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

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

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C–H carboxylation is an attractive transformation for both streamlining synthesis and valorizing CO₂. The high bond strength and very low acidity of most C–H bonds, as well as the low reactivity of CO₂, 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 (M₂CO₃) dispersed in mesoporous TiO₂ supports (M₂CO₃/TiO₂) effect CO₃²⁻-promoted C–H carboxylation of thiophene- and indole-based heteroarenes in gas–solid reactions at 200–320 °C. M₂CO₃/TiO₂ 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 M₂CO₃/TiO₂ enables C3 carboxylation of indole substrates *via* an apparent electrophilic aromatic substitution mechanism. No carboxylations take place when M₂CO₃/TiO₂ is replaced with un-supported M₂CO₃, demonstrating the critical role of carbonate dispersion and disruption of the M₂CO₃ lattice. After carboxylation, treatment of the support-bound carboxylate products with dimethyl carbonate affords isolable esters and the M₂CO₃/TiO₂ material can be regenerated upon heating under vacuum. Our results provide the basis for a closed cycle for the esterification of heteroarenes with CO₂ and dimethyl carbonate.

Received 18th August 2020
Accepted 5th October 2020

DOI: 10.1039/d0sc04548a

rsc.li/chemical-science

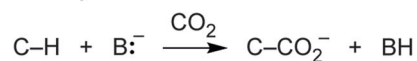
Introduction

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 CO₂ in chemical production.^{1–3} However, carboxylation faces the challenge of overcoming the low reactivity of C–H bonds and CO₂, and it lacks the large intrinsic driving force of other C–H functionalizations such as oxidation or amination. The insertion of CO₂ 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^{2,4–9} (ionic) and radical mechanisms^{2,10–14} 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,

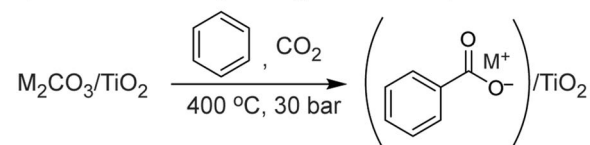
regenerable reagents is critical to create opportunities for scalable CO₂ utilization.

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

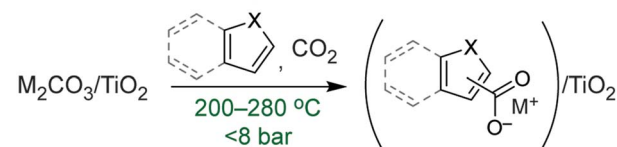
a) C–H Carboxylation



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 (M₂CO₃/TiO₂); (c) C–H carboxylation of heteroarenes using M₂CO₃/TiO₂.

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† 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 CO₂.²⁰ While the carboxylation of indoles and pyrroles has been achieved similarly,^{6,8,21} these reactions have required the use of superstoichiometric LiO^tBu 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 CO₂ pressure.^{4,6–9,21} Hu *et al.* have shown that relatively acidic heteroarenes (pK_a up to 28 in organic solvent) can be carboxylated using Cs₂CO₃ as the base in refluxing DMF.^{4,7} The carboxylation of electron-rich heteroarenes beyond this pK_a threshold, however, has required much stronger bases. For example, the carboxylation of benzothiophene (pK_a of 33 in THF) was not possible under these same conditions.⁴ Recently, Kondo *et al.* have demonstrated the carboxylation of a diverse set of (benzo)thiophenes and (benzo)furans by reaction with excess LiO^tBu, CsF, and crown ether at 160 °C under a CO₂ atmosphere.⁹ However, these conditions were not able to carboxylate protected indoles, such as 1-methylindole, whose C2 carbon has a pK_a near 38. Carboxylation of electron rich heteroarenes functionalized with an amide directing group has been achieved using Ni catalysis with stoichiometric KO^tBu and Mn⁰.²²

Arenes have pK_as that generally lie beyond what can be measured (pK_a > 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.^{23–25} In addition to the directing group and catalyst, these methods also require a strong base (KO^tBu) or Lewis acid activator (AlMe(OMe)₂) 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,²⁶ or stoichiometric aluminum reagents.^{25,27}

