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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 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,

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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 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.

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

$$C-H + B: \longrightarrow C-CO_2 + BH$$

00

b) Benzene Carboxylation (previous work):

$$M_2CO_3/TiO_2 \xrightarrow{(1)}{400 \circ C, 30 \text{ bar}} \begin{pmatrix} O \\ M_2 \end{pmatrix} /TiO_2$$

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_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^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 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^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 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 MHCO₃ 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 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 \sim 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 CO₃²⁻, 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 $(\Delta_{acid}H^{\circ}, also known as the gas phase acidity)$ (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 p K_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_2CO_3 dispersed on TiO₂ (M_2CO_3/TiO_2 , $M^+ = Cs^+$, K^+ , Na⁺), heterocycle substrate, and CO₂ (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_2CO_3/TiO_2 material (Fig. S3†). The products were isolated by aqueous extraction from the TiO₂ support and quantified by ¹H NMR (Fig. S4–S9†). In all cases, control experiments using M_2CO_3 without the TiO₂ support showed no reactivity, whereas M_2CO_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 TiO₂ 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 TiO₂ (190 μ mol g⁻¹ TiO₂) with a 20:1 ratio of 2carboxylate to 3-carboxylate isomers for Cs2CO3/TiO2. Using K_2CO_3/TiO_2 , 207 µmol g⁻¹ TiO₂ 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 Na₂CO₃/TiO₂, 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 TiO₂ of carboxylate products were obtained for benzothiophene at 280 °C and <8 bar total pressure, the maximum yields for benzene carboxylation using the same M₂CO₃/TiO₂ materials were ~100 µmol g⁻¹ TiO₂ 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 $T \le 240$ °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 $\sim 5 \times$ 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 μ mol g⁻¹ TiO₂ to 210 μ mol g⁻¹ TiO₂ 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-2carboxylate isomer (derived from the most acidic C–H bond) observed up to 280 °C. Comparable yields were observed for Cs₂CO₃/TiO₂ and K₂CO₃/TiO₂, while substantially lower yields were seen for Na₂CO₃/TiO₂ (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 This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

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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 M₂CO₃ *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 postreaction 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.* $C_2O_5^{2-}$) 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 $\Delta_{acid}H^{\circ}$ 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 μ mol g⁻¹ TiO₂ was formed along with 9 μ mol 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-2,5dicarboxylate indicates that the initially formed monocarboxylate product undergoes a second C-H carboxylation on the support. In addition to the thiophene carboxylates, ~ 25 μ mol 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 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 $\Delta_{acid}H^{\circ}$ (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 ($\Delta_{acid}H^{\circ}$ 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 μ mol g⁻¹ TiO₂ for the C3-carboxylate (Fig. 3d and S8[†]). At higher temperatures (T > 240 °C) the C2carboxylate 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 $^{\circ}$ 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 CO_3^{2-} -promoted C-H carboxylation vs. the ratio of C_8H_6X to C_8D_6X (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 Na2CO3/TiO2. Because the N-H functionality on indole is much more acidic than the C-H bonds $(\geq 35 \text{ kcal mol}^{-1} \text{ difference in } \Delta_{\text{acid}} H^{\circ})$, it is likely that indole is rapidly deprotonated by M2CO3/TiO2 to form indolide, which can react reversibly with CO₂ to form indole-1-carboxylate (N- CO_2^{-}). Given the very low acidity of the C–H bond at C3 ($\Delta_{acid}H^{\circ}$ = 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 M₂CO₃. 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 CO₂ 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 Na₂CO₃/TiO₂, 94 μ mol g⁻¹ TiO₂ of the C2-carboxylate was obtained at 200 °C. Increasing the temperature to 240 °C boosted the yield to 138 μ mol g⁻¹ TiO₂, 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 CO₂ 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. indolebased 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 K₂CO₃/TiO₂ and Cs₂CO₃/TiO₂, respectively. These values are consistent with a mechanism in which C-H deprotonation is slow and the resulting carbanion reacts rapidly with CO₂ (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 M2CO3/TiO2 materials,34 as well solid base-catalyzed reactions that feature rateas 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 $^{\circ}$ 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 CO₂ 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 \sim 30 kcal mol⁻¹ higher in energy than the substrates (Fig. S19[†]). Interestingly, the zwitterionic intermediate resulting from CO2 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 M₂CO₃/TiO₂ material. The amorphous carbonate provides a dielectric to stabilize the transition state for CO2 addition and a proximal base that can immediately deprotonate the putative zwitterionic intermediate. The higher yield for Na2CO3/TiO2 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 M2CO3/TiO2 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 CO2 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 CO₂ 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)/TiO₂) 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 M2CO3/TiO2. After establishing optimal carboxylation and methylation conditions, we assessed the ability of M2CO3/TiO2 to catalyze a closed heteroarene esterification cycle over multiple iterations (Fig. 5). When a single sample of Cs₂CO₃/TiO₂ 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 μ mol g⁻¹ TiO₂. 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 M₂CO₃/TiO₂ materials, the heteroarene carboxylations investigated here reach higher yields (up to 250 μ mol g⁻¹ TiO₂) 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 temperaturedependent 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 CO₃²⁻-promoted C-H carboxylation and methylation with dimethyl carbonate provides a two-step cycle to convert aromatic heteroarenes into methyl esters with regeneration of M2CO3/TiO2. 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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