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C–H carboxylation of heteroarenes with ambient CO₂†

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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.

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 pre-oxidized 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 Klankermayer/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 now³¹ 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% isolated yield of methylbenzo[*d*]oxazole-2-carboxylate (**3a**) were obtained upon treatment with methyl iodide (**2a**) (Table 1, entry 1). In order to establish a more economical and user-friendly method, the reaction was conducted with simple CuCl as the catalyst under ligand-free reaction conditions, which provided product **3a** in a comparable yield (entry 2). Interestingly, when conducting a test reaction in the absence of a transition metal catalyst solely with the base KOt-Bu³³ in DMF at 100 °C,³⁴ the desired product **3a** was isolated in 80% yield (entry 3).‡ An elevated reaction temperature of 125 °C failed to afford an improvement (entry 4), whilst a reaction conducted at 80 °C proceeded efficiently (entries 4 and 5), clearly highlighting the beneficial features of KOt-Bu as compared to Cs₂CO₃ that required 125 °C (*vide infra*).²⁵ Polar solvents other than DMF, such as NMP, 1,4-dioxane, THF and DMSO,

‡ 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, **2a** (3.00 equiv.) was added and the reaction mixture was stirred at 65 °C for 2 h. At ambient temperature, the reaction mixture was diluted with H₂O (25 mL) and Et₂O (25 mL). The aqueous layer was extracted with Et₂O (3 × 25 mL) and the combined organic layers were dried over Na₂SO₄. Purification by column chromatography (*n*-pentane/Et₂O = 20/1 → 10/1 → 7/1 → 5/1) yielded **3a** (141 mg, 80%) as a colorless solid.

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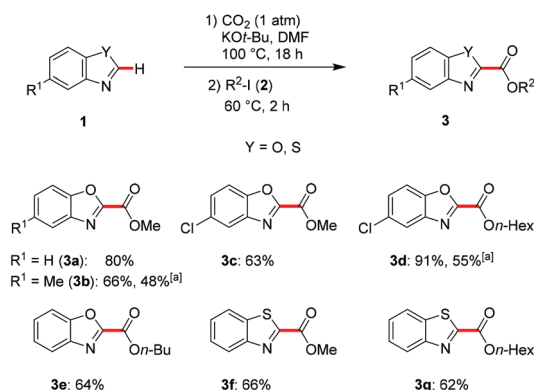
Table 1 Optimization of C–H carboxylation with CO₂^a

Entry	Base	Solvent	T ₁ [°C]	T ₂ [°C]	3a [%]
1	KOt-Bu	DMF	80	65	82 ^b
2	KOt-Bu	DMF	100	65	76 ^c
3	KOt-Bu	DMF	100	65	80
4	KOt-Bu	DMF	125	65	80
5	KOt-Bu	DMF	80	65	71
6	KOt-Bu	DMF	40	40	(10)
7	KOt-Bu	NMP	100	65	69
8	KOt-Bu	1,4-Dioxane	100	65	—
9	KOt-Bu	THF	65	65	(4)
10	KOt-Bu	DMSO	100	65	52
11	KOt-Bu	PhMe	100	65	(11)
12	KOt-Bu	DMA	100	65	77
13	Cs ₂ CO ₃	DMF	100	65	69
14	Rb ₂ CO ₃	DMF	100	65	8
15	Cs ₂ CO ₃	DMF	80	65	23

^a 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%).

provided less satisfactory results (entries 7–10), as did apolar toluene (entry 11). However, the encouraging result obtained with NMP as the solvent (entry 7) indicates the potential of our strategy for the use of greener solvents, such as 1-butylpyrrolidinone or Cyrene.³⁵ On the contrary, the C–H functionalization performed in DMA furnished carboxylic acid ester **3a** with a high efficacy (entry 12). Interestingly, bases other than KOt-Bu, including Cs₂CO₃ or Rb₂CO₃, proved to be considerably less effective under otherwise identical reaction conditions (entries 13 and 14), illustrating the unique power of KOt-Bu as the base, particularly at a reaction temperature of 80 °C (entry 15 *versus* 5).

