxylation mechanisms for (a) benzothiophene and (b) 1-methylindole. Note that  $\text{MHCO}_3$  is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv.  $\text{M}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ , and  $\text{CO}_2$ .

which attack of the  $\pi$  system on  $\text{CO}_2$  precedes C–H deprotonation (Scheme 2). To our knowledge, an EAS reaction between  $\text{CO}_2$  and a neutral substrate has not previously been reported. DFT calculations were performed to assess the feasibility of such a pathway with 1-methylindole. Calculations performed using either vacuum or low dielectric solvents ( $\epsilon < 9$ ) failed to identify a transition state or putative EAS intermediate, suggesting that a gas-phase reaction between 1-methylindole and  $\text{CO}_2$  is unlikely. With a higher dielectric ( $\epsilon > 20$ ), however, an EAS transition state was identified that is  $\sim 30 \text{ kcal mol}^{-1}$  higher in energy than the substrates (Fig. S19†). Interestingly, the zwitterionic intermediate resulting from  $\text{CO}_2$  addition was very close in energy to the transition state, indicating that the reverse reaction is extremely rapid. Together, the KIE and DFT results suggest that the carboxylation of methylindole takes place *via* an EAS mechanism with substrate that is adsorbed onto the  $\text{M}_2\text{CO}_3/\text{TiO}_2$  material. The amorphous carbonate provides a dielectric to stabilize the transition state for  $\text{CO}_2$  addition and a proximal base that can immediately deprotonate the putative zwitterionic intermediate. The higher yield for  $\text{Na}_2\text{CO}_3/\text{TiO}_2$  may reflect a stronger adsorption of 1-methylindole because of the higher charge density for  $\text{Na}^+$ . Further studies incorporating atomistic modeling of the amorphous carbonate surface are needed to assess this pathway more thoroughly. Nonetheless, the DFT results indicate that an EAS-like mechanism is possible.

### Carboxylate esterification and $\text{M}_2\text{CO}_3/\text{TiO}_2$ regeneration

In our previous study of arene C–H carboxylation, we showed that arene carboxylates could be isolated as methyl esters with concomitant regeneration of the  $\text{M}_2\text{CO}_3/\text{TiO}_2$  material by



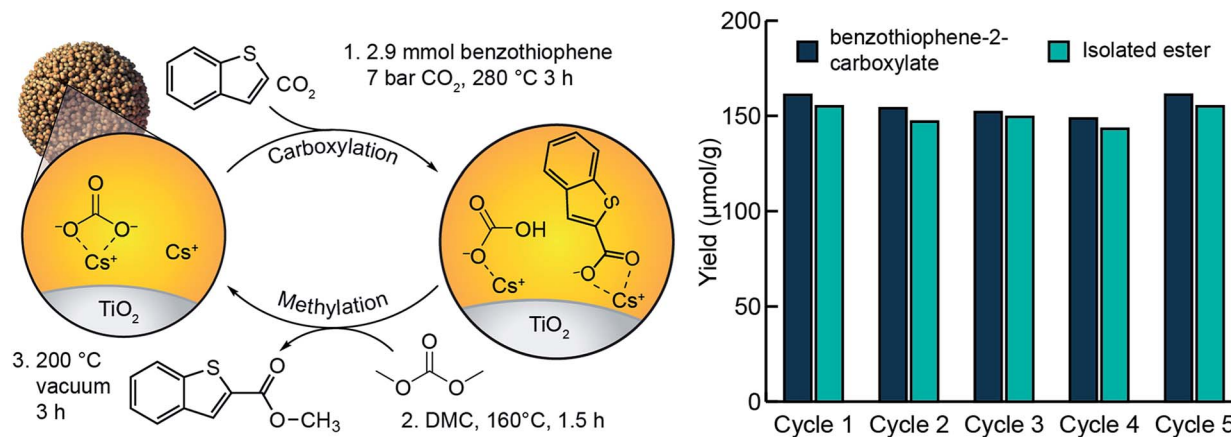


Fig. 5 Cycling steps and yields for benzothiophene esterification using  $\text{Cs}_2\text{CO}_3/\text{TiO}_2$ . Reaction conditions: carboxylation at 280 °C for 3 h, esterification at 160 °C for 1.5 h, followed by a regeneration cycle at 200 °C for 3 h under reduced pressure.

