EDGE ARTICLE

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 CO_2. The high bond strength and very low acidity of most C–H bonds, as well as the low reactivity of CO_2, 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_2CO_3) dispersed in mesoporous TiO_2 supports (M_2CO_3/TiO_2) effect CO_3^{2-}-promoted C–H carboxylation of thiophene- and indole-based heteroarenes in gas–solid reactions at 200–320 °C. M_2CO_3/TiO_2 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_2CO_3/TiO_2 enables C3 carboxylation of indole substrates *via* an apparent electrophilic aromatic substitution mechanism. No carboxylations take place when M_2CO_3/TiO_2 is replaced with un-supported M_2CO_3, demonstrating the critical role of carbonate dispersion and disruption of the M_2CO_3 lattice. After carboxylation, treatment of the support-bound carboxylate products with dimethyl carbonate affords isolable esters and the M_2CO_3/TiO_2 material can be regenerated upon heating under vacuum. Our results provide the basis for a closed cycle for the esterification of heteroarenes with CO_2 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_2 in chemical production.[1–3] However, carboxylation faces the challenge of overcoming the low reactivity of C–H bonds and CO_2, and it lacks the large intrinsic driving force of other C–H functionalizations such as oxidation or amination. The insertion of CO_2 into C–H bonds to form a carboxylic acid is actually endergonic on account of the small ΔH and negative ΔS, 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,
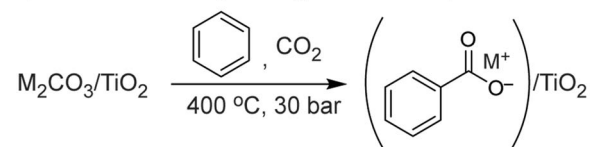
regenerable reagents is critical to create opportunities for scalable CO_2 utilization.

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
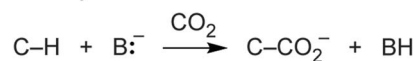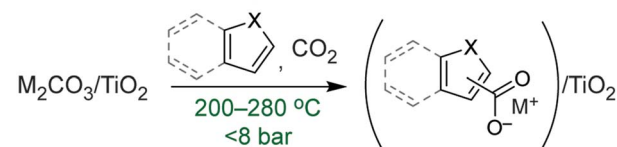

Scheme 1 (a) General scheme for base-promoted C–H carboxylation; (b) C–H carboxylation of benzene using dispersed alkali carbonates (M_2CO_3/TiO_2); (c) C–H carboxylation of heteroarenes using M_2CO_3/TiO_2.

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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_2.[20] While the carboxylation of indoles and pyrroles has been achieved similarly,[6,8,21] these reactions have required the use of superstoichiometric LiO^{t}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_2 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 Cs_2CO_3 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^{t}Bu, CsF, and crown ether at 160 °C under a CO_2 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^{t}Bu and Mn^0.[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^{t}Bu) 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 of (hetero)arenes under mild conditions in which the substrate is activated by one-electron photoreduction and Cs_2CO_3 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 multistep synthesis.

We previously showed that simple alkali carbonates (M_2CO_3) 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,
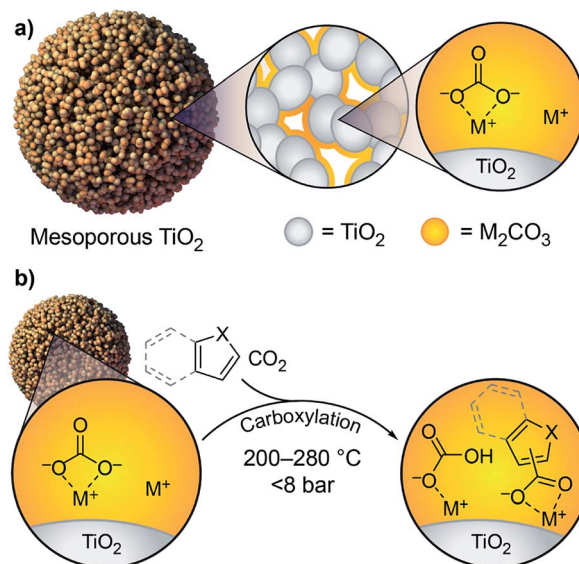

Fig. 1 (a) Schematic view of M_2CO_3/TiO_2 showing the M_2CO_3 dispersed over the mesoporous TiO_2 surface; (b) heteroarene C–H carboxylation promoted by M_2CO_3/TiO_2. Note that $MHCO_3$ is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv. M_2CO_3, H_2O, and CO_2.