Apart from acid–base strategies, a very recent report by König *et al.* has described a photoredox method to carboxylate (hetero)arenes under mild conditions in which the substrate is activated by one-electron photoreduction and Cs₂CO₃ serves as the stoichiometric base.²⁸ 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 (M₂CO₃) can promote C–H carboxylation of very weakly acidic substrates in solvent-free, alkali salt media at elevated temperature.^{29–32} This transformation is particularly useful for converting a monocarboxylate substrate into a dicarboxylate product,

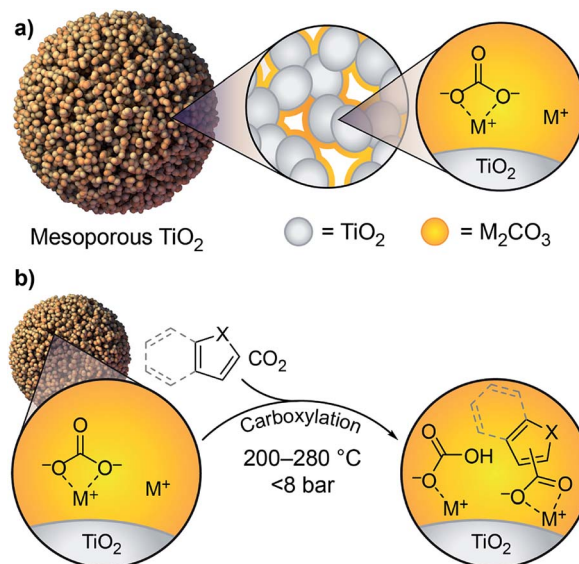


Fig. 1 (a) Schematic view of M₂CO₃/TiO₂ showing the M₂CO₃ dispersed over the mesoporous TiO₂ surface; (b) heteroarene C–H carboxylation promoted by M₂CO₃/TiO₂. Note that MHCO₃ is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv. M₂CO₃, H₂O, and CO₂.

where the substrate enables the formation of a molten reaction medium.³³ More recently, we demonstrated that M₂CO₃ dispersed into mesoporous TiO₂ (M₂CO₃/TiO₂, Fig. 1a) promotes the carboxylation of benzene and other aromatic hydrocarbon C–H bonds in gas–solid reactions (Scheme 1b).³⁴ Dispersion in mesopores disrupts the bulk M₂CO₃ crystal structure, creating an amorphous material that can attain superbase reactivity, even in the presence of CO₂. 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 CO₃^{2–}, as seen previously with arenes. For more nucleophilic indole substrates, however, carboxylation proceeds *via* electrophilic aromatic substitution, which provides a new pathway for CO₂ 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 π-nucleophilicity. The C–H acidities were evaluated by using density functional theory (DFT) to calculate the standard

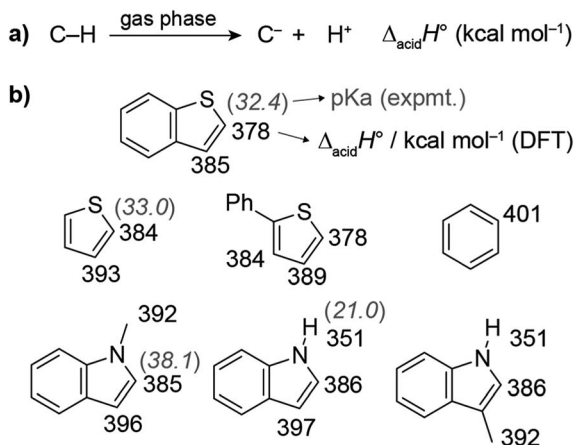


Fig. 2 (a) Schematic depiction of gas-phase heterolytic C–H bond dissociation. The standard enthalpy of this reaction is the gas phase acidity. (b) Calculated gas phase acidities and experimental pK_a s of the most acidic C–H bonds in the heteroarene substrates. Benzene is included as a reference point.

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†).^{35,36} $\Delta_{\text{acid}}H^\circ$ 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 .³⁶ 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 benzothienopyrrole (C2), thiophene (C2), and 1-methylindole (C2) are 32, 33, and 38 according to measurements performed in THF.^{36,37} 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 M_2CO_3 dispersed on TiO_2 ($\text{M}_2\text{CO}_3/\text{TiO}_2$, $\text{M}^+ = \text{Cs}^+$, K^+ , Na^+), heterocycle substrate, and 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 TiO_2 support and quantified by ^1H NMR (Fig. S4–S9†). In all cases, control experiments using M_2CO_3 without the 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 M^+ . Additional control experiments showed minimal reactivity with the mesoporous TiO_2 support alone.