subjecting the carboxylation product to flowing  $\text{CO}_2$  and methanol at elevated temperatures.<sup>34</sup> The same procedure was unsuccessful for isolating heteroarene carboxylate esters because their high boiling points (>300 °C) necessitated temperatures that led to decomposition under the reaction conditions. The use of flowing  $\text{CO}_2$  and dimethyl carbonate enabled isolation of methyl esters, but the yields were <50% (Fig. S20†). Instead, it was found that we could isolate the ester at near quantitative yields by heating the supported heteroarene carboxylate ( $(\text{RCOOM})/\text{TiO}_2$ ) in neat dimethyl carbonate at 160 °C within a stainless-steel batch reactor (Fig. S21†). Subsequent heating of the support material under vacuum resulted in regeneration of  $\text{M}_2\text{CO}_3/\text{TiO}_2$ . After establishing optimal carboxylation and methylation conditions, we assessed the ability of  $\text{M}_2\text{CO}_3/\text{TiO}_2$  to catalyze a closed heteroarene esterification cycle over multiple iterations (Fig. 5). When a single sample of  $\text{Cs}_2\text{CO}_3/\text{TiO}_2$  was used for 5 cycles, methyl benzothiophene-2-carboxylate was isolated as the only detectable product by NMR (Fig. S16†) from each cycle with an average yield of  $150 \mu\text{mol g}^{-1} \text{TiO}_2$ . In each cycle following the methylation step, an aliquot of the support (~50 mg) was analyzed by aqueous extraction and  $^1\text{H}$  NMR to detect unreacted, supported carboxylate. In all cases, no supported carboxylates were observed, indicating complete methylation. Over the five cycles, no indication of catalyst degradation was observed (Fig. 5). These results support previous observations of the ability for dispersed carbonates to catalyze a closed esterification cycle,<sup>34</sup> and extend the substrate scope to include heteroarenes.

## Conclusion

Conventional solution-phase methods for C–H carboxylation of aromatic substrates with low C–H acidity have relied on the use of highly reactive and resource-intensive organic bases. Our results show that  $\text{CO}_3^{2-}$  can serve as a benign, regenerable base for C–H carboxylation *via* a gas–solid reaction utilizing a dispersed, amorphous carbonate material. Compared to

reactions with benzene and other arenes using the same  $\text{M}_2\text{CO}_3/\text{TiO}_2$  materials, the heteroarene carboxylations investigated here reach higher yields (up to  $250 \mu\text{mol g}^{-1} \text{TiO}_2$ ) under substantially milder conditions (200 °C lower temperature, 1/3 the total pressure). Thiophene-based heterocycles react preferentially at the most acidic C–H bond. The temperature-dependent selectivity and KIE measured for benzothiophene are consistent with a mechanism in which C–H deprotonation is followed by C–C bond formation. In contrast, indole-based heterocycles react preferentially at the most nucleophilic position (C3). DFT calculations and the absence of a significant KIE support an EAS mechanism for the carboxylation of 1-methylindole, which nonetheless requires dispersed carbonate. The combination of  $\text{CO}_3^{2-}$ -promoted C–H carboxylation and methylation with dimethyl carbonate provides a two-step cycle to convert aromatic heteroarenes into methyl esters with regeneration of  $\text{M}_2\text{CO}_3/\text{TiO}_2$ . Ongoing work seeks to improve the efficiency of this cycle by using alternative supports to increase the loading of reactive carbonate and access reactivity at lower temperatures.

## Conflicts of interest

The authors declare no competing financial interests.

