Carboxylic Acid Salts as Dual-Function Reagents for Carboxylation and Carbon Isotope Labeling

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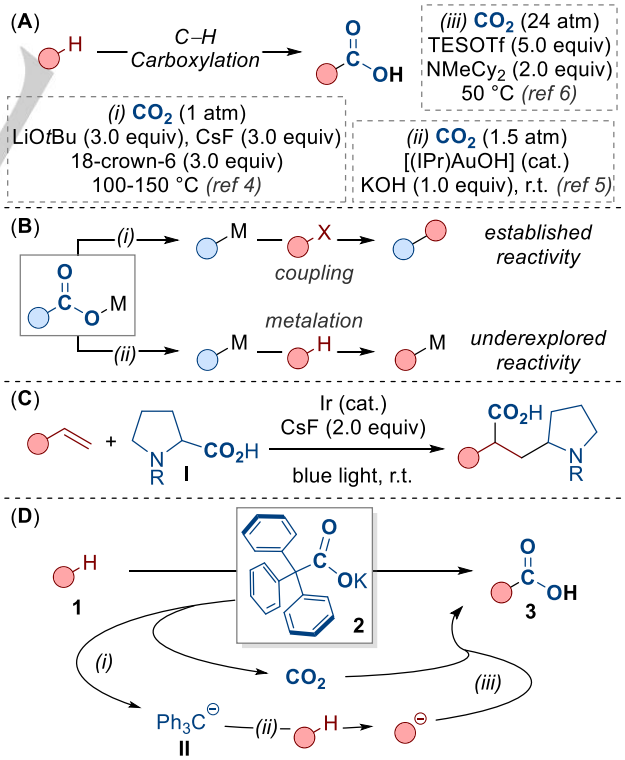
Abstract: The potassium salts of carboxylic acids are developed as efficient carboxylating agents through CO_2 exchange. We describe these carboxylates as dual-function reagents because they function as a combined source of CO_2 and base/metalating agent. By using the salt of a commercially available carboxylic acid, this protocol overcomes difficulties when using CO_2 gas or organometallic reagents, such as pressurized containers or strictly inert conditions. The reaction proceeds under mild conditions, does not require transition metals or other additives, and shows broad substrate scope. Through the preparation of several biologically important molecules, we show how this strategy provides an opportunity for isotope labeling with low equivalents of labeled CO_2.

Carboxylation is a fundamental process in organic synthesis for preparing important building blocks and value-added products.[1] Many strategies for carboxylation require activated substrates, such as organic halides or sensitive organometallic reagents (e.g. organolithium and Grignard reagents).[2] Idealized methods that carboxylate C–H bonds are available, but they generally require high temperatures and/or transition metal catalysts.[3] The groups of Kondo[4] and Nolan[5] have developed promising methods for base-promoted C–H carboxylation of arenes,[6,7,8] however, these protocols suffer from several drawbacks (Scheme 1A, i and ii). For example, the route described by the Kondo group requires high temperatures (generally 100-150 °C) and excess reagents (3.0 equivs of LiO*t*Bu/CsF/18-crown-6).[4] Nolan and co-workers reported a room temperature carboxylation, however, a non-commercially available gold catalyst and pressurized CO_2 (1.5 atm) were needed.[5] During the submission of this manuscript, scientists at Merck & Co., Inc. again demonstrated the importance of this type of C–H carboxylation, but high pressure CO_2 (24 atm) and specialized equipment were used (Scheme 1A, iii).[6] Pressurized vessels or excess CO_2 are routine throughout carboxylation chemistry. This presents significant problems when using these methods for isotope labeling as considerably more expensive gases are needed (e.g. $^{13}CO_2$, $^{14}CO_2$ - 1 mmol of $^{14}CO_2$ >£1000).[9] Overall, little is known about the efficiency of carboxylation reactions in terms of CO_2 stoichiometry.

