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Switchable N–H *vs.* C3–H carboxylation of indoles using dual-function reagents

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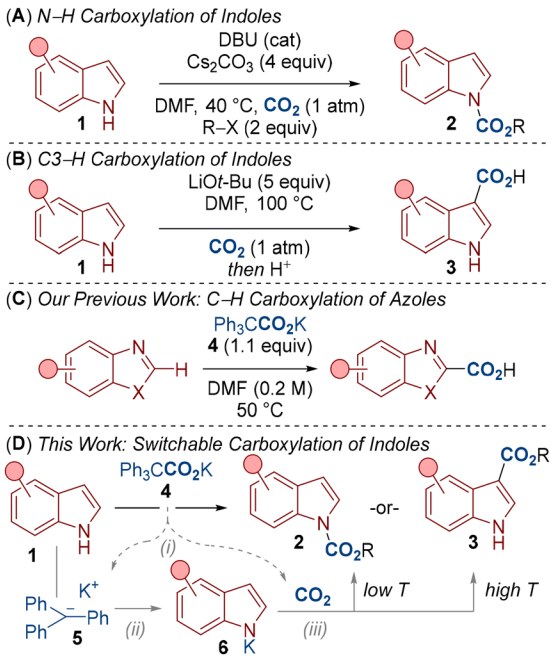
The carboxylation of indoles through a CO_2 transfer reaction with carboxylate salts is described. By altering the reaction conditions either N–H or C3–H carboxylation can occur. The reaction is also applicable to the carboxylation of other indole derivatives and amines. The relevance of this procedure is further demonstrated through the preparation and carbon isotope labelling of several biologically relevant carboxylated indoles/amines.

Indoles are privileged structures in organic synthesis and widely used amongst various disciplines, from dyes and perfumes to medicines, agrochemicals and materials.[1] Their ubiquity has spawned a strong interest in the development of methods for functionalization around the aromatic ring. In particular, the direct functionalization of C–H bonds presents an idealized route for indole modification.[2]

The carboxylation of indoles provides access to key motifs present in pharmaceuticals and natural products.[3] For example, N–H carboxylation affords carbamates which are pro-drug elements in many pharmaceuticals.[4] Alternatively, C–H carboxylation provides indole carboxylic acids, which form the core of several medicines.[5] Considering current literature, the site selective carboxylation of indoles has thus far taken a stepwise approach in which distinct reaction conditions are required for carboxylating the various reactive sites around the indole ring.[6,7] Authors have also been keen to discuss the difficulties associated with directing functionalisation between the N–H and C3–H positions.[8,9] One of the most effective methods for the N–H carboxylation of indoles has recently been reported by Hopmann, Repo and co-workers (Scheme 1A).[6d] In this work, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to effect the N–H carboxylation of indoles **1** under relatively mild conditions (40 °C, 1 atm) and an excess of cesium carbonate (4.0 equiv.) to give the carbamate **2**. However, directing the reactivity towards C3–H carboxylation was not investigated. Indeed, we were also unable to demonstrate C3–H carboxylation under similar conditions in our laboratory.[10] Conversely, Kobayashi and co-workers developed a C3–H selective carboxylation of indoles **1** using an excess of lithium *tert*-butoxide (5.0 equiv.) to give indole carboxylic acid **3** (Scheme 1B).[7b,7c] The reaction again proceeded under an atmospheric pressure of CO_2, though a higher temperature (100 °C) was required, presumably to overcome the higher energy barrier required for C3–H carboxylation. Notably, the Kobayashi group also demonstrated an N–H carboxylation to



Scheme 1 (A) and (B): previous N–H and C3–H carboxylations of indoles. (C) Previous carboxylations using dual-function reagents. (D) This work: N–H and C3–H carboxylation of indoles using dual-function reagents.

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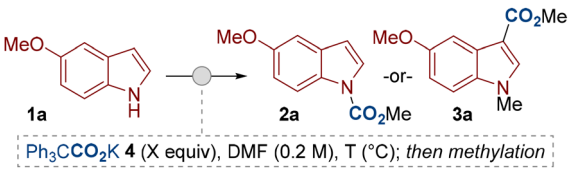
give carbamate **2**, but the process was low yielding (15%).[10] A unified approach for N–H vs C3–H carboxylation therefore presents a significant challenge.