## Acknowledgements

This work was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Science under award DE-SC0020394 and the TomKat Center for Sustainable Energy. T. M. P. gratefully acknowledges support from the Camille and Henry Dreyfus Foundation Postdoctoral Program in Environmental Chemistry. The authors would like to thank Dr Stephen Lynch and the Stanford NMR facility for technical assistance with NMR collection and Dr Jan Meisner for insightful discussions regarding the DFT calculations. The authors also thank the Stanford Research Computing Center for providing computational resources and support.



## References

- 1 I. Tomassi, Direct Carboxylation of C(sp<sup>3</sup>)-H and C(sp<sup>2</sup>)-H Bonds with CO<sub>2</sub> by Transition-Metal-Catalyzed and Base-Mediated Reactions, *Catalysts*, 2017, **7**, 380.
- 2 J. Luo and I. Larrosa, C-H Carboxylation of Aromatic Compounds through CO<sub>2</sub> Fixation, *ChemSusChem*, 2017, **10**(17), 3317–3332.
- 3 J. Hong, M. Li, J. Zhang, B. Sun and F. Mo, C-H Bond Carboxylation with Carbon Dioxide, *ChemSusChem*, 2019, **12**(1), 6–39.
- 4 O. Vechorkin, N. Hirt and X. Hu, Carbon Dioxide as the C1 Source for Direct C-H Functionalization of Aromatic Heterocycles, *Org. Lett.*, 2010, **12**(15), 3567–3569.
- 5 B. Pieber, T. Glasnov and C. O. Kappe, Flash carboxylation: fast lithiation-carboxylation sequence at room temperature in continuous flow, *RSC Adv.*, 2014, **4**(26), 13430–13433.
- 6 W.-J. Yoo, T. V. Q. Nguyen, M. G. Capdevila and S. Kobayashi, Lithium *tert*-Butoxide-Mediated Carboxylation Reactions of Unprotected Indoles and Pyrroles with Carbon Dioxide, *Heterocycles*, 2015, **90**(2), 1196–1204.
- 7 S. Fenner and L. Ackermann, C-H carboxylation of heteroarenes with ambient CO<sub>2</sub>, *Green Chem.*, 2016, **18**(13), 3804–3807.
- 8 J. Luo, S. Preciado, P. Xie and I. Larrosa, Carboxylation of Phenols with CO<sub>2</sub> at Atmospheric Pressure, *Chem.-Eur. J.*, 2016, **22**(20), 6798–6802.
- 9 M. Shigeno, K. Hanasaka, K. Sasaki, K. Nozawa-Kumada and Y. Kondo, Direct Carboxylation of Electron-Rich Heteroarenes Promoted by LiO-*t*Bu with CsF and [18] Crown-6, *Chem.-Eur. J.*, 2019, **25**(13), 3235–3239.
- 10 H. Seo, M. H. Katcher and T. F. Jamison, Photoredox activation of carbon dioxide for amino acid synthesis in continuous flow, *Nat. Chem.*, 2017, **9**(5), 453–456.
- 11 N. Ishida, Y. Masuda, Y. Imamura, K. Yamazaki and M. Murakami, Carboxylation of Benzylic and Aliphatic C-H Bonds with CO<sub>2</sub> Induced by Light/Ketone/Nickel, *J. Am. Chem. Soc.*, 2019, **141**(50), 19611–19615.
- 12 Q.-Y. Meng, T. E. Schirmer, A. L. Berger, K. Donabauer and B. König, Photocarboxylation of Benzylic C-H Bonds, *J. Am. Chem. Soc.*, 2019, **141**(29), 11393–11397.
- 13 H. Seo, L. V. Nguyen and T. F. Jamison, Using Carbon Dioxide as a Building Block in Continuous Flow Synthesis, *Adv. Synth. Catal.*, 2019, **361**(2), 247–264.
- 14 C. S. Yeung, Photoredox Catalysis as a Strategy for CO<sub>2</sub> Incorporation: Direct Access to Carboxylic Acids from a Renewable Feedstock, *Angew. Chem., Int. Ed.*, 2019, **58**(17), 5492–5502.
- 15 *Carbon Dioxide as Chemical Feedstock*, ed. M. Aresta, Wiley-VCH, Weinheim, 2010.