Aided by the ready availability of carboxylic acids, decarboxylation reactions have matured greatly in recent years.[10] This reactivity has been applied in coupling reactions in which decarboxylation generates nucleophilic intermediates in situ (Scheme 1B, i). This is an attractive way to replace difficult-to-handle organometallics with bench-stable carboxylic acid derivatives. However, beyond their utility as nucleophiles, organometallic reagents are also important bases/metalating agents. We therefore considered whether decarboxylation could be harnessed to generate an organometallic in situ and provide a new tool for metalation that avoids sensitive reagents (Scheme 1B, ii).

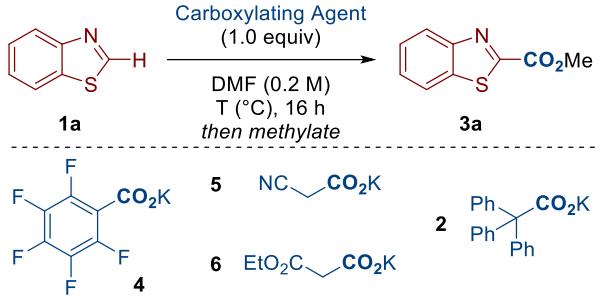
Recently, the Yu group have reported an elegant approach to the carboxylation of alkenes using amino acids **I** as bifunctional reagents (Scheme 1C).[11,12] We were particularly impressed by C–C bond formation via CO_2 transfer with near stoichiometric quantities of carboxylic acid **I**, thus highlighting the efficiency when generating CO_2 in situ.[13,14]



Scheme 1. (A) Base-promoted C–H carboxylation. (B) (i) Organometallic nucleophiles via decarboxylation and (ii) base/metalating agents via decarboxylation. (C) Bifunctional reagents for carboxylation. (D) This work: dual-function reagents for carboxylation: (i) decarboxylation, (ii) deprotonation, (iii) carboxylation.

Here we describe the potassium salt of triphenylacetic acid **2** as a combined source of base and CO_2 for carboxylation (Scheme 1D). Our strategy relied on the decarboxylation of carboxylate **2** to generate CO_2 and the trityl anion **II** (step i).[15] We reasoned that the high basicity of **II** (pK_a of Ph_3CH = 30.6 in DMSO)[16a] would allow deprotonation of a variety of substrates **1** (step ii). Once deprotonated, the substrate would capture the in situ generated CO_2 to give the desired carboxylated product **3** (step iii). This introduces a mechanistically distinct method for carboxylation in which a single reagent acts as both a source of CO_2 and base/metalating agent. In addition, as carboxylates are readily available, safe, and easy-to-store/handle, this would provide an accessible route to carboxylation that avoids specialized equipment and sensitive reagents.

