Aldehyde-Catalyzed Carboxylate Exchange in α-Amino Acids with Isotopically Labeled CO_2

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Summary Paragraph α-Amino acids are among the essential chemical building blocks of life.[1] These structures are embedded in many small molecule pharmaceuticals and are the primary components of peptide-based therapeutics and biologics.[2] Isotopically labeled α-amino acids and their derivatives have widespread use in structural and mechanistic biochemistry,[3] quantitative proteomics,[4] absorption distribution metabolism and excretion (ADME) profiling,[5-6] and as imaging agents in positron emission tomography (PET) techniques.[7-9] The preparation of carbon-labeled α-amino acids remains difficult and time consuming, with established methods involving label incorporation at an early stage of synthesis. This explains the high cost and scarcity of C-labeled products and presents a major challenge in ^{11}C applications (^{11}C $t_{1/2}$ = 20 min). Here we report that simple aldehydes catalyze the isotopic carboxylate exchange of native α-amino acids with $*CO_2$ (* = 14, 13, 11). Proteinogenic α-amino acids and many non-natural variants containing diverse functional groups undergo labeling. The reaction likely proceeds via the trapping of $*CO_2$ by imine-carboxylate intermediates to generate aminomalonates that are prone to monodecarboxylation.[10] Tempering catalyst electrophilicity was key to preventing irreversible aldehyde consumption. The pre-generation of the imine carboxylate intermediate allows for the rapid and late-stage ^{11}C-radiolabeling of α-amino acids in the presence of $^{11}CO_2$.

The preparation of molecular targets where a native isotope is substituted with a heavier or radioactive isotope is essential to drug development and medical imaging.[11] It is often preferable to use carbon-based isotope labels rather than hydrogen isotopomers (^2H or ^3H) because carbon labels are not prone to washing out, and they do not cause metabolic shifting.[12] Despite over 70 years of study, the synthesis of α-amino acids incorporating carbon isotopes remains a challenge and generally involves the early introduction of the *C label into a precursor molecule followed by several additional synthetic steps (Fig 1a). Representative methods include substitution or addition reactions of electrophiles with $*CN^-$ sources,[13] the early-stage addition of simple alkyl or aryl organometallics to $*CO_2$,[14] alkylations using labeled electrophiles like $*CH_3I$,[15] and sequences that start with *C-acetate.[16-17] Auxiliary-controlled asymmetric syntheses of *C-amino acids exist, however they occur with low to moderate radiochemical yields and require time-consuming, multi-step approaches.[18-20] The biosynthesis of labeled α-amino acids by fermentation in the presence of *C-glucose or *C-acetate is possible but requires specialized equipment, carefully optimized pilot studies, and tedious isolation and purification of labeled products.[5, 21-22] Furthermore, the short half-life of ^{11}C (20 minutes) makes the multi-step preparation of amino acid targets needed for PET problematic. Current approaches are restricted to cyanation/hydrolysis reactions using $^{11}CN^-$, and for certain products like ^{11}C-methionine, methylation with $^{11}CH_3I$.[23-24] Additionally, ^{11}C glutamine or glutamate can be prepared by conjugate additions of ^{11}C-acrylates.[25] In this regard, a general approach to prepare C-labeled α-amino acids that uses a late-stage

label incorporation strategy conceptually analogous to hydrogen isotope exchange[26-28] would help accelerate drug development and would allow the expansion of amino acid radiotracers in PET imaging.

Carbon dioxide is the primary source of all isotopically labeled carbon reagents.[14] The use of $*CO_2$ in late-stage labeling applications is difficult because of the lack of methods for its effective capture and incorporation without resorting to the use of highly nucleophilic reaction intermediates and large excesses of $*CO_2$.[29-30] In concert with Audisio and co-workers, we established that certain electronically stabilized carboxylic acids, like aryl acetates and malonic half-esters, undergo reversible decarboxylation in polar aprotic solvents.[31-32] α-Amino acids lack the required anion stabilizing ability to undergo decarboxylation under normal laboratory conditions and their spontaneous decarboxylation is exceptionally slow.[33] Net carboxylate exchange reactions[34] of carboxylic acids using *N*-hydroxyphthalimide derivatives in the presence of Ni-promotors can be used to generate [^{13}C]-C5-labeled glutamic acid, however C1-carboxylate and amino group protection is required and the process is not general for other amino acids.[35]

