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Direct reversible decarboxylation from stable organic acids in dimethylformamide solution

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Many classical and emerging methodologies in organic chemistry rely on CO_2 extrusion to generate reactive intermediates for bond-forming events. Synthetic reactions that involve the microscopic reverse, the carboxylation of reactive intermediates, have conventionally been undertaken using very different conditions. We report that chemically stable C(sp^3) carboxylates, such as arylacetic acids and malonate half-esters, undergo uncatalyzed reversible decarboxylation in dimethylformamide solution. Decarboxylation/carboxylation occurs with substrates resistant to protodecarboxylation by Brønsted acids under otherwise identical conditions. Isotopically labeled carboxylic acids 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. An understanding of carboxylate reactivity in solution enables conditions for the trapping of aldehydes, ketones, and α,β-unsaturated esters.

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*, *2*). Decarboxylase enzymes accelerate these reactions by stabilizing developing intermediates (typically carbanions) and promoting CO_2 diffusion from the active site, thereby enabling otherwise unfeasible decarboxylations to occur under physiological conditions (Fig. 1A) (*3*, *4*). Acid substrates lacking strong anion-stabilizing groups adjacent to the reactive carbon center have been construed to be inert toward spontaneous decarboxylation without resorting to thermolysis conditions (Fig. 1B) (*5*). As a result, synthetic reactions driven by decarboxylation are often carried out using high reaction temperatures (*6*), added oxidizing agents (*7*, *8*), or prior stoichiometric chemical modification of the carboxylate unit (*9*–*12*).

Carboxylation reactions, the microscopic reverse of decarboxylations, are equally valuable processes in biology and synthetic chemistry. Despite the possibility of a shared reaction pathway, the biochemical machinery that promotes carboxylation in CO_2 fixation pathways operates with a distinct set of substrates and enzymes from those that promote decarboxylation in all but a few cases (*13*–*17*). Similarly, synthetic techniques that generate carboxylic acid derivatives from CO_2 have tended to apply strongly nucleophilic organometallics and/or in-situ stoichiometric (electro)chemical substrate reduction (*18*, *19*).

The potential for the reversibility of decarboxylation/carboxylation mechanisms is largely ignored in reports of synthetic methodologies that rely on these elementary steps. Reports of direct non-enzymatic reversible CO_2-exchange of carboxylic acids are restricted to specialized substrate/mediator pairs (*20*, *21*). Exchange of carboxylate groups in simple aliphatic acids with CO_2 has been documented, but requires heating of neat substrates at 280–400°C (*22*, *23*). Nonetheless, in the course of our studies on catalytic decarboxylative cross-coupling reactions (*24*, *25*), we questioned whether the apparent stability of organic carboxylates could arise from reversible decarboxylation/carboxylation events in solution. Supporting this hypothesis, we observed that certain simple organic acids that are stable toward protodecarboxylation in solution undergo spontaneous incorporation of $^{13}CO_2$ when this heavier isotope is supplied at atmospheric pressure (Fig. 1C).

The potassium salt of arylacetic acid **1** exemplifies the reversible decarboxylation/carboxylation behavior of otherwise chemically stable carboxylic acids. A 0.1 M solution of **1** in dimethylformamide (DMF) at 20°C underwent CO_2 exchange when placed under an atmosphere of $^{13}CO_2$. In a reaction where approximately six equivalents of $^{13}CO_2$ were supplied (13 mL of CO_2 at ~1 atm, dissolved [CO_2] = 0.20 M), equilibrium between ^{12}C and ^{13}C was achieved in 15 hours (Fig. 1C, red trace). Quantitative recovery of carboxylate **1** with 83% ^{13}C-enrichment was possible by acid/base extractive workup. Under similar conditions at 20°C with five equivalents of a weak Brønsted acid (MeOH) no protodecarboxylation of **1** was observed (Fig. 1C, black trace). These results demonstrate that capture of the putative nucleophilic intermediate generated from **1** with dissolved CO_2 is significantly more favorable than protonation. The process tolerates up to 0.01 M H_2O and does not require rigorous exclusion of air (see fig. S2). During the review of this work, isotopic exchange of carboxylate

groups in cesium arylacetic acid salts with ^{14}C-, ^{13}C-, and ^{11}C-labeled CO_2 in DMSO at 80–190°C was reported (*26*).