We first assessed the temperature dependence of C–H carboxylation under a common set of conditions using 1.5 mmol substrate, a CO_2 loading corresponding to $4\text{--}5 \text{ bar}$ at the reaction temperature, and a reaction time of 3 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°C). Thus, the overall pressure of the reactor at temperature was $<8 \text{ bar}$ for all of the reactions in this temperature screen. For benzothienopyrrole (Fig. 3a), the onset of carboxylation reactivity was observed at 200°C . Optimal results were seen at 280°C , where $190 \mu\text{mol}$ of benzothienopyrrole carboxylation product was obtained per gram of 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 benzothienopyrrole 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 Cs^+ and 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 benzothienopyrrole 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 benzothienopyrrole at 280°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 kcal mol^{-1} enables higher yielding carboxylation reactions under substantially milder conditions (100°C lower temperature, $1/3$ the total pressure). Furthermore, the benzothienopyrrole results also demonstrate that a 7 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°C), the vapor pressure of benzothienopyrrole 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 benzothienopyrrole 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°C for 3 h using different amounts of benzothienopyrrole corresponding to calculated pressures ranging from 0.5 bar to 3.5 bar , which is approximately the saturation pressure at 280°C . The total benzothienopyrrole 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 benzothienopyrrole carboxylation yield in Fig. 3a is primarily a result of the temperature effect on the rate constant.

Phenylthienopyrrole reacted in a very similar manner to benzothienopyrrole. The onset of carboxylation was observed at 200°C with very high selectivity for the 5-phenylthienopyrrole-2-carboxylate isomer (derived from the most acidic C–H bond) observed up to 280°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 phenylthienopyrrole pressure ($0.5\text{--}3.5 \text{ bar}$) at 320°C (Fig. S17†). The similarity in the