Nature catalyzes CO_2 extrusion from α-amino acids with decarboxylases, which convert amino acids to Schiff bases (imines) via condensation with pyridoxal phosphate (Fig 1b). After condensation between an α-amino acid and the aldehyde unit of pyridoxal phosphate, decarboxylation leads to an aza-allyl quinonoid intermediate which is subsequently protonated and hydrolyzed to give an amine product.[36-37] In contrast, the small molecule catalysis of α-amino acid decarboxylation is known but occurs only at high temperatures (150 ºC).[38] Given the propensity of α-amino acid derived imino carboxylic acids to undergo α-H/D exchange in the presence of D_2O[39] and the potential for decarboxylation to be reversible in a range of contexts,[40-42] we viewed this reaction manifold as an opportunity to develop methods for the direct C1-labeling of α-amino acids using $*CO_2$. This process can be realized by using simple aryl aldehyde catalysts (Fig 1c). The reaction is general for most proteinogenic substrates and can be modified to accommodate (radio)labeling with ^{14}C, ^{13}C, or ^{11}C.

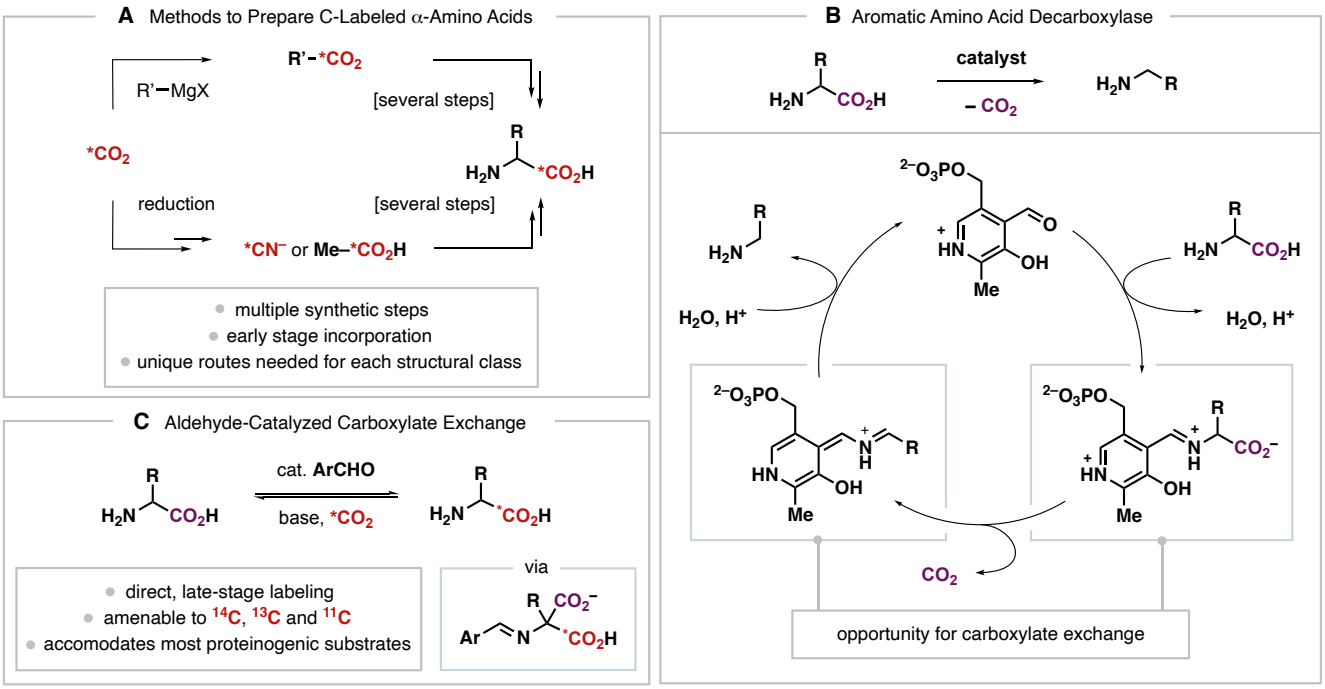

Figure 1 A Overview of methods to prepare C-labeled α-amino acids. **B** Simplified mechanism for pyridoxal phosphate catalyzed α-amino acid decarboxylation with aromatic L-amino acid decarboxylase. **C** Aldehyde-catalyzed C1-carboxylate exchange of α-amino acids.

