Direct Reversible Decarboxylation from Stable Organic Acids in Solution

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Abstract Many classical and emerging methodologies in organic chemistry rely on carbon dioxide extrusion to generate reactive intermediates for subsequent bond-forming events. Synthetic reactions that involve the microscopic reverse, the carboxylation of reactive intermediates such as organometallic nucleophiles, occur under vastly different reaction conditions. We found that under appropriate conditions chemically stable C(sp^3) carboxylates undergo rapid, uncatalyzed reversible decarboxylation in solution. The decarboxylation/carboxylation process occurs through the generation and trapping of otherwise undetectable carbanion intermediates that are largely resistant to protodecarboxylation in the presence of Brønsted acids or to trapping by external electrophiles. Isotopically labelled carboxylic acids, including drug molecules and valuable synthetic intermediates, can be prepared in high chemical and isotopic yield by simply supplying an atmosphere of $^{13}CO_2$ to carboxylate salts in polar aprotic solvents. Our results indicate that the reversibility of decarboxylation from organic acids should be taken into consideration when designing and executing decarboxylative functionalization processes.

Decarboxylation is a fundamental step in biochemical processes and synthetic organic chemistry. Fermentation, respiration, and the biosynthesis of many secondary metabolites involve the loss of CO_2 from organic acids.[1] Decarboxylases accelerate these reactions by stabilization of developing reactive intermediates, often a carbanion, and encourage CO_2 diffusion from the active site, enabling otherwise unfeasible decarboxylations to occur under physiological condition (Fig 1A).[2] Acid substrates lacking anion stabilizing groups adjacent to the reactive carbon center are inert towards spontaneous decarboxylation without resorting to pyrolysis conditions (Fig 1B).[3] Thus, synthetic reactions driven by decarboxylation often require high reaction temperatures,[4] the use of oxidizing agents,[5] or stoichiometric chemical modification of the carboxylate unit.[6]

Carboxylation reactions, the microscopic reverse of decarboxylation, are equally valuable processes in biology and synthetic chemistry. Despite a shared reaction pathway, the biochemical machinery that promote carboxylation in CO_2 fixation operate by a distinct set of substrates and enzymes from those that promote decarboxylation in all but a few rare exceptions.[7] Similarly, synthetic techniques

that generate carboxylic acid derivatives from CO_2 require strongly nucleophilic organometallics and/or in-situ stoichiometric (electro)chemical substrate reduction.[8]

The potential for the reversibility of decarboxylation/carboxylation mechanistic steps is largely ignored in synthetic methodologies that rely on these reactions. Reports of direct non-enzymatic reversible CO_2-exchange processes of carboxylic acids are restricted to specialized substrate/mediator pairs.[9] Exchange of carboxylate groups in simple aliphatic acids with CO_2 has been documented, but requires heating of neat substrates at 280–400 ºC.[10] Currently, state-of-the-art methods to prepare $C(sp^3)$–$^{13/14}CO_2$ labeled carboxylic acid-derived targets, sought after in (pre)clinical absorption, distribution, metabolism, and excretion (ADME) studies,[11] involve circuitous pathways consisting of chemical activation-decarboxylation-metalation-carboxylation steps mediated by transition metals (Fig 1C).[12] The exchange of $C(sp^2)$-carboxylate groups catalyzed by transition metals has been demonstrated, however reactivity is restricted to stabilized aromatic substrates at high temperature (≥280 ºC).[13] While valuable methods for obtaining labelled targets, these indirect techniques are accompanied by low chemical yields and modest incorporation of isotopic label. Due to these limitations, classical nucleophilic substitution reactions with labelled cyanide followed by hydrolysis or processes that use labelled carbon monoxide remain widely used.[14]

In the course of our studies on catalytic decarboxylative cross-coupling reactions,[15] we questioned whether the apparent stability of organic carboxylates could arise from reversible decarboxylation/carboxylation events in solution. Supporting this hypothesis, we observed that simple organic acids that are stable towards protodecarboxylation in solution undergo spontaneous incorporation of $^{13}CO_2$ when supplied at atmospheric pressure (Fig 1D). This behavior is general to a range of $C(sp^3)$ carboxylic acids that feature modest electron-withdrawing groups adjacent to the carboxylate unit (aromatics, carbonyls, imines, nitriles). An understanding of this phenomenon can be exploited to prepare isotopically labelled drug molecules and synthetic precursors in an operationally trivial manner.

