Introduction

Strategies for the fixation of carbon dioxide (CO2) as an easily accessible, inexpensive, naturally abundant, and renewable C1 source towards valuable commodity chemicals\(^1\)\(^-\)\(^2\) have attracted major topical interest.\(^3\) While significant progress has been witnessed in the chemical use of CO2 during the recent decade,\(^4\)-\(^14\) the vast majority of these procedures require pre-functionalized substrates, such as aryl halides or aryl boronic acids.\(^1\) The synthesis of the prerequisite preoxidized arenes calls for a number of reaction steps, which contradicts the principles of green chemistry.\(^15\) In contrast, the direct functionalization of otherwise inert C–H bonds represents a considerably more atom- and step-economical strategy,\(^16\) with important advances in direct carboxylations\(^17\)-\(^18\) accomplished by Iwasawa,\(^19\)-\(^21\) Nolan,\(^22\)-\(^23\) Hou,\(^24\) Hu,\(^25\) Klankemayer/Leitner,\(^11\) and Beller,\(^26\)-\(^27\) among others.\(^28\) Within our program on catalytic C–H activation,\(^29\)-\(^30\) we became attracted by devising reaction conditions for sustainable C–H carboxylation with ambient CO2 under mild conditions.\(^31\) As a result of our efforts, we have developed a highly effective protocol for step-economical C–H carboxylations of heteroarenes with ambient CO2 under transition metal-free reaction conditions, on which we now\(^31\) wish to report herein. In contrast to previously reported methods,\(^22\)-\(^24\) our C–H carboxylation protocol is operative in the absence of transition metals at relatively low temperatures of only 80–100 °C.

Results and discussion

At the outset of our studies, we chose reaction conditions similar to the ones previously described for the carboxylations of organoboronic esters with CO2 (Table 1).\(^32\) Thus, when reacting benzo[d]oxazole (1a) in the presence of 10 mol% of the well-defined N-heterocyclic carbene copper(i) complex [Cu(IPr)Cl] in DMF at 80 °C under an atmosphere of CO2, \(^82\%

\^1\) Representative procedure for the C–H carboxylation using CO2: synthesis of methylbenzo[d]oxazole-2-carboxylate (3a): a mixture of 1a (118 mg, 0.99 mmol), KOt-Bu (135 mg, 1.20 mmol) and DMF (5.0 mL) was degassed in a Schlenk-tube. The Schlenk-tube was then flushed with CO2 via a balloon and CO2 was bubbled through the reaction mixture for 10–20 minutes. After removal of the balloon, the reaction mixture was heated to 100 °C for 18 h. After cooling to 65 °C, 3a (141 mg, 80%) as a colorless solid.

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C–H carboxylation of heteroarenes with ambient CO2†

Sabine Fenner and Lutz Ackermann*

The C–H carboxylation of heteroarenes was achieved under transition metal-free reaction conditions with naturally abundant CO2 as the C1 source at relatively low temperature. The C–H carboxylation was mediated by KOt-Bu at atmospheric pressure of CO2, and thereby provided atom- and step-economical access to various heteroaromatic carboxylic acid derivatives.
A series of representative heteroarenes 1 was successfully converted into the desired carboxylic acid esters 3 under transition metal-free reaction conditions with atmospheric CO2.

Various alkyl carboxylates 3 were obtained upon subsequent esterification with different alkyl iodides 2 under rather mild reaction conditions. Methyl- as well as chloro-substituted benzo[α]oxazoles 1b and 1c were site-selectively functionalized, affording the 2-substituted carboxylic acid esters 3b–d in high yields after treatment with the corresponding alkyl iodide 2. Notably, the use of Cs2CO3 as the base under otherwise identical reaction conditions resulted in an inferior yield of only 48% for product 3b. Likewise, it is noteworthy that chloro-substituted azole 1c provided the corresponding product 3d in an excellent yield of 91%, whereas Cs2CO3 delivered only 55% of the desired ester 3d.