The counter-cation of the carboxylate salt impacts carboxylate exchange reactivity (Fig. 1D). The carboxylic acid of **1** manifested no evident $^{13}CO_2$ exchange or protodecarboxylation in DMF at 70°C. Li^+ and Na^+ salts of **1** reacted more slowly, while the Cs^+ salt reacted more quickly. Divalent metal salts of **1** (Zn^{2+} or Cu^{2+}) were inert and the addition of $M^{2+}Cl_2$ salts completely inhibited the reaction ($MgCl_2$, $CaCl_2$, $MnCl_2$, see fig. S3). The use of polar aprotic solvents (DMF, DMA, DMSO; dielectric constant $\varepsilon > 30$) is essential for the transformation: reactions conducted in THF, DCE, or water resulted in recovery of unlabeled **1** at 20°C. The addition of 18-crown-6 (18-C-6) led to an approximate two-fold rate enhancement of carboxylate exchange (see fig. S4) (*27*). The free acid underwent carboxylate exchange when 1.5 equivalents of K_2CO_3 and 18-C-6 were added (>90% yield and ^{13}C incorporation in 19 hours). Collectively, these observations suggest that the generation of a solvent-separated ion pair leads to enhanced decarboxylative reactivity.

Reversible decarboxylation occurred for an array of carboxylate containing molecules that contain adjacent aryl, carbonyl, cyano, or sulfonyl groups, including valuable synthetic precursors, drug molecules, and amino acid derivatives (Fig. 2). The incorporation of $^{13}CO_2$ and product recovery remained 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 ~50 equivalents is provided (see fig. S5). For successful cases, this carboxylate exchange process compares favorably in terms of operational simplicity to current state-of-the-art methods to prepare C(sp^3)–$^{13/14}CO_2$ labeled carboxylic acid-derivatives sought after in (pre)clinical absorption, distribution, metabolism, and excretion (ADME) studies (*28*). Reported approaches require either chemical activation-decarboxylation-metalation-carboxylation sequences mediated by transition metals (*29–31*), indirect nucleophilic substitution reactions with labeled cyanide followed by hydrolysis (*32*), or introduction of labeled carbon monoxide in place of CO_2 (*33*, *34*). The direct exchange of C(sp^2)-carboxylate groups catalyzed by transition metals has been demonstrated; however, reactivity is restricted to nitro- or sulfonyl-containing arenes or 2-heteroatom substituted electron-rich heterocycles at high temperature (≥150°C) (*35*).

(Hetero)arylacetic acid salts with anion-stabilizing groups underwent exchange at moderate temperatures (Fig. 2, **1**–**4**, **9**, **10**, **11**–**15** at 20 to 80°C), whereas arylacetates with strongly electron-donating OMe or NMe_2 groups required higher temperatures (**17**–**20** at 100 to 130°C) and benefitted from the addition of 18-C-6. The simplicity of the process enabled 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**, pyrimidine **28,** isoxazole **30**, thiophene **31**). Alkyl and aryl substitution adjacent to the carboxylate was tolerated, including examples of trisubstituted, non-enolizable arylacetic acid salts (**23**, **24**). Other classes of potassium carboxylates that underwent reversible decarboxylation include malonate half-esters (**32**-**35**), keto acids (**36**), β-carboxysulfonyls (**37**, **38**), cyanoacetates (**39**), and carboxylactams (**40**). Alkene and terminal alkyne functional groups did not interfere with the process (**34**, **35**). Potassium malonates underwent CO_2 exchange at higher temperature (135°C) to give a mixture of mono- and doubly-labeled product along with ^{13}C-enriched monoacid (**41**, **42**).

Carboxylate exchange could also be used to directly prepare isotopically labeled drug molecules, including arylacetic acid salts and propionate NSAIDs of varying complexity (**43**-**52**, Fig. 2). Pharmaceuticals featuring amide or ester groups were obtained via derivatization of the acid group (Zolpidem **53**, Aprofene **55**) or could be prepared according to established literature protocols (Propiverine **54**, Netupitant **56**, Repaglinide **57**). Consistent with the generation of a carbanion, racemization of enantiopure Naproxen (**46**) was observed (fig. S6). Reversible decarboxylation may explain reports of aryl propionate racemization required for kinetic resolution manufacturing processes (*36*, *37*). Simple alkyl carboxylates did not undergo CO_2 exchange; however isotopically labeled products of this class can be readily obtained by carboxylate exchange/desulfonylation reactions of β-sulfonyl acids or exchange/decarboxylation sequences of malonic acids in three steps (**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 labeled amino acids (*38*).