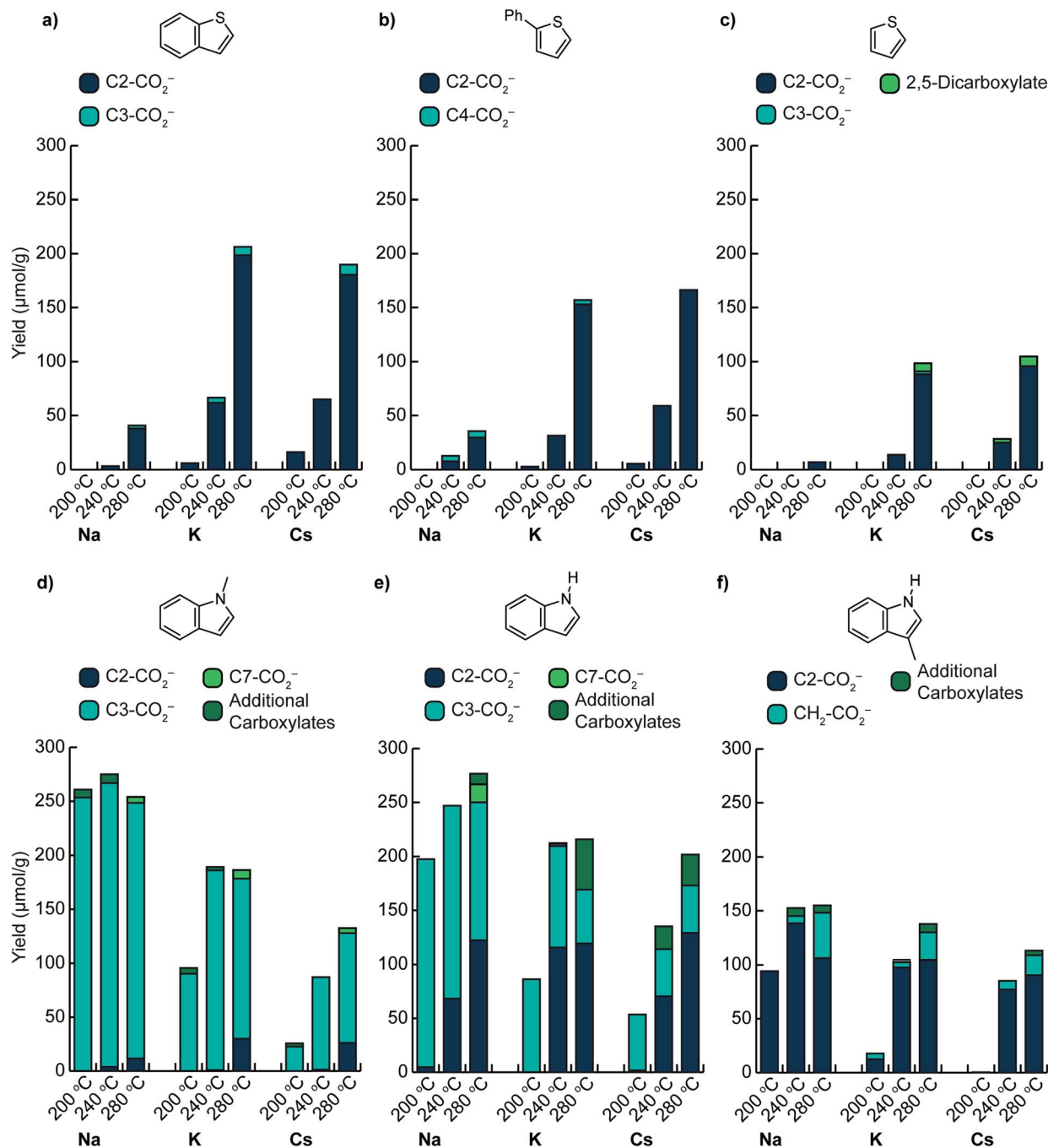


Fig. 3 Summary of C–H carboxylation for heteroarenes using M_2CO_3/TiO_2 and CO_2 at various temperatures ((a) benzothiophene, (b) 2-phenylthiophene, (c) thiophene, (d) 1-methylindole, (e) indole, (f) 3-methylindole). Reactions were performed using glass culture tubes to separate un-vaporized organics 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 $\Delta_{acid}H^\ddagger$ 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 CO₂ 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 CO₂ dissolves in the substrate upon melting and lowers its vapor pressure substantially. An additional contributing factor may be that higher CO₂ pressure results in the formation of polycarbonate species (e.g. C₂O₅²⁻) on the M₂CO₃/TiO₂ material, which are weaker bases than CO₃²⁻, 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⁻¹ higher Δ_{acid}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⁻¹ TiO₂ was formed along with 9 μmol g⁻¹ TiO₂ thiophene-2,5-dicarboxylate when using Cs₂CO₃/TiO₂. Comparable yields were obtained with K₂CO₃/TiO₂, while Na₂CO₃/TiO₂ 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⁻¹ TiO₂ 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 CO₂ pressure dependence was observed for thiophene at 280 °C. Given the much higher volatility of thiophene, CO₂ 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.³⁸ 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_{acid}H° (384 kcal mol⁻¹) is very close to the C(2)–H bond of thiophene (Fig. 2). The most nucleophilic position, however, is C3,³⁹ which has a much less acidic C–H bond (Δ_{acid}H° of C(3)–H is 11 kcal mol⁻¹ 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 Na₂CO₃/TiO₂. Optimal results were obtained using Na₂CO₃/TiO₂ at 200 °C, with a yield of 250 μmol g⁻¹ TiO₂ 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 CO₂, but have required the use of stoichiometric organoaluminum reagents.^{25,40,41} Na₂CO₃/TiO₂ provides a benign and much less resource-intensive alternative.

Selective C3 carboxylation was also observed with indole at 200 °C using M₂CO₃/TiO₂ (Fig. 3e). The M₂CO₃ dependence followed the same trend as for 1-methylindole, with optimal