Figure 2a provides an overview of experimental parameters important to observing productive α-amino acid carboxylate exchange with externally supplied $^{13}CO_2$. In the presence of 20 mol% 4-anisaldehyde and 40 mol% Cs_2CO_3 in DMSO at 70 ºC, C1-exchange in phenylalanine to generate 1-[^{13}C]-phenylalanine is observed with 75% ^{13}C incorporation and 84% yield when ~8 equivalents of $^{13}CO_2$ are supplied. Side products, including aldehyde-trapped species and protodecarboxylation, are detected but in <5% under the standard conditions (see the SI for details). Other polar aprotic solvents (DMF or DMA) can be used but the extent of incorporation is decreased. The reaction does not occur in MeOH or H_2O and unlabeled substrate is quantitatively recovered. Trace carboxylate exchange is detected at room temperature with near-quantitative recovery of substrate, while at 130 ºC high incorporation and yields are observed after 30 minutes using 75% catalyst (60% incorporation, 80% yield). When approximately one equivalent of $^{13}CO_2$ is supplied, exchange equilibrium is nearly achieved with a moderate reduction in yield (40% incorporation, 65% yield). Catalyst loadings as low as 5 mol% can be used in combination with higher reaction temperatures (90 ºC). The addition of one equivalent of water under the standard conditions slows reactivity, presumably by shifting the equilibrium away from imine condensation intermediates, however, it does not increase the amount of α-amino acid protodecarboxylation. Without catalyst, no isotope exchange is observed up to 160 ºC (see the SI for additional details and control experiments).

4-Anisaldehyde is the optimal catalyst for carboxylate exchange because of its balanced electrophilicity. The use of more electrophilic aryl aldehyde catalysts[43] resulted in lower yields due to competitive trapping, while less electrophilic catalysts mediate slow rates of isotope exchange (Fig 2a). Pyridoxal phosphate, alkyl aldehydes, and various ketones catalyze carboxylate exchange but only with low levels of incorporation (8–14%). The impact of catalyst electrophilicity on reaction rates and α-amino acid recovery was examined in more detail (Fig 2b, note that reaction sampling decreases final ^{13}C incorporation compared to standard conditions in a sealed vial). 4-Anisaldehyde provided relatively slow rates of exchange but exhibited a long lifetime, ultimately resulting in a larger amount of labeled product. The more electrophilic catalysts 4-CF_3- or 4-CN-benzaldehyde gave fast initial rates of carboxylate exchange but are consumed quickly in the reaction (<20% catalyst remains after 1 hour, compared to 60% for 4-anisaldehyde). This catalyst decomposition results in worse terminal ^{13}C incorporation and reduced phenylalanine mass balance (~30% incorporation and 80% yield).

The process can be readily modified to introduce ^{14}C-labels for applications in radiolabeling studies (Fig 2c). $^{14}CO_2$ is generated in-situ from $Ba^{14}CO_3$ and can be used to label Phe with 53% ^{14}C incorporation, which was obtained in 51% yield after HPLC purification (14% overall radiochemical yield from $Ba^{14}CO_3$). The reaction cleanly generates ^{14}C-Phe with no significant radiolabeled side-products (Fig 2c, inset).