where the substrate enables the formation of a molten reaction medium.[33] More recently, we demonstrated that M_2CO_3 dispersed into mesoporous TiO_2 (M_2CO_3/TiO_2, 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 M_2CO_3 crystal structure, creating an amorphous material that can attain superbase reactivity, even in the presence of CO_2. 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_3^{2-}, as seen previously with arenes. For more nucleophilic indole substrates, however, carboxylation proceeds *via* electrophilic aromatic substitution, which provides a new pathway for CO_2 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

a) $C–H \xrightarrow{\text{gas phase}} C^- + H^+ \quad \Delta_{acid}H^\circ \text{ (kcal mol}^{-1})$
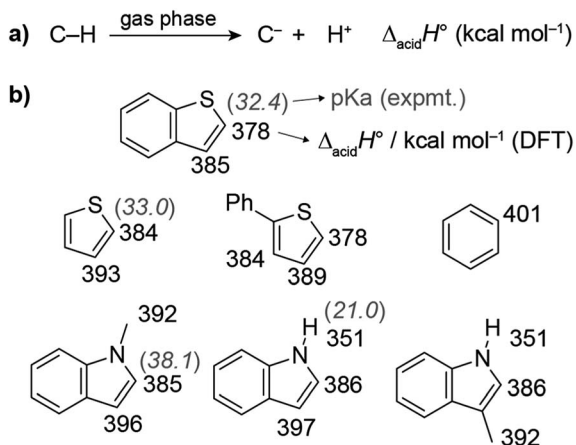
b)