The reversible CO_2 exchange process likely involves the formation of a carbon nucleophile either from direct decarboxylation, or potentially in the case of enolizable substrates, through an enolate intermediate. The reaction rates and required temperatures for $^{12}CO_2/^{13}CO_2$ interconversion correlate with the substrate's capacity to stabilize negative charge and not with oxidation potential (compare **1**, **14**, **16**, and **17**). The addition of radical inhibitors (TEMPO, BHT) had no impact on the decarboxylative reactivity of **1** nor was cyclization of the pendant olefin in **34** detected.

Exchange of CO_2 via carbanion equivalents without competing quenching by other electrophiles (ketones, aldehydes, weak Brønsted acids) likely stems in part from the relatively high solubility of CO_2 in DMF and the slow kinetics of CO_2 evaporation into the reaction vessel headspace. For example, a 0.25 M solution of $^{13}CO_2$ in DMF retains a concentration of 0.2 M under a headspace of N_2 over one day (measured by ^{13}C NMR). For substrate **1** the rate of CO_2 exchange at 70°C was

~10-fold faster than for reaction with benzaldehyde. Perhaps counterintuitively, the rate of protodecarboxylation by weak Brønsted acids is inversely related to acidity (Fig. 3A, in order of decreasing rate of protonolysis: piperidine, aniline, methanol, phenol; see fig. S7 for details). This observation could be attributed to the relative capacity of these species to act as nucleophiles to sequester the liberated CO_2. Trapping of CO_2 prevents back reaction of the carbanion to the carboxylate leading to an increase in the observed rate of protodecarboxylation.

At 70°C under N_2, **1** underwent slow 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. 3B). Product **62** likely arises from deprotonation of a second equivalent of aryl acetate to generate a dienolate nucleophile. The dienolate intermediate can react with the 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 arenes generated by protodecarboxylation does not convert back to the carboxylate under the conditions where carboxylate exchange is observed (Fig. 3C). 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-H₂** and **1-D₂** under CO_2 (Fig. 3D, see fig. S9 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 capacity of non-enolizable carboxylates, such as **23** and **24**, to undergo reversible decarboxylation indicates that dienolate or enol intermediates are not essential for carboxylate exchange.

Finally, with an understanding of the factors that contribute to transient substrate decarboxylation, conditions were identified that allowed for the direct decarboxylative trapping of alternative classes of electrophiles (Fig. 3E). Carbon–carbon bond forming reactions by the trapping of aldehydes (**64**–**69**), a trifluoromethyl ketone (**70**), and an α,β-unsaturated ester (**71**) occurred in reasonable yields under conditions similar to those for reversible decarboxylation. The rates of product formation in aldehyde trapping experiments correlate with substrate electrophilicity. In some cases, it was beneficial (but not essential) to add 18-C-6 to improve decarboxylative reactivity or aniline to sequester liberated CO_2 (see SM for complete details). H/D-exchange followed by deuterodecarboxylation provides a simple approach to prepare CD_3 labeled toluenes and heterocycles from D_2O (**72**–**75**).

Efficient reversible decarboxylation/carboxylation masks the inherent reactivity of otherwise stable carboxylates. An appreciation of this phenomenon enables simple, direct protocols for isotopic exchange of carboxylic acids with $^{13}CO_2$ and methods for decarboxylative carbon–carbon bond forming reactions. The potential for reversible decarboxylation should be considered more generally when designing and executing decarboxylative functionalization processes.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S9
HRMS and NMR Spectra
References (*39*–*49*)