Table 1. Screening of reaction conditions

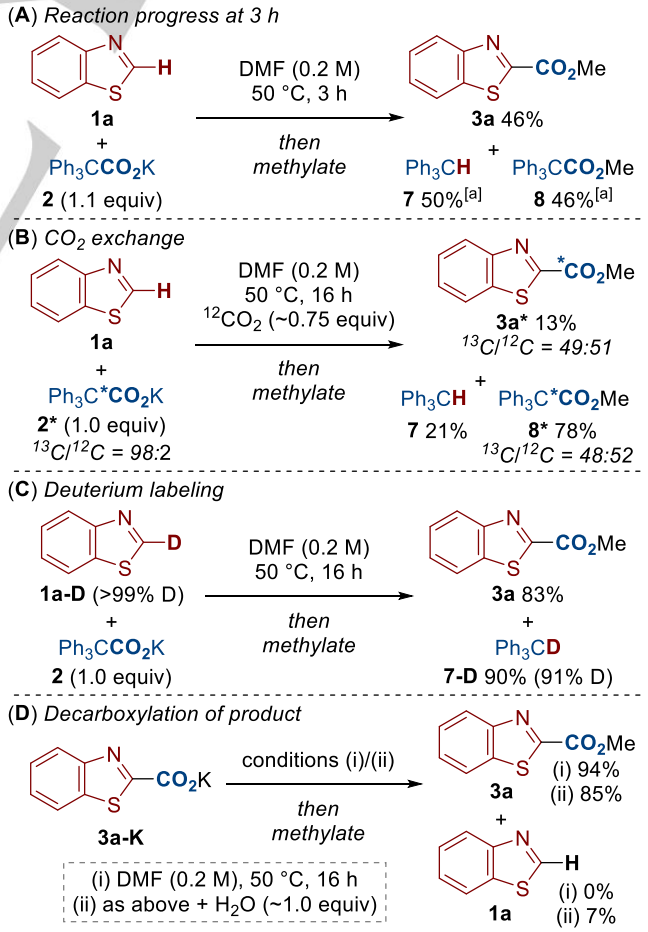


Entry	Carboxylating Agent	T (°C)	NMR yield **3a** (%)
1[a]	**4**	100	87
2	**4**	100	0
3	**5**	100	75
4	**6**	100	90
5	**2**	100	92
6	**2**	50	87
7	**2**[b]	50	92, (89)[c] (92)[d], (74)[e], 85[f]

Reaction conditions: **1a** (0.5 mmol), carboxylating agent (1.0 equiv), DMF (0.2 M), 50 or 100 °C, 16 h. *Then* MeI (8.0 equiv), 50 or 65 °C, 2 h. DMF = *N*,*N*-Dimethylformamide. [a] Cs_2CO_3 (3.0 equiv) was added. [b] **2** (1.1 equiv). [c] Isolated yield. [d] Isolated yield of potassium benzothiazole-2-carboxylate (**3a-K**). [e] Isolated yield of benzothiazole-2-carboxylic acid (**3a-H**). [f] One-pot reaction from Ph_3CCO_2H and K_2CO_3. See the SI for further details.

Guided by our experience in decarboxylation chemistry,[17] we tested a range of carboxylic acids as CO_2 surrogates (Table 1). Initial results showed potassium benzoate **4** as a possible CO_2 source (Entry 1).[18] However, additional base (Cs_2CO_3) was required suggesting **4** was unable to perform as a dual-function base and CO_2 reagent (Entry 2).[19] By turning to carboxylates that could form more stabilized intermediates,[20] both **5** and **6** provided encouraging results, but required elevated temperatures (Entries 3 and 4). Carboxylate **2** derived from triphenylacetic acid enabled carboxylation at temperatures as low as 50 °C (Entries 5 and 6). Triphenylacetic acid is commercially available (CAS: 595-91-5) or preparable through various routes.[21] Other solvents and alkali salts were tested but reagent **2** in anhydrous DMF gave optimal results (Entry 7).[22] The products in this study were isolated as the corresponding methyl esters, but both the potassium salt **3a-K** and the carboxylic acid **3a-H** were isolable (Entry 7).