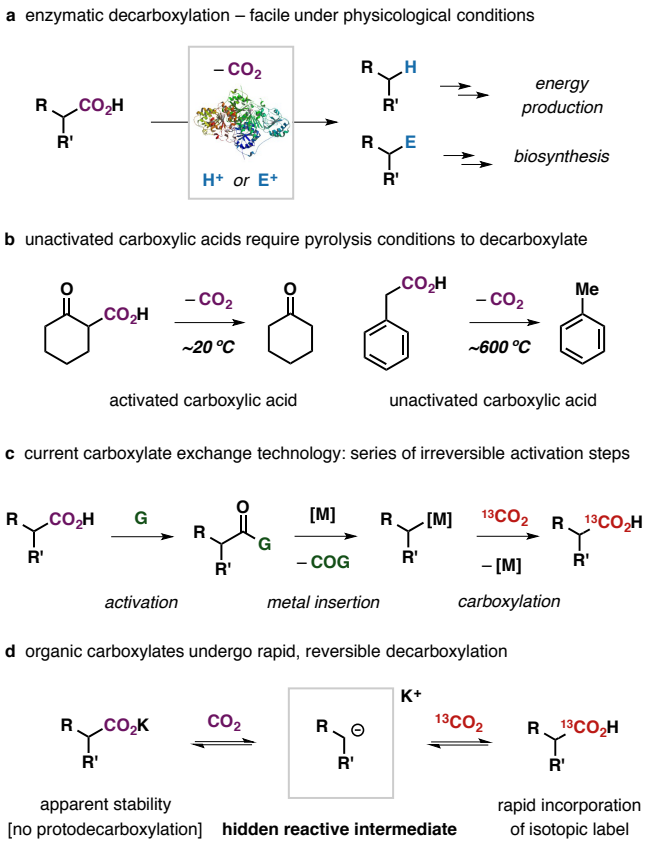
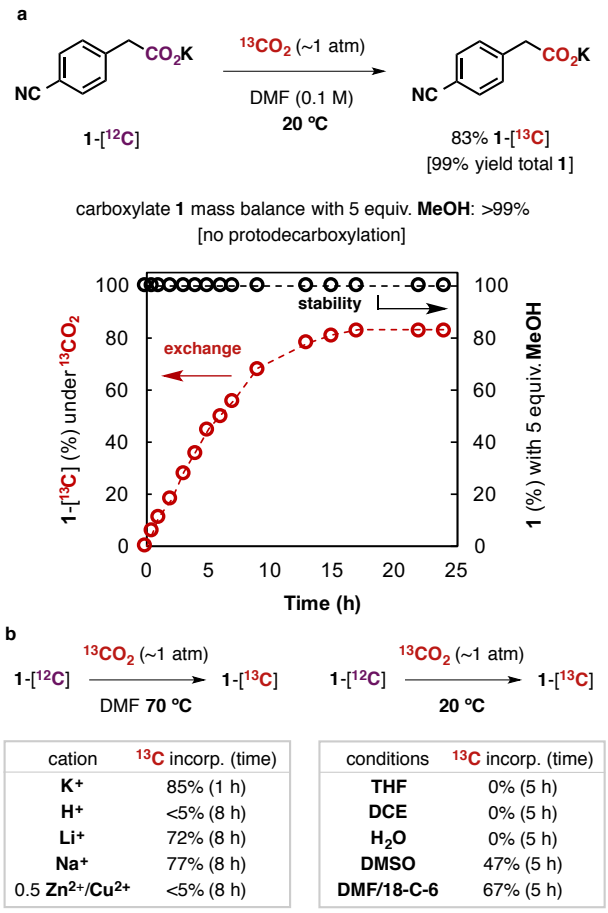


Fig 1. Overview of decarboxylative processes and carboxylate exchange. (**a**) Decarboxylation is catalyzed by enzymes under physiological conditions (E^+: electrophile). (**b**) The feasibility of protodecarboxylation depends on the stability of the carbanion intermediate generated. (**c**) Current carboxylate exchange technology requires a series of irreversible activation steps. (**d**) This work.