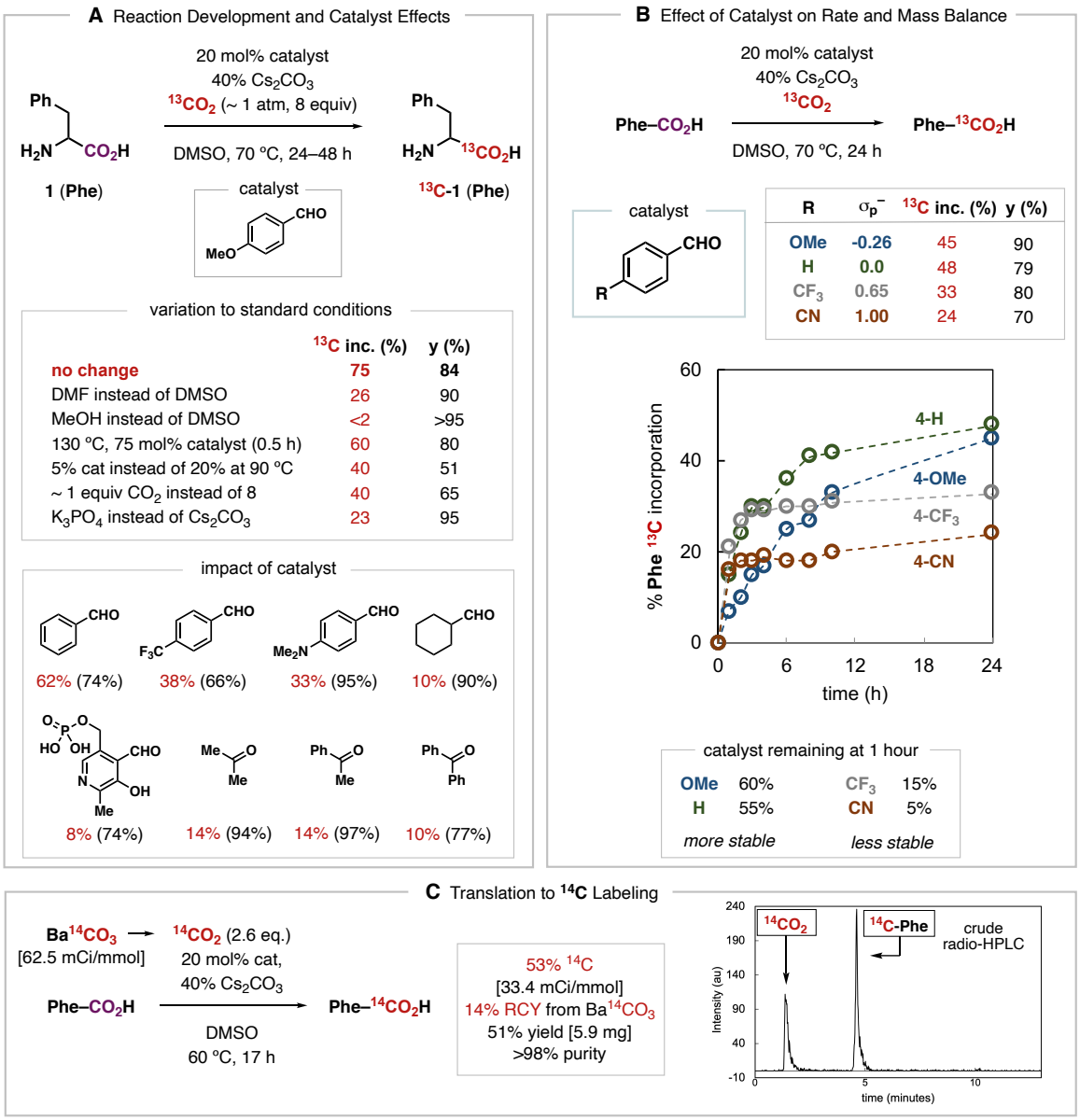

Figure 2 A Overview of impact of reaction parameters and catalyst structure on the carboxylate exchange of α-amino acids. **B** Kinetic analysis and lifetime of aldehyde catalysts on the carboxylate exchange of phenylalanine. **C** Translation of α-amino acid carboxylate exchange to ^{14}C radiolabeling.