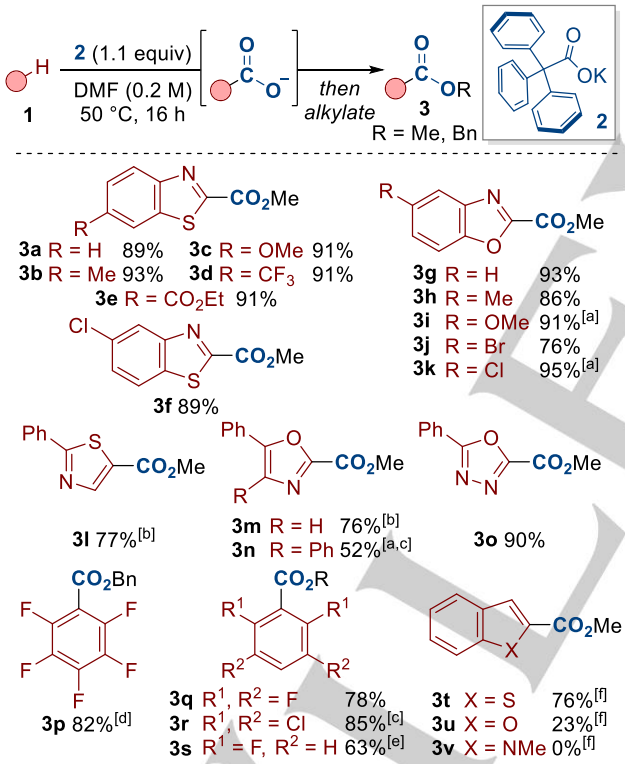
We have assessed the dual-function role of reagent **2** and scrutinized the mechanism outlined in Scheme 1D. First, we recorded the progress of the reaction at 3 h and found roughly equal amounts of product **3a** and side product **7** had formed alongside recovery of reagent **2** (analyzed as the methyl ester **8**, Scheme 2A). This suggested that carboxylated product **3a** forms (Scheme 1D, step iii) as reagent **2** steadily decarboxylates (Scheme 1D, step i). Interestingly, this carboxylation was inhibited when performed under an atmosphere (~0.75 equivalents) of CO_2 (Scheme 2B). Also, by using the labeled reagent **2*** in this experiment, we observed isotope exchange in both the starting material (analyzed as the methyl ester **8***) and product **3a***. These observations supported the formation of CO_2 during the reaction and suggested that the decarboxylation of **2** was reversible (Scheme 1D, step i).[15,20] To provide support for the deprotonation step (Scheme 1D, step ii), deuterated benzothiazole **1a-D** was submitted to our standard reaction conditions to yield carboxylated product **3a** alongside deuterated compound **7-D** (Scheme 2C). Finally, we examined the reversibility of the final carboxylation step (Scheme 1D, step iii). When heating the potassium salt of the carboxylated product **3a-K** in anhydrous DMF, no decarboxylation was observed (Scheme 2D, i). However, when repeating this reaction in the presence of ~1.0 equivalent of H_2O, a small amount of decarboxylation occurred (Scheme 2D, ii), suggesting the carboxylation is somewhat reversible. From these results, we believe this carboxylation relies on a set of



Scheme 2. Mechanistic studies. Further experimental details are provided in the supporting information. [a] Yields are with respect to **2**.

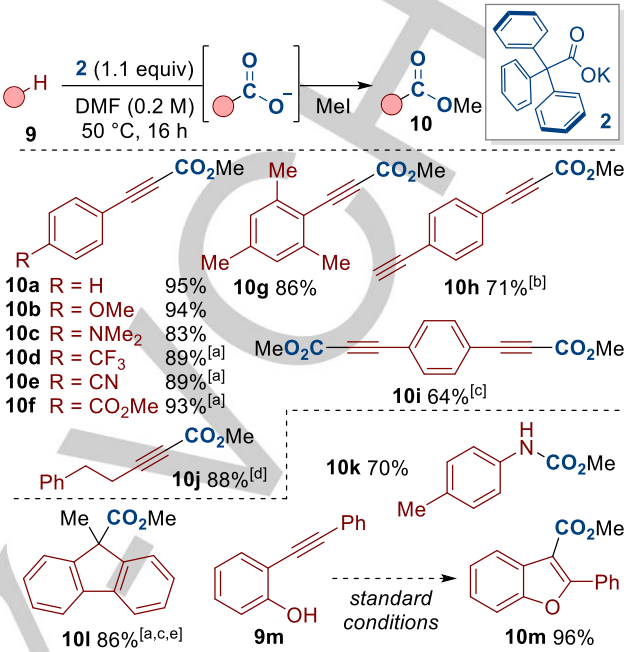
equilibriums that are shifted towards the product under the standard reaction conditions.[23] Further experiments and discussion are provided in the supporting information. These studies also highlight several interesting features of our procedure: i) carboxylates act as a convenient source of CO_2 and metalating agent without the need for specialized equipment; ii) carboxylates, which are weakly basic (pK_a of $MeCO_2H$ = 12.3 in DMSO)[16a], generate strong bases (pK_a of Ph_3CH = 30.6 in DMSO)[16a] upon facile decarboxylation; and iii) the reaction proceeds with just 1 equivalent of the CO_2 source.