The potassium aryl acetate **1** exemplifies the reversible decarboxylation/carboxylation behavior of otherwise chemically stable carboxylic acids. A 0.1 M solution of **1** in DMF at 20 ºC undergoes CO_2 exchange when placed under an atmosphere of $^{13}CO_2$. In a reaction where approximately seven equivalents of $^{13}CO_2$ is supplied (13 mL of CO_2 at ~1 atm, dissolved $^{13}CO_2$ concentration of 0.25 M), equilibrium between ^{12}C and ^{13}C is achieved in 15 hours (Fig 2A, red trace). Quantitative recovery of carboxylate **1** with 83% ^{13}C-enrichment was possible by acid/base extractive workup. Under similar conditions with five equivalents of a weak Brønsted acid (MeOH) no protodecarboxylation of **1** is observed (Fig 2A, black trace). These results demonstrate that re-capture of the putative carbanion intermediate generated by decarboxylation of **1** with dissolved CO_2 is significantly more favorable than protonation. The apparent stability of **1** arises from efficient recapture of CO_2 by an otherwise hidden intermediate.

The counter-cation of the carboxylate salt impacts carboxylate exchange reactivity (Fig 2B). The carboxylic acid of **1** is not reactive, no $^{13}CO_2$ exchange or protodecarboxylation was observed in DMF at



cation	^{13}C incorp. (time)
K$^+$	85% (1 h)
H$^+$	<5% (8 h)
Li$^+$	72% (8 h)
Na$^+$	77% (8 h)
0.5 **Zn^{2+}/Cu^{2+}**	<5% (8 h)

conditions	^{13}C incorp. (time)
THF	0% (5 h)
DCE	0% (5 h)
H$_2$O	0% (5 h)
DMSO	47% (5 h)
DMF/18-C-6	67% (5 h)

Fig 2. Carboxylate exchange of a stable aryl acetic acid. (**a**) Comparison of CO_2 exchange (red) and protonation with MeOH (black). (**b**) Impact of salt and reaction conditions.

70 °C. Li^+ and Na^+ salts of **1** react more slowly, while transition metal salts (Zn^{2+} or Cu^{2+}) are inert. The use of polar aprotic solvents is essential for the transformation, reactions conducted in THF, DCE, or water resulted in recovery of unlabeled **1**. The addition of 18-crown-6 (18-C-6) results in an approximate two-fold rate enhancement of carboxylate exchange (see SI Fig S2).[16] The free acid undergoes carboxylate exchange when 1.5 equivalents of K_2CO_3 and 18-C-6 are added (>90% yield and ^{13}C incorporation in 19 h). Collectively, these observations suggest that the generation of a solvent-separated ion pair leads to enhanced decarboxylative reactivity. Reversible decarboxylation occurs for an array of carboxylate containing molecules, including valuable synthetic precursors, drug molecules, and amino acid derivatives (Fig 3 and 4). The incorporation of $^{13}CO_2$ and product recovery remains high (>80%) across several substrate classes. The degree of incorporation is largely a function of the amount of $^{13}CO_2$ supplied, >95% enrichment can be obtained when a significant excess is provided (see SI Fig S3). Regardless of electronic properties, aryl acetates undergo $^{13}CO_2$ incorporation by conducting reactions at suitable temperatures. (Hetero)aryl acetates with anion stabilizing groups exchange at moderate temperatures (**1**-**4**, **9**, **10**, **11**-**15** at 20–80 °C), while aryl acetates with strongly electron-donating