With the optimized reaction conditions in hand, the scope of the C–H carboxylation was explored next (Scheme 1).³⁶

**Scheme 1** C–H carboxylation with ambient CO₂. ^aCs₂CO₃ as the base.

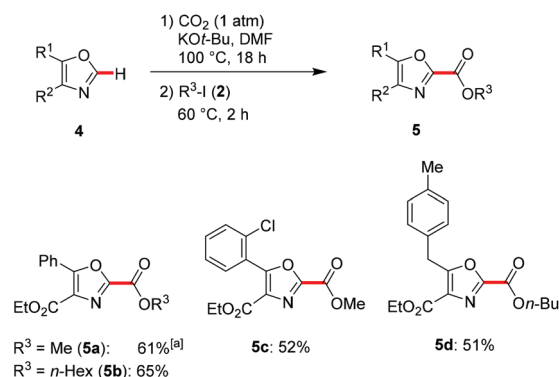
A series of representative heteroarenes **1** was successfully converted into the desired carboxylic acid esters **3** under transition metal-free reaction conditions with atmospheric CO₂.

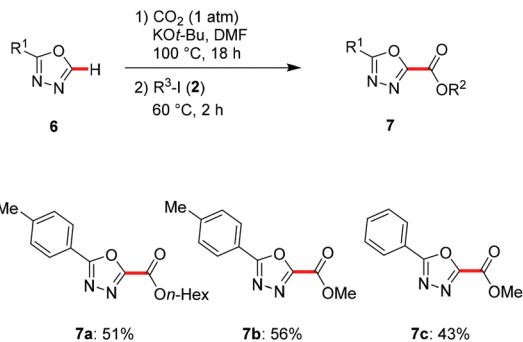
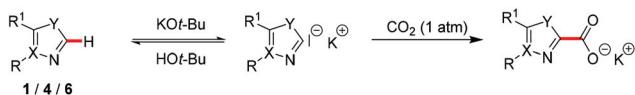
Various alkyl carboxylates **3** were obtained upon subsequent esterification with different alkyl iodides **2** under rather mild reaction conditions. Methyl- as well as chloro-substituted benzo[*d*]oxazoles **1b** and **1c** were site-selectively functionalized, affording the 2-substituted carboxylic 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-substitutedazole **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 benzothiazole 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).³⁷ 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,^{25,38} 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.

**Scheme 2** C–H carboxylation of oxazoles **4**. ^aGC-conversion.

Scheme 3 C–H carboxylation of oxadiazoles **6**.

Scheme 4 Proposed mechanism for the C–H carboxylation.

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, KO^t-Bu enabled efficient C–H functionalizations on heteroarenes with an ample substrate scope under mild³⁹ reaction conditions, namely at a rather low reaction temperature and ambient pressure of CO₂.