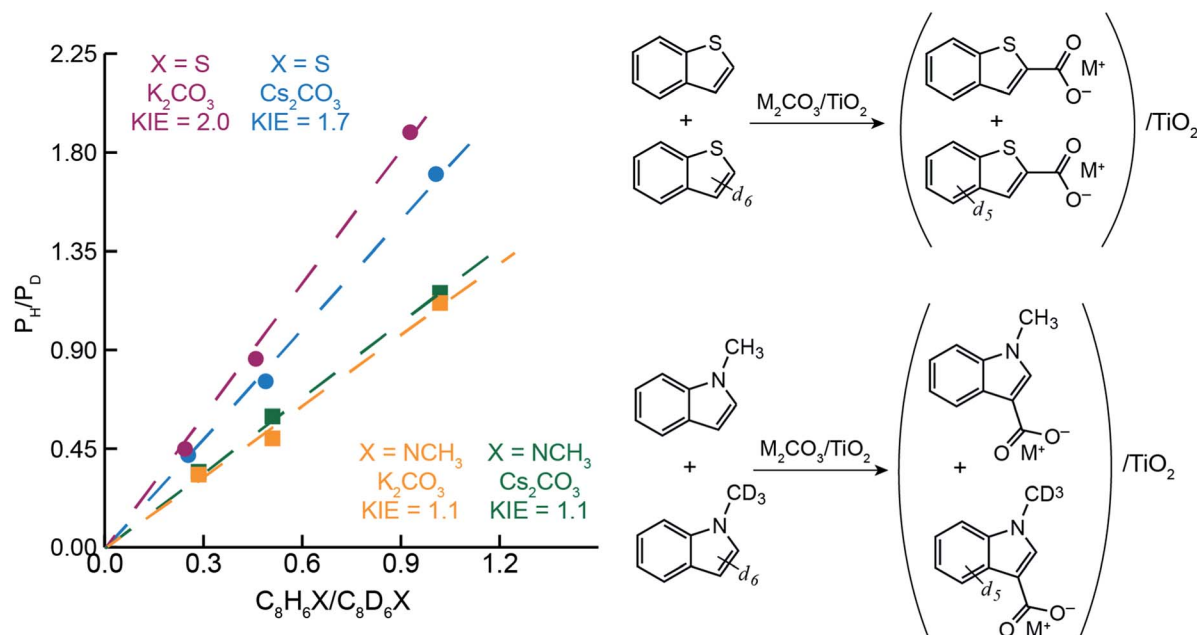


Fig. 4 Ratio of protiated to deuterated products obtained from CO₃²⁻-promoted C–H carboxylation vs. the ratio of C₈H₆X to C₈D₆X (where X = S, NCH₃, or NCD₃) at 260 °C and 0.5 h for benzothiophene (top-right) and 200 °C and 1.5 h for methylindole (bottom-right).

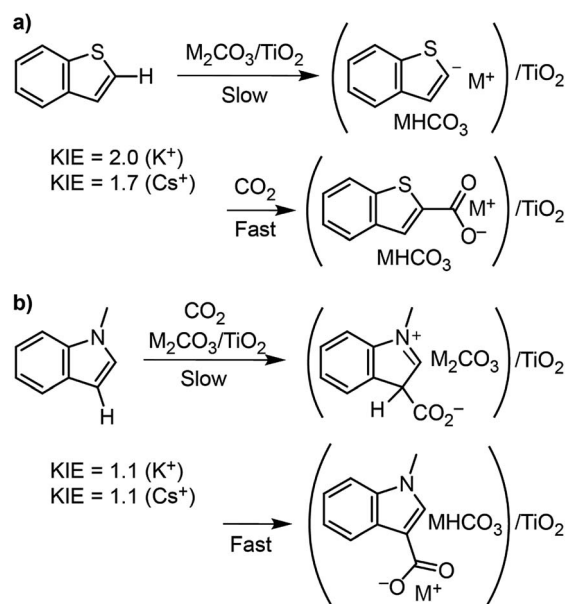
results obtained using $\text{Na}_2\text{CO}_3/\text{TiO}_2$. Because the N–H functionality on indole is much more acidic than the C–H bonds ($\geq 35 \text{ kcal mol}^{-1}$ difference in $\Delta_{\text{acid}}H^\circ$), it is likely that indole is rapidly deprotonated by $\text{M}_2\text{CO}_3/\text{TiO}_2$ to form indolide, which can react reversibly with CO_2 to form indole-1-carboxylate (N-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°C is consistent with an EAS mechanism in which deprotonated indole is the reactive nucleophile.³⁹ Beyond 200°C , however, the reaction yielded a mixture of C3, C2, and C7 carboxylation products. At 280°C , C2 carboxylation accounted for 44–64% of the total carboxylation products depending on the choice of M_2CO_3 . Substitution at C2 is commonly seen alongside C3 in solution-phase EAS reactions with indole.⁴² Both methylindole and indole showed very similar pressure dependences on both heterocycle and 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°C . Increasing the temperature to 240°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 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.⁴³ C–H carboxylation reactions were performed for 1-methylindole (200°C , 1.5 h) and benzothiophene (260°C , 0.5 h) using various ratios of protiated and deuterated substrate (Fig. 4).³⁴ 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 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.^{39,44,45} 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,³⁴ as well as solid base-catalyzed reactions that feature rate-determining deprotonation.⁴⁶