OMe or NMe_2 groups require higher temperatures (**17**-**20** at 100–130 ºC) and benefit from the addition of 18-C-6. The simplicity of the process enables broad functional group compatibility, including tolerance to boronic esters (**6**), aryl halides (I, Br, Cl, F; **4**, **7**, **8**, **10**), ketones (**11**), aldehydes (**12**) esters (**14**), amides (**13**), sulfonyls (**15**), and potentially reactive heterocycles (chromenone **25,** NH-indole **26**, pyridines **27**, **29**, pyrimidines **28,** isoxazole **30**, thiophene **31**). Alkyl and aryl substitution adjacent to the carboxylate is tolerated, including examples of trisubstituted, non-enolizable aryl acetates (**21**-**24**). Other classes of potassium carboxylates that undergo productive CO_2 exchange include malonate half-esters (**32**-**35**), β-keto acids (**36**), β-carboxysulfonyls (**37**, **38**), cyanoacetates (**39**), and carboxylactams (**40**). Alkene and terminal alkyne functional groups do not interfere with the process (**34**, **35**). Potassium malonates undergo exchange at higher temperature (135 ºC) to give a mixture of mono- and bis-labelled product along with ^{13}C-enriched monoacid (**41** and **42)**.

Carboxylate exchange can be used to directly prepare isotopically labelled drug molecules, including aryl acetate and propionate NSAIDs of varying complexity (Fig 4 **43**-**52**). Pharmaceuticals featuring amide or ester groups are obtained via derivatization of the acid group (Zolpidem **53**, Aprophen **55**) or can be prepared according to established literature protocols (Propiverine **54**, Netupitant **56**, Repaglinide **57**). Consistent with ionization to generate a carbanion, racemization of enantiopure Naproxen (**46**) is observed (see SI Fig S4). Reversible decarboxylation may explain reports of aryl propionate racemization required for kinetic resolution manufacturing processes.[17] Unsubstituted alkyl carboxylic acids do not undergo CO_2 exchange, however isotopically labelled products of this class can be readily obtained by carboxylate exchange/desulfonylation reactions of sulfonyl acids or exchange/decarboxylation sequences of malonic acids in three step processes (**58**-**60**). The facile generation of ^{13}C-diphenylmethylidene glycine at room temperature (**61** 93% incorporation, 76% yield) serves as a starting point for the synthesis of other labelled amino acids.[18]