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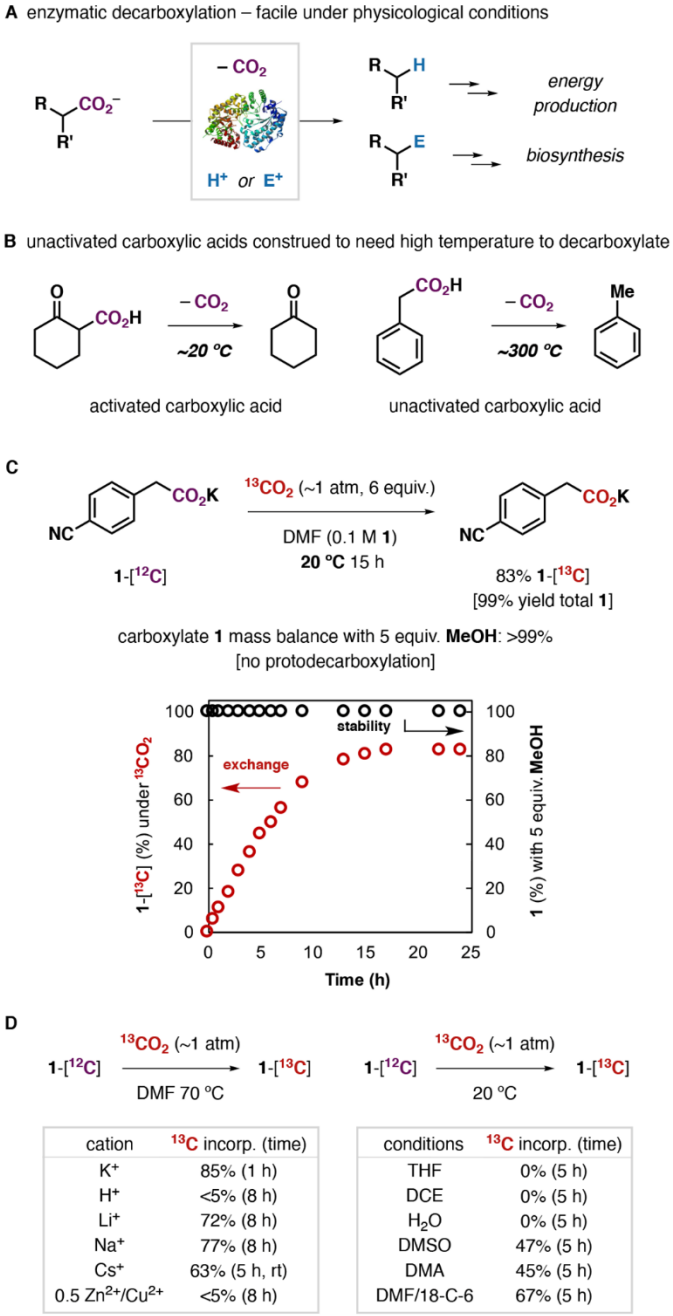

cation	^{13}C incorp. (time)
K^+	85% (1 h)
H^+	<5% (8 h)
Li^+	72% (8 h)
Na^+	77% (8 h)
Cs^+	63% (5 h, rt)
0.5 Zn^{2+}/Cu^{2+}	<5% (8 h)

conditions	^{13}C incorp. (time)
THF	0% (5 h)
DCE	0% (5 h)
H_2O	0% (5 h)
DMSO	47% (5 h)
DMA	45% (5 h)
DMF/18-C-6	67% (5 h)

Fig. 1. Overview of decarboxylative processes and carboxylate exchange. (**A**) Decarboxylation catalyzed by enzymes under physiological conditions (PDB ID: 2INF). (**B**) Comparison of conditions used for thermal decarboxylation of different substrates. (**C**) Comparison of CO_2 exchange (red) and protonation with MeOH (black) for 4-cyanophenylacetate (**1**). (**D**) Impact of salt and reaction conditions. E^+, electrophile; DMF, dimethylformamide; THF, tetrahydrofuran; DCE, 1,2-dichloroethane; DMSO, dimethylsulfoxide; DMA, dimethylacetamide; 18-C-6, 18-crown-6.