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_as 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 ($\Delta_{acid}H^\circ$, also known as the gas phase acidity) (Fig. 2 and S1†).[35,36] $\Delta_{acid}H^\circ$ 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 ~400 °C, has a $\Delta_{acid}H^\circ$ of 401 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 $\Delta_{acid}H^\circ$) than benzene by 15–23 kcal mol^{-1}, while the separation between the two most acidic C–H bonds in each substrate was 6–11 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.[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$_2$CO$_3$ dispersed on TiO$_2$ (M$_2$CO$_3$/TiO$_2$, M$^+$ = 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 M$_2$CO$_3$/TiO$_2$ material (Fig. S3†). The products were isolated by aqueous extraction from the TiO$_2$ support and quantified by ^{1}H NMR (Fig. S4–S9†). In all cases, control experiments using M$_2$CO$_3$ without the TiO$_2$ support showed no reactivity, whereas M$_2$CO$_3$/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 4–5 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 ~2.5 bar at the highest temperature evaluated (320 °C). Thus, the overall pressure of the reactor at temperature was <8 bar for all of the reactions in this temperature screen. For benzothiophene (Fig. 3a), the onset of carboxylation reactivity was observed at 200 °C. Optimal results were seen at 280 °C, where 190 μmol of benzothiophene carboxylation product was obtained per gram of TiO$_2$ (190 μmol g^{-1} TiO$_2$) with a 20 : 1 ratio of 2-carboxylate to 3-carboxylate isomers for Cs$_2$CO$_3$/TiO$_2$. Using K$_2$CO$_3$/TiO$_2$, 207 μmol g^{-1} 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 Cs$^+$ and K$^+$, much lower reactivity was observed with Na$_2$CO$_3$/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 μmol g^{-1} TiO$_2$ of carboxylate products were obtained for benzothiophene at 280 °C and <8 bar total pressure, the maximum yields for benzene carboxylation using the same M$_2$CO$_3$/TiO$_2$ materials were ~100 μmol g^{-1} TiO$_2$ at 420–440 °C and ~30 bar total pressure. Thus, reducing the C–H bond acidity ($\Delta_{acid}H^\circ$) 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 benzothiophene 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 benzothiophene is expected to reach its saturation pressure at $T \leq 240$ °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 ~5× over the 200–320 °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 benzothiophene corresponding to calculated pressures ranging from 0.5 bar to 3.5 bar, which is approximately the saturation pressure at 280 °C. The total benzothiophene carboxylate yield showed a modest variation from 150 μmol g^{-1} TiO$_2$ to 210 μmol g^{-1} 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 °C with very high selectivity for the 5-phenylthiophene-2-carboxylate isomer (derived from the most acidic C–H bond) observed up to 280 °C. Comparable yields were observed for Cs$_2$CO$_3$/TiO$_2$ and K$_2$CO$_3$/TiO$_2$, while substantially lower yields were seen for Na$_2$CO$_3$/TiO$_2$ (Fig. 3b). The carboxylate yield varied by ~50% over a 7-fold variation in phenylthiophene pressure (0.5–3.5 bar) at 320 °C (Fig. S17†). The similarity in the
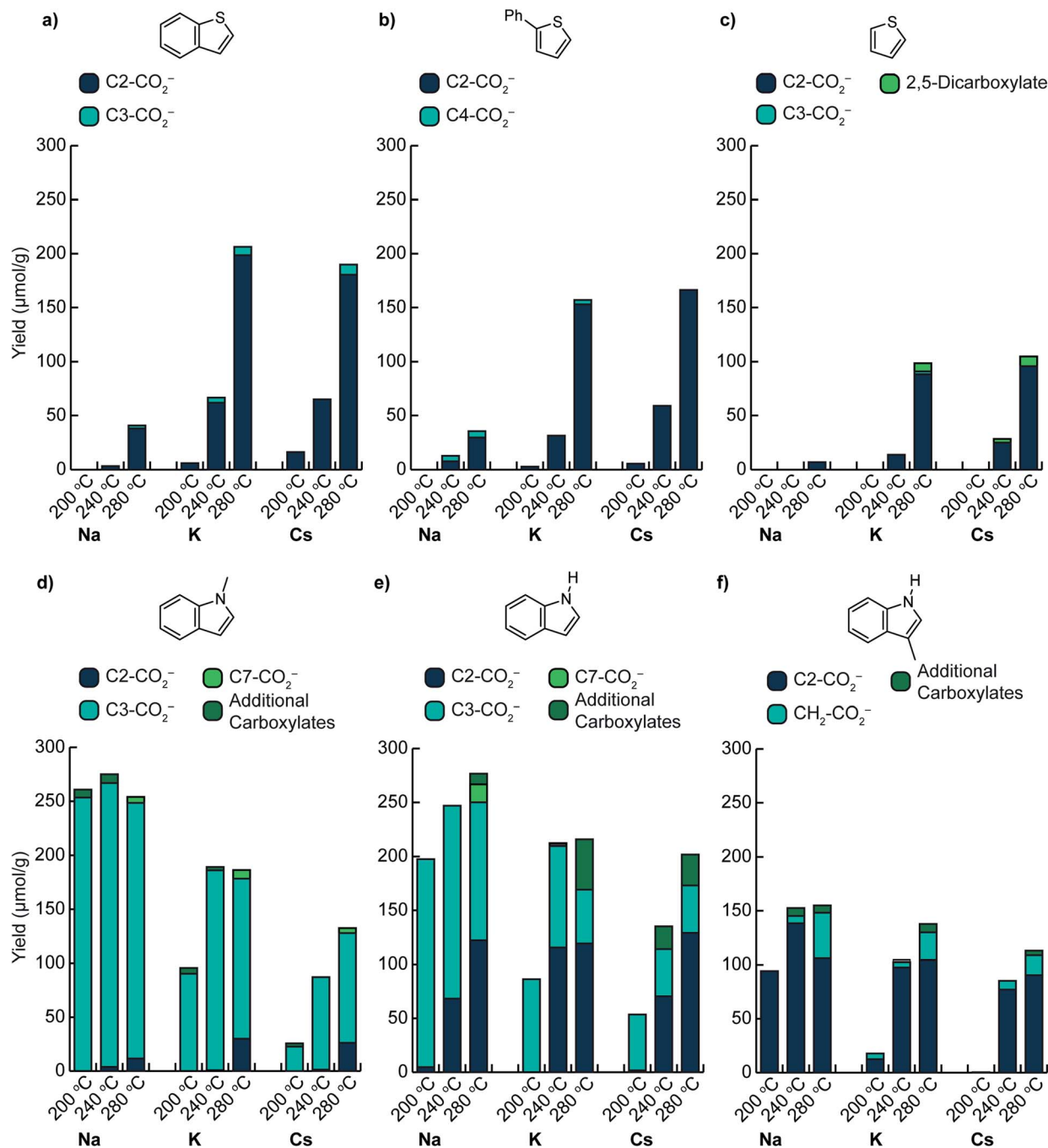
Fig. 3 Summary of C–H carboxylation for heteroarenes using M_2CO_3/TiO_2 and CO_2 at various temperatures ((a) benzothiophene, (b) 2-phenylthiophene, (c) thiophene, (d) 1-methylindole, (e) indole, (f) 3-methylindole). Reactions were performed using glass culture tubes to separate un-vaporized organics 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 $\Delta_{acid}H^\circ$ 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_2 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_2 dissolves in the substrate upon melting and lowers its vapor pressure substantially. An additional contributing factor may be that higher CO_2 pressure results in the formation of polycarbonate species (*e.g.* $C_2O_5^{2-}$) on the M_2CO_3/TiO_2 material, which are weaker bases than CO_3^{2-}, 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 $\Delta_{acid}H°$ 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} TiO_2 was formed along with 9 μmol g^{-1} TiO_2 thiophene-2,5-dicarboxylate when using Cs_2CO_3/TiO_2. Comparable yields were obtained with K_2CO_3/TiO_2, while Na_2CO_3/TiO_2 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} TiO_2 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_2 pressure dependence was observed for thiophene at 280 °C. Given the much higher volatility of thiophene, CO_2 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 $\Delta_{acid}H°$ (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 ($\Delta_{acid}H°$ 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 Na_2CO_3/TiO_2. Optimal results were obtained using Na_2CO_3/TiO_2 at 200 °C, with a yield of 250 μmol g^{-1} TiO_2 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_2, but have required the use of stoichiometric organoaluminum reagents.[25,40,41] Na_2CO_3/TiO_2 provides a benign and much less resource-intensive alternative.