The aldehyde catalyzed carboxylate exchange is amenable to labeling a diverse range of unprotected α-amino acids, including most proteinogenic substrates and non-natural variants containing potentially reactive functional groups (Fig 3). Aliphatic and aromatic α-amino acids can be labeled in 31–75% ^{13}C-incorporation with >50% yield (phenylalanine, alanine, leucine, glycine, tyrosine, tryptophan, methionine; **1**–**3**, **6**–**9**) (Fig 3a). In most cases, products were isolated as the corresponding *N-tert*-butyloxycarbonyl (N-Boc) products for convenience. β-Branched aliphatic substrates like isoleucine (**4** 23%), valine (**5** 18%), and proline (**10** 9%) were labeled to a lower extent under modified conditions. Acidic or basic side-chain groups were generally well tolerated to give 28–81% incorporation

of label (arginine, lysine, glutamic acid, asparagine, glutamine; **12**–**14**, **16**–**17**). Aspartic acid (**15**) and serine (**11**) underwent successful exchange but to a lower degree (18% and 27% respectively). Nonetheless, in all cases except histidine, cysteine, and threonine, levels of isotope incorporation useful for ADME studies were obtained.[35] In cases where very high label incorporation is needed, the product can be re-subjected to the exchange conditions, for example in the case of Phe, where 96% ^{13}C labeling and 54% yield is achieved after a second exchange cycle.

Racemization of the α-amino acid occurs under the standard reaction conditions, as expected for reactions proceeding by imino carboxylate condensation intermediates.[44-45] Enantioenriched labeled products (≥94% ee) can be readily obtained by established approaches. Chymotrypsin catalyzed ester hydrolysis allowed labeled L-phenylalanine to be obtained in 99% ee (**1a** 86% ^{13}C incorp., 26% overall yield). Acylase catalyzed hydrolysis of N-acetyl leucine was used to prepare L-leucine in >99% ee (**3a** 38% ^{13}C incorp., 38% overall yield). In cases where it is preferable to achieve >50% product yields, Ni-mediated dynamic kinetic resolution (DKR)[46] can be used, as demonstrated for L-phenylalanine (**1a** 63% ^{13}C incorp., 70% overall yield, 97% ee) and L-methionine (**9a** 58% ^{13}C incorp., 54% overall yield, 94% ee). Chromatographic resolution can also be readily accomplished from the corresponding Fmoc-Phe derivative (L-**1b,** 96% ee).

The exchange process is not impeded by various functional groups, as seen in phenylalanine derivatives containing fluoride, bromide, and iodide groups, (**21**–**23**), or azide (**24**), nitro (**25**), and boronic acid groups (**26**) (Fig 3b). Other aromatic containing α-amino acids, including thyroxine (**27**), 3-(2-naphthyl)alanine (**28**), quinolone-derivative (**29**), and homophenylalanine (**30**) undergo labeling with useful yields and incorporation. Alkyl-substituted α-amino acids N^6-benzoyl lysine (**31**), glutathione (**32**), norvaline (**33**), and norleucine (**34**) are each amenable to carboxylate exchange. Cyclopropyl (**35**) and terminal alkyne groups (**36**), along with selenomethionine (**37**) smoothly undergo isotopic labeling under the standard conditions. Labeled targets containing protic and/or electrophilic groups would be difficult to prepare by de-novo methods without chemical protection. Substrates that do not undergo carboxylate exchange include β-amino acids, *N*-protected α-amino acids, and dipeptides (see the SI for details).