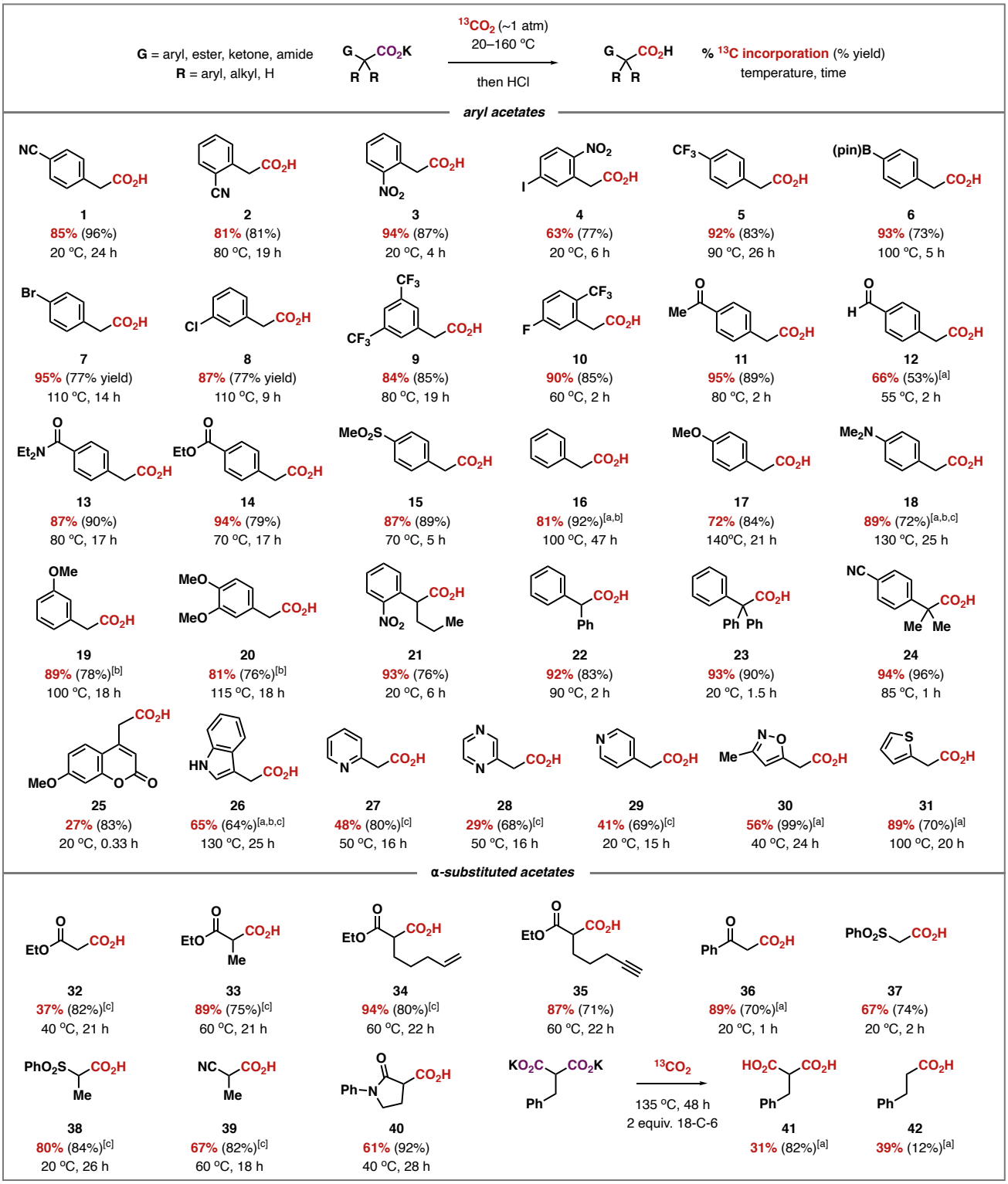


Fig 3. Carboxylate exchange substrate scope. Unless noted yields are of isolated material. [a] calibrated ^{1}H NMR spectroscopy yield; [b] 18-C-6 added; [c] % ^{13}C incorporation and yield determined by analysis of the corresponding ester obtained by reaction with MeI or BnBr. See SI for complete details.