Selective C3 carboxylation was also observed with indole at 200 °C using M_2CO_3/TiO_2 (Fig. 3e). The M_2CO_3 dependence followed the same trend as for 1-methylindole, with optimal
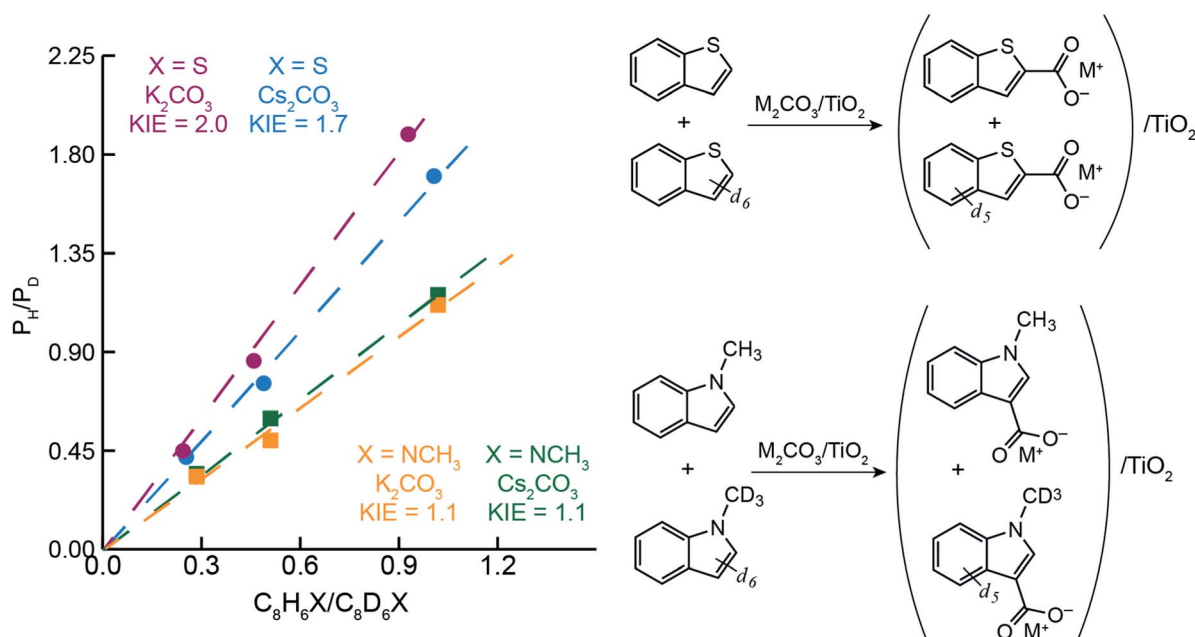

Fig. 4 Ratio of protiated to deuterated products obtained from CO_3^{2-}-promoted C–H carboxylation *vs.* the ratio of C_8H_6X to C_8D_6X (where X = S, NCH_3, or NCD_3) at 260 °C and 0.5 h for benzothiophene (top-right) and 200 °C and 1.5 h for methylindole (bottom-right).