As showcased in a representative set of C–H functionalizations, our sustainable approach was not restricted to the use of methyl iodide as the electrophile, but also allowed esterification with a variety of alkyl iodides 2. Moreover, our protocol set the stage for the C–H carboxylation of benzoazoles in a step-economical fashion. Indeed, the corresponding methyl ester 3f and hexyl ester 3g were isolated in 66% and 62% yield, respectively.

Furthermore, oxazoles 4 served as viable substrates for the C–H carboxylation, delivering the corresponding carboxylic acid derivatives 5a–d in a step- and atom-economical manner (Scheme 2). Intriguingly, valuable chlorine substituents on the heteroarenes were well tolerated under the optimized reaction conditions, which should prove instrumental for further late-stage diversification by inter alia cross-coupling technology.

Finally, we were pleased to observe that 1,3,4-oxadiazoles 6 proved to be viable substrates for the C–H carboxylation under an ambient CO2 atmosphere as well, providing the desired carboxylic acid esters 7a–c with high levels of selectivity control (Scheme 3).

Based on the literature precedents, we propose the reaction to proceed by initial reversible C–H cleavage (Scheme 4), along with subsequent C–C formation by the action of ambient CO2.

Table 1  Optimization of C–H carboxylation with CO2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>T1 [°C]</th>
<th>T2 [°C]</th>
<th>3a [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>KOt-Bu</td>
<td>DMF</td>
<td>80</td>
<td>65</td>
<td>82b</td>
</tr>
<tr>
<td>2</td>
<td>KOt-Bu</td>
<td>DMF</td>
<td>100</td>
<td>65</td>
<td>76c</td>
</tr>
<tr>
<td>3</td>
<td>KOt-Bu</td>
<td>DMF</td>
<td>100</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>KOt-Bu</td>
<td>DMF</td>
<td>125</td>
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<td>80</td>
</tr>
<tr>
<td>5</td>
<td>KOt-Bu</td>
<td>DMF</td>
<td>80</td>
<td>65</td>
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</tr>
<tr>
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<td>DMF</td>
<td>40</td>
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<td>10</td>
</tr>
<tr>
<td>7</td>
<td>KOt-Bu</td>
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<tr>
<td>8</td>
<td>KOt-Bu</td>
<td>1,4-Dioxane</td>
<td>100</td>
<td>65</td>
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<tr>
<td>9</td>
<td>KOt-Bu</td>
<td>THF</td>
<td>65</td>
<td>65</td>
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<td>100</td>
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<td>DMF</td>
<td>100</td>
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<td>8</td>
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<tr>
<td>15</td>
<td>Cs2CO3</td>
<td>DMF</td>
<td>80</td>
<td>65</td>
<td>23</td>
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</tbody>
</table>

*Reaction conditions: 1a (1.0 mmol), base (1.2 mmol), solvent (5.0 mL), CO2 (1 atm), T1, 18 h; 2a (3.0 mmol), T2, 2 h; yields of isolated products; GC-conversion in parentheses. b With [Cu(IPr)Cl] (10 mol%). c With CuCl (10 mol%).
mild reaction conditions, namely at a rather low temperature and ambient pressure of CO2. Hence, KOt-Bu enabled efficient C–H functionalizations on heteroarenes with an ample substrate scope under mild reaction conditions, namely at a rather low reaction temperature and ambient pressure of CO2.

Conclusions

In summary, we have reported on the use of CO2 as an easily accessible, inexpensive, and renewable C1 source for green C–H carboxylations under transition metal-free reaction conditions. Hence, KOr-Bu enabled efficient C–H functionalizations on heteroarenes with an ample substrate scope under mild reaction conditions, namely at a rather low reaction temperature and ambient pressure of CO2.

Acknowledgements

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Notes and references

KOT-Bu was purchased from Sigma-Aldrich, where it was sublimed and analyzed by ICP-MS, which revealed only trace amounts of transition metals (inter alia <0.5 ppm Fe; <0.1 ppm Cu, Pd, Ni).


36 All direct carboxylation reactions were performed in new glassware using novel stirring bars.

37 For detailed information see the ESL†