We have recently demonstrated that carboxylates, for example the triphenylacetate salt **4**, are able to promote the carboxylation of arenes bearing C–H bonds *via* CO_2 transfer (Scheme 1C).[11–13] We described carboxylate **4** as a dual-function reagent as it provided a combined source of base and CO_2 for the reaction. We therefore questioned whether this reactivity could be applied to the carboxylation of indoles **1** (Scheme 1D). In this process, carboxylate **4** would initially undergo decarboxylation to provide the trityl anion **5** and CO_2 (step i). The highly basic trityl anion **5** (pK_a of Ph_3CH = 30.6)[14] would then be capable of deprotonating the indole **1** (pK_a = 21.0)[14] to deliver the intermediate **6** (step ii). At this point, we proposed to tune the conditions to deliver selective N–H or C3–H carboxylation. In this way, the deprotonated indole **6** would react with the *in situ* generated CO_2 to give either N–H or C3–H carboxylated products **2** or **3**. Here we report a unified approach to indole carboxylation and demonstrate the applicability of this carboxylation to other amine classes and carbon isotope labelling.

We began our study by subjecting indole **1a** to our previously reported reaction conditions at 50 °C.[11a] The potassium salt of triphenylacetic acid **4** was used as the dual-function reagent to provide the source of base and CO_2. (Table 1). After routine methylation with methyl iodide, the *N*-carboxylated product **2a** was isolated in high yield (entry 1). Aware of the interest in directing functionalization around the indole ring, we were keen to explore the possibility of a related C3–H carboxylation. Indeed, by performing the reaction at higher temperature (100 °C) the C3-carboxylated product **3a** was observed (entry 2). Optimal conditions for C3–H carboxylation were achieved by using 2.0 equivalents of the dual-function reagent **4** and by increasing the reaction temperature to 140 °C (entry 4). We chose to proceed with using 2.0 equivalents of the carboxylating agent **4** as our standard conditions for C3–H carboxylation as we were satisfied with the good yields this achieved with most substrates (*vide infra*), though higher yields can be achieved by further increasing the equivalents of **4** (entry 5). The C3-carboxylated product was isolated as the methylated derivative **3a** to ease isolation and avoid costly deuterated solvents during analysis (*e.g.* acetone-d_6), however, we have demonstrated that the free indole-3-carboxylic acid **3aH** can be isolated if desired (entry 6). Other variables, such as other metal salts of **4** and solvents were also tested during optimisation, but no improvements in reactivity were observed.[15]

Table 1 Optimization of the N–H and C3–H carboxylation of indoles

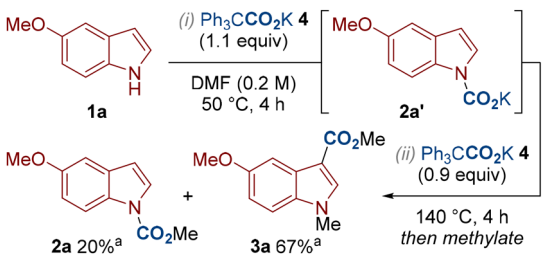


Entry	Ph_3CCO_2K **4** (equiv.)	T (°C)	2a (%)[a]	3a (%)[a]
1	1.1	50	94 (87)[b]	0
2[c]	1.1	100	38	25
3[c]	2.0	100	44	35
4[c]	2.0	140	20	67 (66)[b]
5	3.0	140	7	85
6	2.0	140	n.d.[d]	65[be]

DMF = *N*,*N*-dimethylformamide. [a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yields. [c] The remaining mass balance was largely recovered starting material (observed as the free indole or *N*-methylindole). Indole recovery: entry 2 = 28%, entry 3 = 12%., entry 4 = 4%. [d] n.d. = not determined. [e] The product was isolated as the indole-3-carboxylic acid **3aH**. After carboxylation, the methylation step was not performed. Instead, the reaction was quenched with 1 M HCl (aq.). See the SI for further details.

To gain some insight into the reaction mechanism, we subjected indole **1a** to the standard conditions for N–H carboxylation in which the carbamate intermediate **2a′** presumably forms (Scheme 2, step i). However, instead of performing the alkylation step towards isolating the N–H carboxylated product **2a**, we added additional Ph_3CCO_2K **4** and heated to 140 °C to mimic the C3–H carboxylation conditions (Scheme 2, step ii). This produced the same yields of **2a** and **3a** compared to our standard C3–H carboxylation conditions (c.f. Table 1, entry 4). This suggests that N–H carboxylation is a reversible process and that the C3–H carboxylated product **3a** can be generated from the carbamate **2a′**. Under N–H carboxylation conditions, the carbamate intermediate **2a′** can be trapped by the alkylating agent to give **2a**. Presumably, more electron-rich substrates are better at N–H carboxylation as they push the carboxylation/decarboxylation equilibrium towards carbamate **2a′** (*e.g.* compare the yields of **2a** and **2*gin*** in Scheme 3). Under C3–H carboxylation conditions, we suggest that N–H carboxylation can occur, however this is a reversible process that is superseded by irreversible C3–H carboxylation at higher temperatures. The higher temperature for C3–H carboxylation is presumably required as the process involves an electrophilic aromatic substitution-type mechanism in which aromaticity is disturbed.