results obtained using Na_2CO_3/TiO_2. Because the N–H functionality on indole is much more acidic than the C–H bonds (≥ 35 kcal mol^{-1} difference in $\Delta_{acid}H°$), it is likely that indole is rapidly deprotonated by M_2CO_3/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 ($\Delta_{acid}H°$ = 397 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 Na_2CO_3/TiO_2, 94 μmol g^{-1} TiO_2 of the C2-carboxylate was obtained at 200 °C. Increasing the temperature to 240 °C boosted the yield to 138 μmol g^{-1} 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 K_2CO_3/TiO_2 and Cs_2CO_3/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 M_2CO_3/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
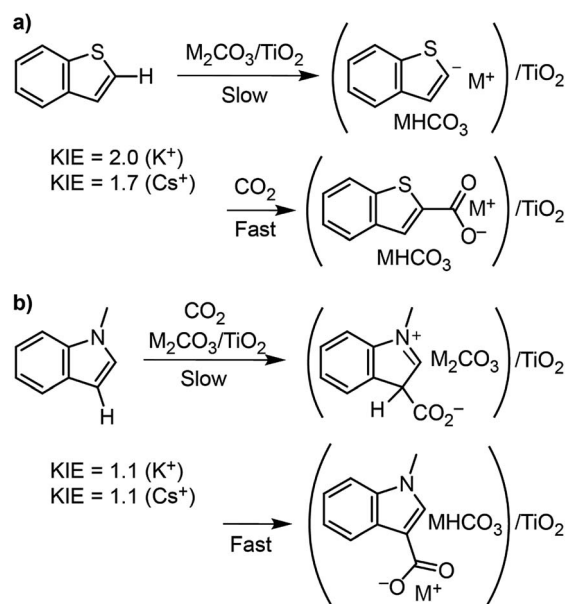
Scheme 2 Proposed C–H carboxylation mechanisms for (a) benzothiophene and (b) 1-methylindole. Note that $MHCO_3$ is shown for simplicity, but under the reaction conditions it is thermally unstable and will convert to 0.5 equiv. M_2CO_3, H_2O, and CO_2.

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 ($\varepsilon < 9$) 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 ($\varepsilon > 20$), however, an EAS transition state was identified that is ~30 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 M_2CO_3/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 Na_2CO_3/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 M_2CO_3/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 M_2CO_3/TiO_2 material by
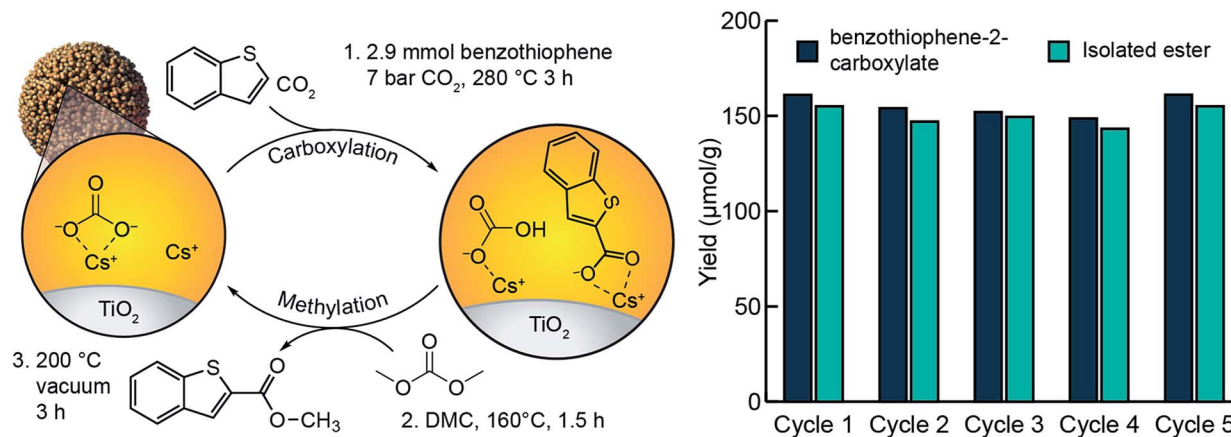
Fig. 5 Cycling steps and yields for benzothiophene esterification using Cs_2CO_3/TiO_2. Reaction conditions: carboxylation at 280 °C for 3 h, esterification at 160 °C for 1.5 h, followed by a regeneration cycle at 200 °C for 3 h under reduced pressure.

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 ($(RCOOM)/TiO_2$) 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 M_2CO_3/TiO_2. After establishing optimal carboxylation and methylation conditions, we assessed the ability of M_2CO_3/TiO_2 to catalyze a closed heteroarene esterification cycle over multiple iterations (Fig. 5). When a single sample of Cs_2CO_3/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 μmol g^{-1} 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 M_2CO_3/TiO_2 materials, the heteroarene carboxylations investigated here reach higher yields (up to 250 μmol g^{-1} 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 M_2CO_3/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.

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