- 16 M. Börjesson, T. Moragas, D. Gallego and R. Martin, Metal-Catalyzed Carboxylation of Organic (Pseudo)halides with CO<sub>2</sub>, *ACS Catal.*, 2016, **6**(10), 6739–6749.
- 17 L. J. Gooßen, N. Rodríguez and K. Gooßen, Carboxylic Acids as Substrates in Homogeneous Catalysis, *Angew. Chem., Int. Ed.*, 2008, **47**(17), 3100–3120.
- 18 D. Kumar, N. Maruthi Kumar, K.-H. Chang and K. Shah, Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles, *Eur. J. Med. Chem.*, 2010, **45**(10), 4664–4668.
- 19 H. Maag, Prodrugs of Carboxylic Acids, in *Prodrugs: Challenges and Rewards Part 1*, ed. V. J. Stella, R. T. Borchardt, M. J. Hageman, R. Oliyai, H. Maag and J. W. Tilley, Springer New York, New York, NY, 2007, pp. 703–729.
- 20 O. Boullard, H. Leblanc and B. Besson, Salicylic Acid, *Ullmann's Encyclopedia of Industrial Chemistry*, 2000.
- 21 W.-J. Yoo, M. G. Capdevila, X. Du and S. Kobayashi, Base-Mediated Carboxylation of Unprotected Indole Derivatives with Carbon Dioxide, *Org. Lett.*, 2012, **14**(20), 5326–5329.
- 22 C. Pei, J. Zong, S. Han, B. Li and B. Wang, Ni-Catalyzed Direct Carboxylation of an Unactivated C-H Bond with CO<sub>2</sub>, *Org. Lett.*, 2020, **22**(17), 6897–6902.
- 23 H. Mizuno, J. Takaya and N. Iwasawa, Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO<sub>2</sub> via Chelation-Assisted C-H Bond Activation, *J. Am. Chem. Soc.*, 2011, **133**(5), 1251–1253.
- 24 L. Fu, S. Li, Z. Cai, Y. Ding, X.-Q. Guo, L.-P. Zhou, D. Yuan, Q.-F. Sun and G. Li, Ligand-enabled site-selectivity in a versatile rhodium(II)-catalysed aryl C-H carboxylation with CO<sub>2</sub>, *Nat. Catal.*, 2018, **1**(6), 469–478.
- 25 T. Suga, H. Mizuno, J. Takaya and N. Iwasawa, Direct carboxylation of simple arenes with CO<sub>2</sub> through a rhodium-catalyzed C-H bond activation, *Chem. Commun.*, 2014, **50**(92), 14360–14363.
- 26 M. Schlosser, H. C. Jung and S. Takagishi, Selective mono- or dimetalation of arenes by means of superbasic reagents, *Tetrahedron*, 1990, **46**(16), 5633–5648.
- 27 G. A. Olah, B. Török, J. P. Joschek, I. Buci, P. M. Esteves, G. Rasul and G. K. Surya Prakash, 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.*, 2002, **124**(38), 11379–11391.
- 28 M. Schmalzbauer, T. D. Svejstrup, F. Fricke, P. Brandt, M. J. Johansson, G. Bergonzini and B. König, Redox-Neutral Photocatalytic C-H Carboxylation of Arenes and Styrenes with CO<sub>2</sub>, *Chem*, 2020, DOI: 10.1016/j.chempr.2020.08.02.
- 29 A. Banerjee, G. R. Dick, T. Yoshino and M. W. Kanan, Carbon dioxide utilization via carbonate-promoted C-H carboxylation, *Nature*, 2016, **531**(7593), 215–219.
- 30 G. R. Dick, A. D. Frankhouser, A. Banerjee and M. W. Kanan, A scalable carboxylation route to furan-2,5-dicarboxylic acid, *Green Chem.*, 2017, **19**(13), 2966–2972.
- 31 A. Banerjee and M. W. Kanan, Carbonate-Promoted Hydrogenation of Carbon Dioxide to Multicarbon Carboxylates, *ACS Cent. Sci.*, 2018, **4**(5), 606–613.
- 32 A. W. Lankenau and M. W. Kanan, Polyamide monomers via carbonate-promoted C-H carboxylation of furfurylamine, *Chem. Sci.*, 2020, **11**(1), 248–252.
- 33 A. D. Frankhouser and M. W. Kanan, Phase Behavior That Enables Solvent-Free Carbonate-Promoted Furoate Carboxylation, *J. Phys. Chem. Lett.*, 2020, **11**(18), 7544–7551.
- 34 D. J. Xiao, E. D. Chant, A. D. Frankhouser, Y. Chen, A. Yau, N. M. Washton and M. W. Kanan, A closed cycle for