With optimized conditions in hand, we went about investigating the scope of the reaction (Scheme 3). A range of electron-donating and electron-withdrawing substituents were compatible for both N–H and C3–H carboxylation, including halogen and cyano groups (see **1e–1g**). For N–H carboxylation, an indole bearing a Bpin (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) substituent also gave respectable yield (see **2d**). The N–H carboxylation with 5-cyanoindole **1g** and 7-azaindole **2k** were low yielding. We suggest that the lower nucleophilicity of these substrates disfavours carbamate formation, in agreement with



Scheme 2 Mechanistic investigation. [a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.

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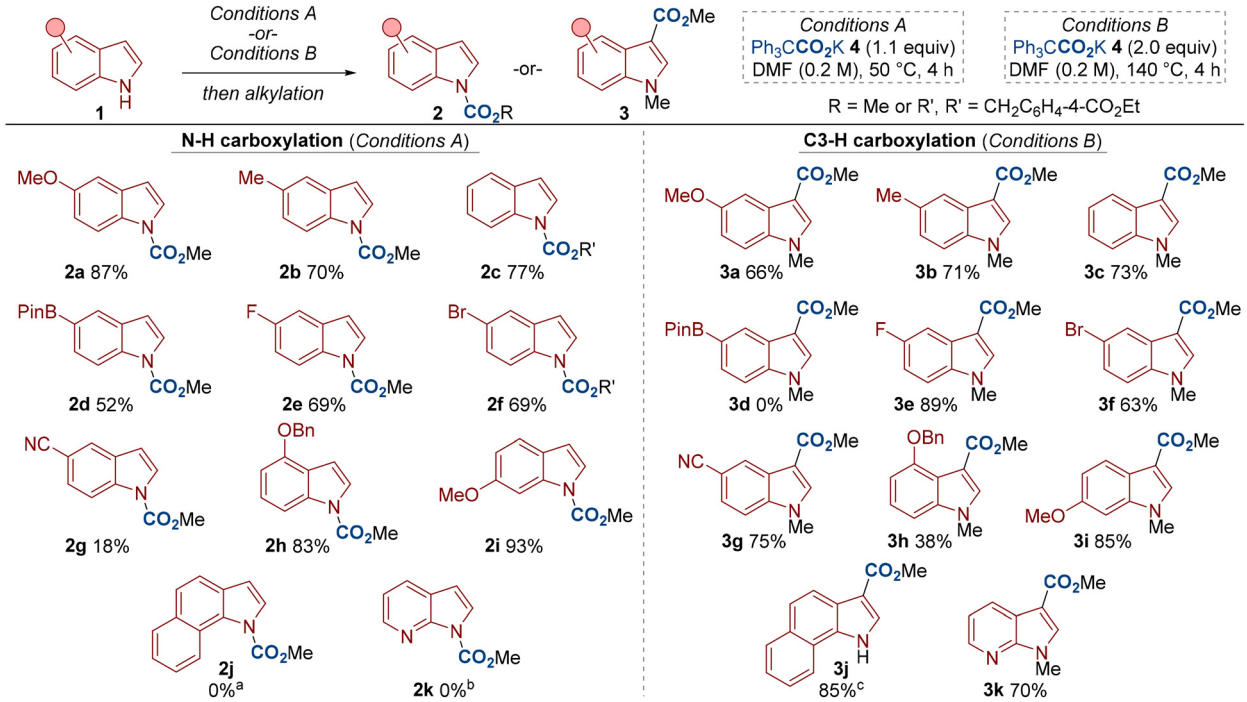


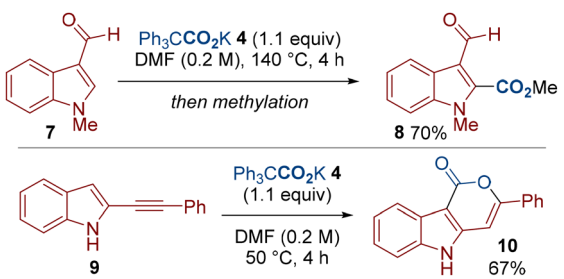
Scheme 3 Scope of the N–H and C3–H carboxylation of indoles. [a] **2j** was not formed. Instead, C3–H carboxylation was observed, see compound **3j**. [b] The mass recovery was largely *N*-methylated indole (67%). [c] Conditions A were used.