With regard to the scope (Scheme 3), benzothiazoles (pK_a = 27.0 in DMSO)[16a] and benzoxazoles (pK_a = 24.4 in DMSO)[16a] bearing electron-withdrawing or electron-donating substituents reacted efficiently to give **3a**-**3k**. Thiazoles, oxazoles and oxadiazoles also performed well to give **3l**-**3o**. The reactivity with simple arenes to give **3p**-**3s** was particularly impressive as the current state-of-the-art requires high temperatures (≥100 °C) or a costly gold catalyst (*c.f.* Scheme 1A).[4,5] At present, this procedure seems limited to substrates bearing C–H bonds with a pK_a value of ~30 or less. Nonetheless, benzothiophene (pK_a = 32.0 in DMSO)[16b] and benzofuran (pK_a = 33.2 in DMSO)[16b] were carboxylated to give **3t** and **3u** when more forcing conditions were used.

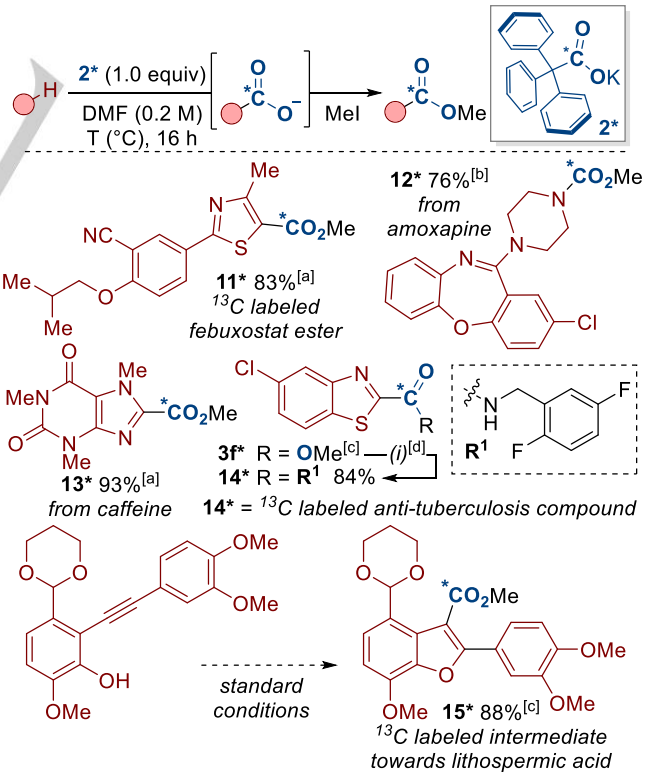


Scheme 3. Scope of the C–H carboxylation of arenes with dual-function reagent **2**. Reaction conditions: **1** (1.0 mmol), **2** (1.1 equiv), DMF (0.2 M), 50 °C, 16 h. See the SI for details on the alkylation step. [a] 60 °C. [b] 80 °C. [c] 65 h. [d] room temperature. [e] 100 °C, [f] **2** (2.0 equiv), 160 °C.