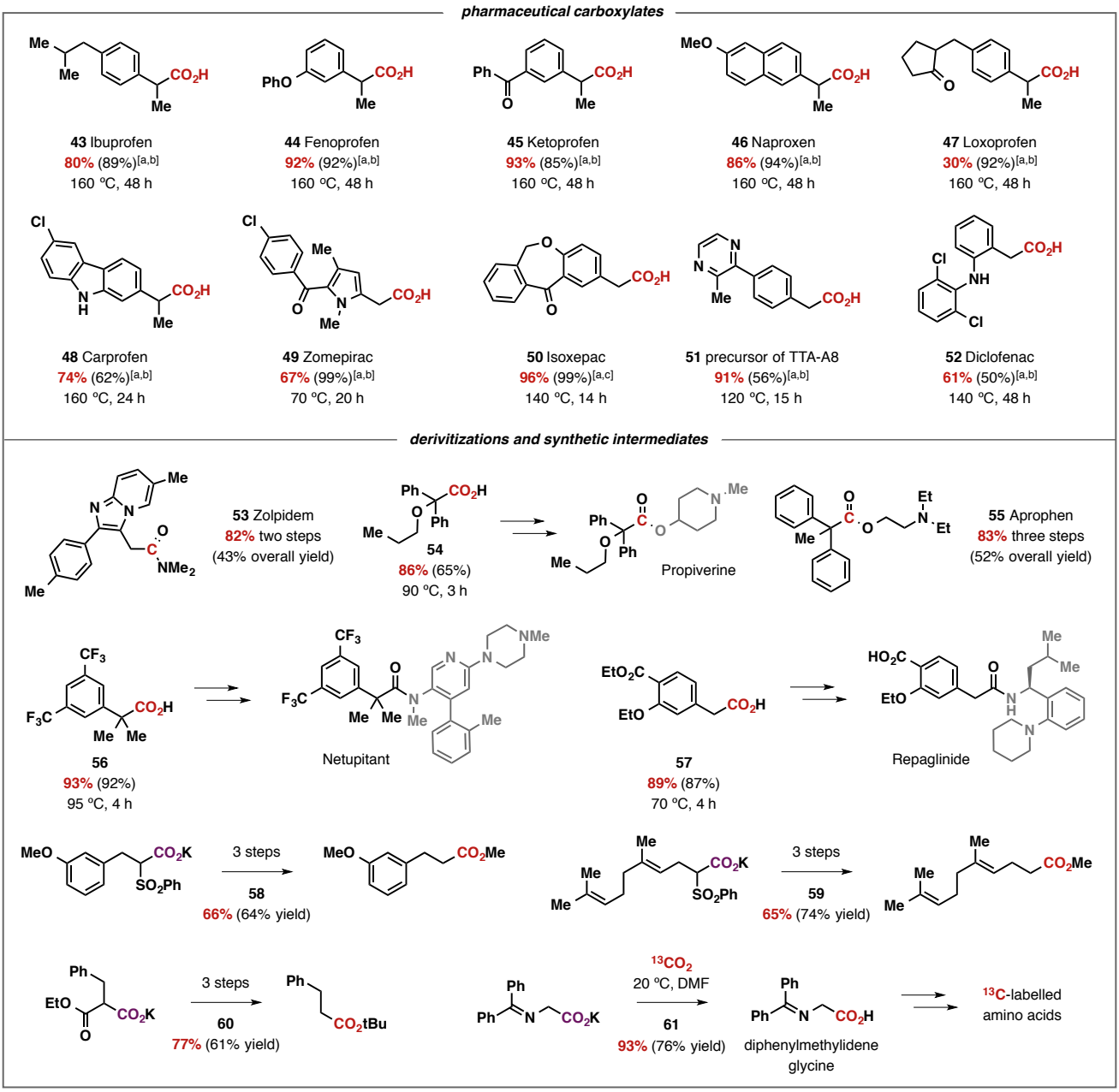


Fig 4. Application of carboxylate exchange, see Fig 3 for experimental details [a] yield determined by ^{1}H NMR spectroscopy; [b] DMSO instead of DMF; [c] 1.0 equiv 18-C-6 added.

A mechanism for the reversible CO_2 exchange supported by control experiments and structure-reactivity studies involves the direct ionization of the potassium carboxylate to generate a carbanion. The reaction rates and required temperatures for $^{12}CO_2/^{13}CO_2$ interconversion correlate with the substrate's ability to stabilize negative charge and not with oxidation potential (compare **1**, **14**, **16**, and **17**). The addition of radical inhibitors (TEMPO, BHT) has no impact on the decarboxylative reactivity of **1** and cyclization of the pendant olefin in **34** is not detected.