studies by Repo and Hoppman.[6d,16] Nonetheless, 5-cyanoindole **1g** proved a good substrate for C3–H carboxylation to give **3g**. Substituents at other positions around the indole ring were also compatible in both methods (see **1h** and **1i**). Finally, although indoles **1j** and **1k** did not undergo N–H carboxylation (to give **2j**/**2k**), good yields of C3–H carboxylation were observed (see **3j**/**3k**). Interestingly, C3–H carboxylated product **3j** formed in excellent yield at 50 °C and with 1.1 equivalents of carboxylating agent **4**. The high yield of **3k** was also satisfying as 7-azaindole is a privileged motif in medicinal chemistry.[17]

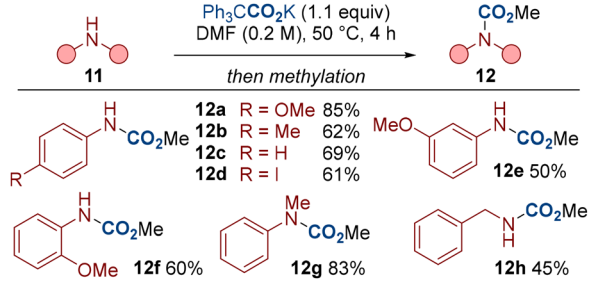
We were keen to further test the limits of this methodology in related indole carboxylations (Scheme 4). We therefore demonstrated a C2–H carboxylation of indole **7**.[18] We have also applied our methodology to the carboxylation of 2-alkynylindole **9** to give the 6-*endo-dig* cyclized product **10**.[19] Notably, the formation of compound **10** previously required higher temperatures (100 °C *vs.* 50 °C).[19a]

To further illustrate the generality of our procedure, we have also conducted a series of N–H carboxylations with various amines **11** (Scheme 5).[20] Electron-rich and electron-deficient substrates, and anilines bearing ortho, meta and para substituents all displayed respectable reactivity (**12a–12f**). Secondary amine **11g** and benzylamine **11h** were also compatible.

Our method has shown that a range of indoles and other amines can undergo carboxylation with near equimolar quantities of the carboxylating agent **4**. This presents a useful strategy for carbon isotope labelling in which limiting the equivalents of the labelling reagent holds significant advantages.[21] For example, labelled CO_2 gases (*e.g.* $^{14}CO_2$, $^{13}CO_2$) are more expensive and less available than non-labelled CO_2 (for example, $^{14}CO_2$ > £1000 mmol^{-1}).[22] The carboxylating reagent **4** is also a bench stable solid, thereby presenting practicality benefits over gaseous labelled reagents. We have therefore carboxylated a range of biologically relevant compounds, including the isotope labelled compounds **14d*** and **3c-H*** by using the labelled dual-function reagent **4*** (Scheme 6). We also note that no erosion in the enantiomeric excess was observed in the preparation of the



Scheme 4 Other carboxylations of indoles.



Scheme 5 N–H carboxylation of amines.

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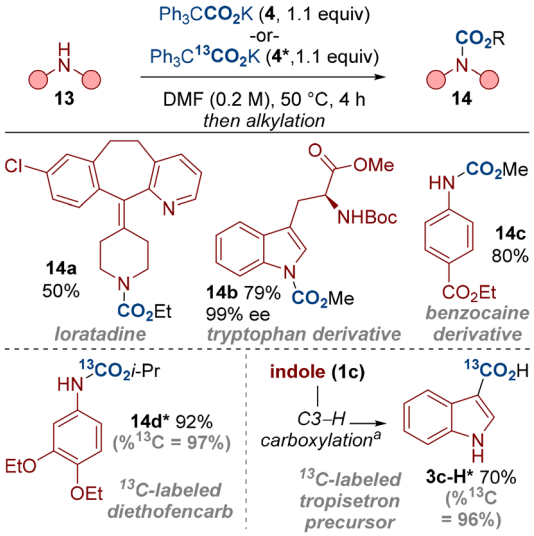

Scheme 6 Carboxylation and isotope labelling of biologically relevant molecules.

tryptophan derivative **14b**, highlighting the mild conditions we have developed.

In summary, we have developed a CO_2 transfer reaction of indoles and other amines using the dual-function reagent **4** as a combined source of base and CO_2. Indoles can undergo N–H carboxylation or C3–H carboxylation depending on the reaction conditions. The carboxylation was also applicable to other amines and related carboxylation reactions with other indole architectures. Finally, we have applied this method to the incorporation of carbon isotopes into biologically relevant molecules using low equivalents of the labelled carboxylating reagent.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6cc00532b.

Acknowledgements

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15 See the supporting information for further details. $NCCH_2CO_2K$ and $EtO_2CCH_2CO_2K$ were tested as alternative dual-function reagents. $NCCH_2CO_2K$ showed poor reactivity in both N–H and C3–H carboxylation. $EtO_2CCH_2CO_2K$ was poorly reactive in the N–H carboxylation, but did show comparable reactivity to Ph_3CCO_2K in the C3–H carboxylation to give 60% of **3a**.

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