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Notes and references

- Q. Liu, L. Wu, R. Jackstell and M. Beller, *Nat. Commun.*, 2015, **6**, 5933.
- T. E. Mueller and W. Leitner, *Beilstein J. Org. Chem.*, 2015, **11**, 675–677.
- For selected recent reviews, see: (a) L. Zhang and Z. Hou, *Chem. Sci.*, 2013, **4**, 3395–3403; (b) Y. Tsuji and T. Fujihara, *Chem. Commun.*, 2012, **48**, 9956–9964; (c) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann and F. E. Kühn, *Angew. Chem., Int. Ed.*, 2011, **50**, 8510–8537; (d) M. Beller and U. T. Bornscheuer, *Angew. Chem., Int. Ed.*, 2014, **53**, 4527–4528; (e) K. Huang, C.-L. Sun and Z.-J. Shi, *Chem. Soc. Rev.*, 2011, **40**, 2435–2452; (f) T. Sakakura, J.-C. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365–2387, and references cited therein.
- I. I. F. Boogaerts and S. P. Nolan, *Chem. Commun.*, 2011, **47**, 3021–3024.
- L. Yang and H. Wang, *ChemSusChem*, 2014, **7**, 962–998.
- R. Martin and A. W. Kleij, *ChemSusChem*, 2011, **4**, 1259–1263.
- T. Sakakura, J.-C. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365–2387.
- P. Braunstein, D. Matt and D. Nobel, *Chem. Rev.*, 1988, **88**, 747–764.
- A. Boddien, F. Gaertner, C. Federsel, P. Sponholz, D. Mellmann, R. Jackstell, H. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 6411–6414.
- K. Beydoun, G. Ghattas, K. Thenert, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2014, **53**, 11010–11014.
- K. Beydoun, T. vom Stein, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2013, **52**, 9554–9557.
- X. Wang, M. Nakajima and R. Martin, *J. Am. Chem. Soc.*, 2015, **137**, 8924–8927.
- X. Wang, Y. Liu and R. Martin, *J. Am. Chem. Soc.*, 2015, **137**, 6476–6479.
- A. Correa and R. Martin, *J. Am. Chem. Soc.*, 2009, **131**, 15974–15975.
- L. Ackermann, A. R. Kapdi, H. K. Potukuchi and S. I. Kozhushkov, in *Handbook of Green Chemistry*, ed. C.-J. Li, Wiley-VCH, Weinheim, 2012, pp. 259–305.
- Representative reviews on C–H activation: (a) J. G. Kim, K. Shin and S. Chang, *Top. Organomet. Chem.*, 2016, **55**, 29–51; (b) M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498–525; (c) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (d) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66–81; (e) N. Kuhl, N. Schroeder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443–1460; (f) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (g) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375; (h) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936–946; (i) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212–11222; (j) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (k) R. G. Bergman, *Nature*, 2007, **446**, 391–393, and references cited therein.
- A. Uhe, M. Hoelscher and W. Leitner, *Chem. – Eur. J.*, 2012, **18**, 170–177.
- S. D. Stoychev, C. M. Conifer, A. Uhe, M. Hoelscher and W. Leitner, *Dalton Trans.*, 2014, **43**, 11180–11189.
- H. Mizuno, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2011, **133**, 1251–1253.
- T. Suga, H. Mizuno, J. Takaya and N. Iwasawa, *Chem. Commun.*, 2014, **50**, 14360–14363.
- K. Sasano, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2013, **135**, 10954–10957.
- I. I. F. Boogaerts, G. C. Fortman, M. R. L. Furst, C. S. J. Cazin and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2010, **49**, 8674–8677.
- I. I. F. Boogaerts and S. P. Nolan, *J. Am. Chem. Soc.*, 2010, **132**, 8858–8859.
- L. Zhang, J. Cheng, T. Ohishi and Z. Hou, *Angew. Chem., Int. Ed.*, 2010, **49**, 8670–8673.



- 25 O. Vechorkin, N. Hirt and X. Hu, *Org. Lett.*, 2010, **12**, 3567–3569.
- 26 Y. Li, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2014, **53**, 10476–10480.
- 27 Y. Li, I. Sorribes, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 12156–12160.
- 28 L. Ackermann, *Angew. Chem., Int. Ed.*, 2011, **50**, 3842–3844.
- 29 L. Ackermann, *Synlett*, 2007, 507–526.
- 30 L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.
- 31 S. Fenner, PhD thesis, Georg-August-University, 2012.
- 32 L. Zhang, J. Cheng, T. Ohishi and Z. Hou, *Angew. Chem., Int. Ed.*, 2010, **49**, 8670–8673.
- 33 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).
- 34 (a) For representative pK_a values, see <http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>; (b) For calculated pK_a values, see: K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576, and references cited therein. (c) For DFT studies on carboxylations of heteroarenes by copper(i) complexes, see: A. Ariafard, F. Zarkoob, H. Batebi, R. Stranger and B. F. Yates, *Organometallics*, 2011, **30**, 6218–6224.
- 35 J. Sherwood, M. D. Bruyn, A. Constantinou, L. Moity, C. R. McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunta and J. H. Clark, *Chem. Commun.*, 2014, **50**, 9650–9652.
- 36 All direct carboxylation reactions were performed in new glassware using novel stirring bars.
- 37 For detailed information see the ESI.†
- 38 A. Banerjee, G. R. Dick, T. Yoshino and M. W. Kanan, *Nature*, 2016, **531**, 215–219.
- 39 J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761.