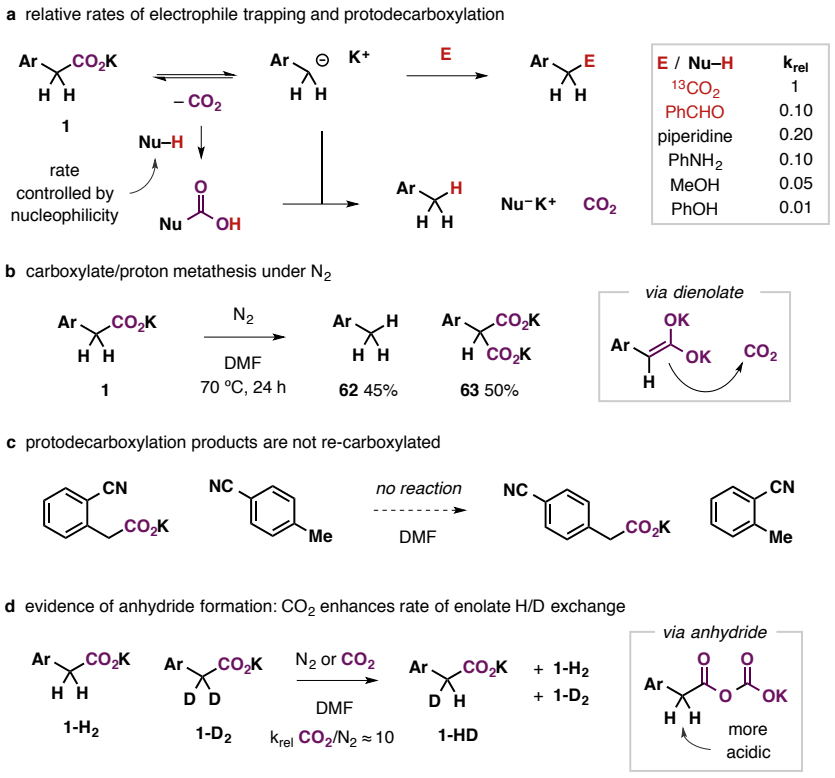


Fig 5. Carbanion trapping studies and mechanistic control experiments. Ar = (4-CN)C_6H_4.

Exchange of CO_2 via a carbanion without competing quenching by other electrophiles (ketones, aldehydes, weak Brønsted acids), stems in part from the relatively high solubility of CO_2 in DMF and the slow kinetics of CO_2 dissolution into the reactor headspace. For example, a 0.25 M solution of CO_2 in DMF retains a concentration of 0.2 M under a headspace of N_2 over one day. For substrate **1** the rate of CO_2 exchange at 70 ºC is ~10-fold faster than for reaction with benzaldehyde. Counterintuitively, the rate of protodecarboxylation by weak Brønsted acids is inversely related to acidity (Fig 5a; piperidine, aniline, methanol, phenol see the SI Fig S5 for details). This observation could be attributed to the relative ability of these species to act as nucleophiles to trap the liberated CO_2, rather than directly protonate a carbanion. At 20 ºC <10% trapping with these additives is observed after 8 hours. At 70 ºC under N_2, **1** undergoes net carboxylate/proton metathesis to generate a half equivalent of the protodecarboxylated product **62** and a half equivalent of the CO_2-trapped malonate **63** (Fig 5b). Product **62** likely arises from deprotonation of a second equivalent of aryl acetate to generate a dienolate nucleophile. The dienolate can be carboxylated by CO_2 released by the initial decarboxylation event. This observation demonstrates the striking efficiency of CO_2 capture by carbon nucleophiles under suitable conditions. Alkyl arene generated by protodecarboxylation does not convert back to carboxylate under the conditions where carboxylate exchange is observed (Fig 5c). Carbonic anhydride intermediates are likely generated under

the reaction conditions on the basis of the observed increase in α-carboxyl H/D exchange rates with **1-H_2 and 1-D_2** under CO_2 (Fig 5d, see SI Fig S7 for details). The generation of a dienolate from the more acidic potassium carbonic anhydride may explain these reactivity differences. Direct detection of anhydride intermediates was not achieved. The ability of non-enolizable carboxylates, such as **23** and **24**, to undergo reversible decarboxylation indicate that a dienolate intermediate is not essential for carboxylate exchange.

The observation that chemically stable carboxylates undergo rapid and reversible decarboxylation/carboxylation processes enable a simple protocol to prepare isotopically labelled small molecules with enriched CO_2. This phenomenon should be taken into consideration when designing and executing decarboxylative functionalization processes.

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