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°C in



Scheme 2 Proposed C–H carboxylation mechanisms for (a) benzothiophene and (b) 1-methylindole. Note that MHCO_3 is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv. M_2CO_3 , H_2O , and CO_2 .

which attack of the π system on CO_2 precedes C–H deprotonation (Scheme 2). To our knowledge, an EAS reaction between 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 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 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 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 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

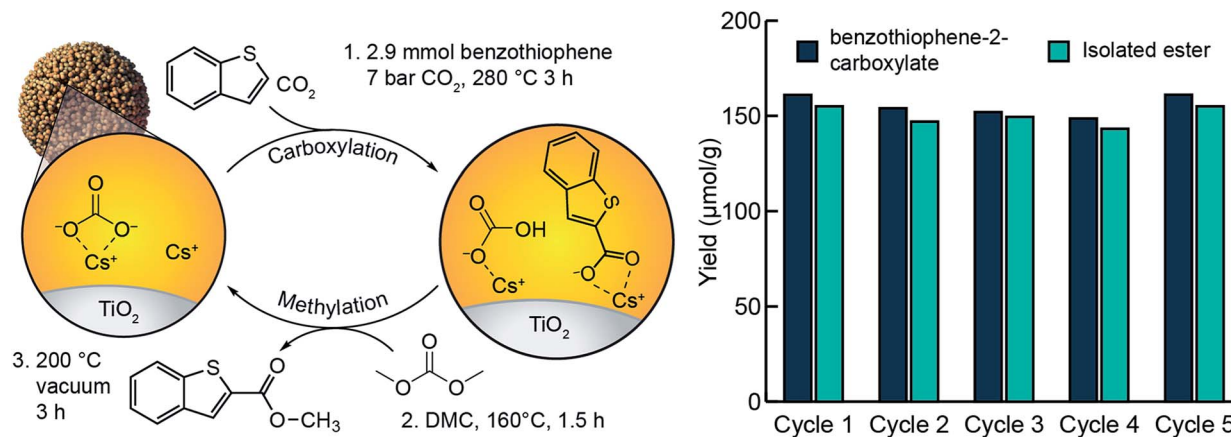


Fig. 5 Cycling steps and yields for benzothiophene esterification using $\text{Cs}_2\text{CO}_3/\text{TiO}_2$. Reaction conditions: carboxylation at 280 °C for 3 h, esterification at 160 °C for 1.5 h, followed by a regeneration cycle at 200 °C for 3 h under reduced pressure.

subjecting the carboxylation product to flowing CO_2 and methanol at elevated temperatures.³⁴ 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 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 ^1H 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,³⁴ 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 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 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(sp³)-H and C(sp²)-H Bonds with CO₂ 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 CO₂ 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 CO₂, *Green Chem.*, 2016, 18(13), 3804–3807.
- 8 J. Luo, S. Preciado, P. Xie and I. Larrosa, Carboxylation of Phenols with CO₂ 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 CO₂ 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 CO₂ 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 CO₂, *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 CO₂, *Org. Lett.*, 2020, 22(17), 6897–6902.
- 23 H. Mizuno, J. Takaya and N. Iwasawa, Rhodium(I)-Catalyzed Direct Carboxylation of Arenes with CO₂ 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 CO₂, *Nat. Catal.*, 2018, 1(6), 469–478.
- 25 T. Suga, H. Mizuno, J. Takaya and N. Iwasawa, Direct carboxylation of simple arenes with CO₂ 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. Bucsi, P. M. Esteves, G. Rasul and G. K. Surya Prakash, Efficient Chemoselective Carboxylation of Aromatics to Arylcarboxylic Acids with a Superelectrophilically Activated Carbon Dioxide—Al₂Cl₆/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 CO₂, *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 CO₂ 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_a 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, π -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, Me₂AlCl-mediated carboxylation, ethoxycarbonylation, and carbamoylation of indoles, *Tetrahedron*, 2016, **72**(5), 734–745.
- 41 S. Tanaka, K. Watanabe, Y. Tanaka and T. Hattori, EtAlCl₂/2,6-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.