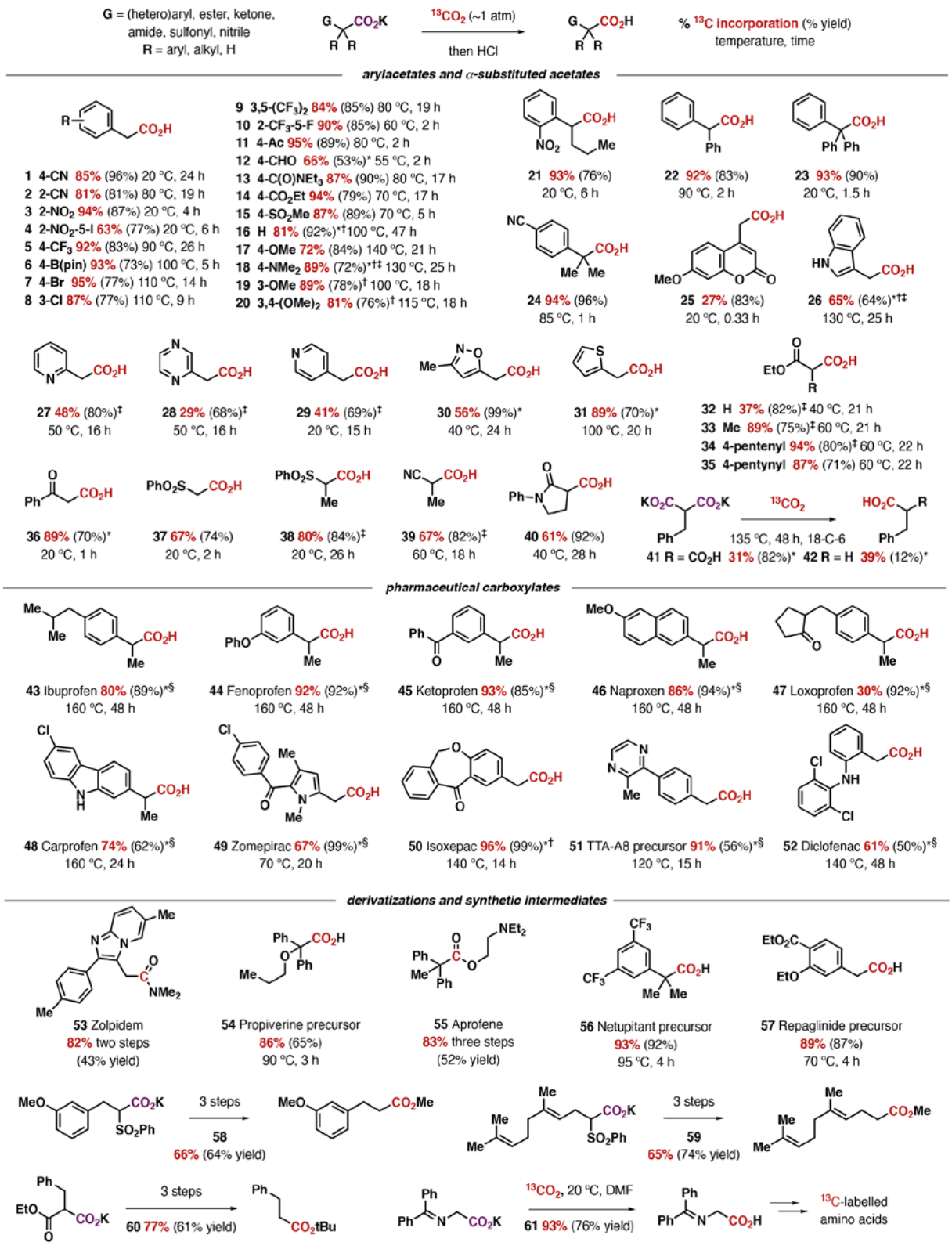

Fig. 2. Carboxylate exchange scope and application. Unless noted yields are of isolated material. *Calibrated ^{1}H NMR spectroscopy yield. †1 Equivalent 18-C-6 added. ‡%^{13}C Incorporation and yield determined by analysis of the corresponding methyl or benzyl ester. § DMSO used instead of DMF. See the supplementary materials for complete details. NMR, nuclear magnetic resonance.