Various terminal alkynes (pK_a of PhC≡CH = 28.8)[16a,24] underwent carboxylation to give **10a**-**10j**, including those bearing sensitive functionalities, such as amino (**9c**), cyano (**9e**) and ester (**9f**) groups (Scheme 4). As reagent **2** is a weighable solid, the selectivity between mono- and dicarboxylation was easily controlled (**10h** *c.f.* **10i**).[25] Other substrates underwent carboxylation, for example *p*-toluidine gave carbamate **10k**, fluorene gave acetate **10l** and 2-(phenylethynyl)phenol gave benzofuran **10m** via cyclization. Previously, *p*-toluidine was unreactive under copper catalyzed conditions[26] and the formation of benzofuran **10m** required pressurized CO_2 (10 atm).[27]



Scheme 4. Continued scope of the carboxylation with dual-function reagent **2**. Reaction conditions: **9** (1.0 mmol), **2** (1.1 equiv), DMF (0.2 M), 50 °C, 16 h. See the SI for details on the alkylation step. [a] room temperature. [b] **9h** (1.0 mmol. 2.0 equiv), **2** (0.5 mmol, 1.0 equiv). [c] **2** (2.0 equiv). [d] 80 °C. [e] From fluorene.



Scheme 5. Scope of the carboxylation with labeled dual-function reagent **2***. Reaction conditions: Substrate (0.25 mmol), **2*** (1.0 equiv), DMF (0.2 M), T (°C), 16 h. See the SI for details on the alkylation step. [a] 100 °C. [b] 60 °C. [c] 50 °C. [d] (i) remove volatiles *then* NH_4Cl (20 mol %), (2,5-difluorobenzylamine (2.5 equiv), 100 °C, 4 h.

Carbon isotope labeling plays an important role in mechanistic studies and drug discovery.[28,29] As labeled carbon dioxide gases are prohibitively expensive, an ideal method would use stochiometric amounts of the labeled gas.[9] However, due to the intrinsic problems in handling gases, specialized equipment is required to prevent gas loss. In Scheme 5 we show that several labeled molecules (**11*-15***) can be assembled with 1 equivalent of weighable carboxylating agent **2***.[30,31] This further illustrates the functional group compatibility of this procedure and provides a practical route for carbon isotope labeling.

In conclusion, we have introduced the potassium salt of triphenylacetic acid **2** as a dual-function reagent for the carboxylation of various bond types, including aryl C(sp^2)–H, alkynyl C(sp)–H, benzylic C(sp^3)–H and amine N–H bonds. The method proceeds at relatively low temperatures, avoids transition metals and does not require specialized equipment. Mechanistic studies highlight the dual-function role of reagent **2** as both a metalating agent and source of CO_2. This reactivity has been extended to the ^{13}C-labeling of various biologically/medicinally significant compounds. We believe the ready availability of reagent **2** and the practicality of this procedure will aid others to explore carboxylation and isotope labeling chemistry.

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Keywords: carboxylation • decarboxylation • dual-function reagent • isotope labeling • metalation

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[30] The preparation of triphenylacetic acid is possible with near stoichiometric amounts (1.6 equiv) of carbon dioxide. See the supporting information (page S9) for further details.

[31] For details on compound **14*** and **15*** see: a) P. Shah, T. M. Dhameliya, R. Bansal, M. Nautiyal, D. N. Kommi, P. S. Jadhavar, J. P. Sridevi, P. Yogeeswari, D. Sriram, A. K. Chakraborti, *Med. Chem. Commun.* **2014**, *5*, 1489–1495. b) J. Fischer, G. P. Savage, M. J. Coster, *Org. Lett.* **2011**, *13*, 3376–3379.

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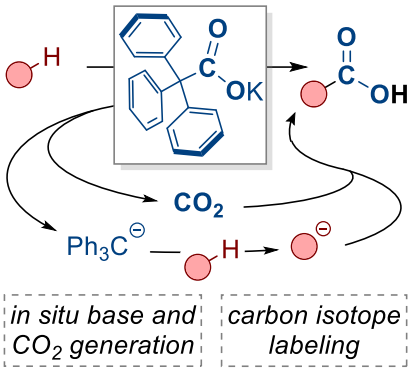

The potassium salt of triphenylacetic acid is developed as a combined source of CO_2 and base/metalating agent. This method avoids specialized equipment and is used in the carboxylation of a range of compound classes. This provides a mechanistically distinct approach to carboxylation that has also been applied in carbon isotope labeling.

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