- esterifying aromatic hydrocarbons with CO<sub>2</sub> and alcohol, *Nat. Chem.*, 2019, **11**(10), 940–947.
- 35 E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, 2006.
  - 36 K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, What are the pK<sub>a</sub> values of C–H bonds in aromatic heterocyclic compounds in DMSO?, *Tetrahedron*, 2007, **63**(7), 1568–1576.
  - 37 R. R. Fraser, T. S. Mansour and S. Savard, Acidity measurements in THF. V. Heteroaromatic compounds containing 5-membered rings, *Can. J. Chem.*, 1985, **63**(12), 3505–3509.
  - 38 H. Mayr, B. Kempf and A. R. Ofial,  $\pi$ -Nucleophilicity in Carbon–Carbon Bond-Forming Reactions, *Acc. Chem. Res.*, 2003, **36**(1), 66–77.
  - 39 T. Eicher, S. Hauptmann and A. Speicher, Five-Membered Heterocycles: Sections 5.1–5.21, *The Chemistry of Heterocycles*, 2003, pp. 52–121.
  - 40 K. Nemoto, S. Tanaka, M. Konno, S. Onozawa, M. Chiba, Y. Tanaka, Y. Sasaki, R. Okubo and T. Hattori, Me<sub>2</sub>AlCl-mediated carboxylation, ethoxycarbonylation, and carbamoylation of indoles, *Tetrahedron*, 2016, **72**(5), 734–745.
  - 41 S. Tanaka, K. Watanabe, Y. Tanaka and T. Hattori, EtAlCl<sub>2</sub>/2,6-Disubstituted Pyridine-Mediated Carboxylation of Alkenes with Carbon Dioxide, *Org. Lett.*, 2016, **18**(11), 2576–2579.
  - 42 M. Westermaier and H. Mayr, Electrophilic Allylations and Benzylations of Indoles in Neutral Aqueous or Alcoholic Solutions, *Org. Lett.*, 2006, **8**(21), 4791–4794.
  - 43 E. M. Simmons and J. F. Hartwig, On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes, *Angew. Chem., Int. Ed.*, 2012, **51**(13), 3066–3072.
  - 44 V. Ji Ram, A. Sethi, M. Nath and R. Pratap, Chapter 5 – Five-Membered Heterocycles, in *The Chemistry of Heterocycles*, ed. V. Ji Ram, A. Sethi, M. Nath and R. Pratap, Elsevier, 2019, pp. 149–478.
  - 45 J. K. Kajorinne, J. C. M. Steers, M. E. Merchant and C. D. MacKinnon, Green halogenation reactions for (hetero)aromatic ring systems in alcohol, water, or no solvent, *Can. J. Chem.*, 2018, **96**(12), 1087–1091.
  - 46 Y. Ono and H. Hattori, Characterization of Solid Base Catalysts, in *Solid Base Catalysis*, ed. Y. Ono and H. Hattori, Springer Berlin Heidelberg, Berlin, Heidelberg, 2011, pp. 11–68.