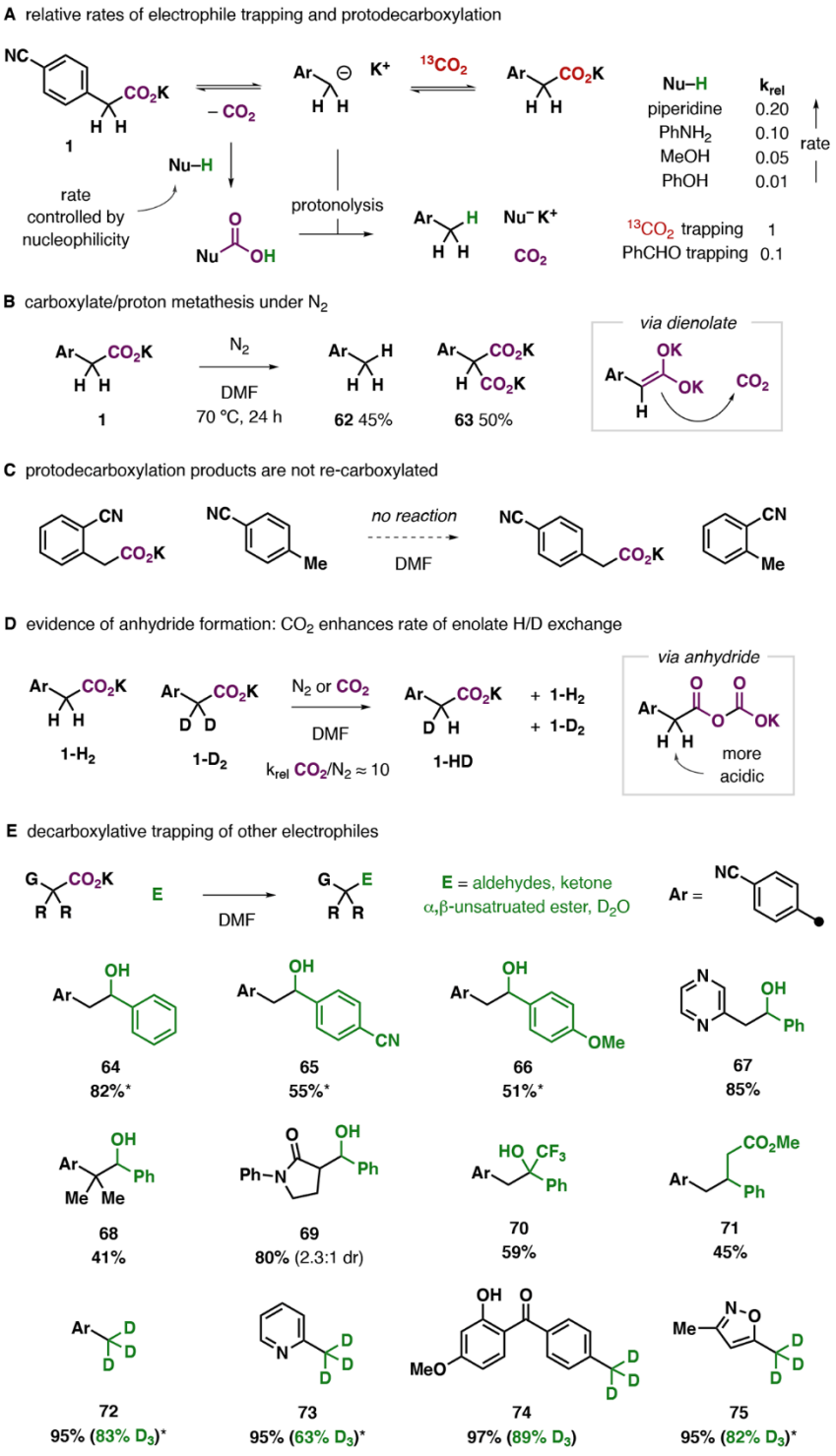

Fig. 3. Mechanistic control experiments and electrophile trapping. (A) Relative rates for arylacetic acid salt protodecarboxylation by Brønsted acids and decarboxylative trapping by benzaldehyde. (B) Net carboxylate/proton metathesis of 1 in the absence of additional CO_2. (C) CO_2 transfer between arylacetic acid salt and alkylarene does not occur. (D) The presence of CO_2 accelerates the rate of methylene C–H/D exchange in 1. (E) Scope examples for the decarboxylative trapping of alternative classes of electrophiles. See the supplementary materials for complete details and full reaction conditions. *Yield determined by ^{1}H NMR spectroscopy. Ar, (4-CN)C_6H_4.

Direct reversible decarboxylation from stable organic acids in dimethylformamide solution

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