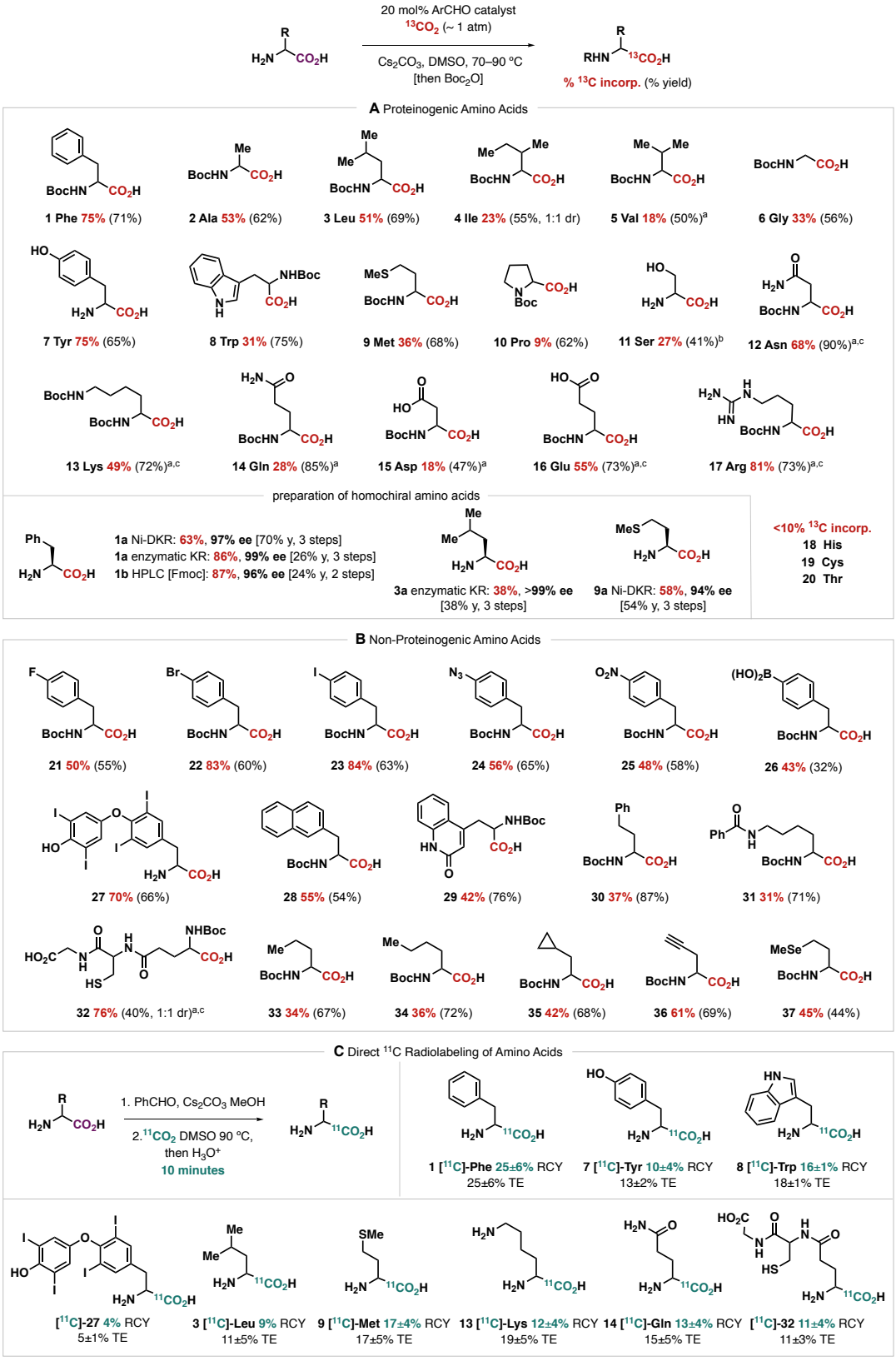

Figure 3 A Aldehyde-catalyzed carboxylate exchange of proteinogenic α-amino acids with $^{13}CO_2$. **B** Scope with non-proteinogenic α-amino acids. **C** α-Amino acid scope of ^{11}C labeling. RCY = TE × radiochemical purity. See the SI for complete details. [a] Yield determined by ^1H NMR spectroscopy. [b] From pre-formed imine. [c] 75 mol% catalyst, 100% Cs_2CO_3, 0.017 M.

Modification of the reaction conditions enables direct radiolabeling of α-amino acids using $^{11}CO_2$. To promote faster reactions, pre-formed imine carboxylates were generated quantitatively by condensation of α-amino acids with aryl aldehydes in basic MeOH[47] and examined as reagents for carboxylate exchange. Benzaldehyde-derived imines outperformed 4-anisaldehyde or 4-cyanobenzaldehyde analogs to give 33% ^{13}C incorporation when using 3 equivalents of $^{13}CO_2$ after 30 minutes, which could be improved to 62% incorporation at 90 ºC (Extended Data Fig 1a). Translation of these conditions allowed for preparation of [^{11}C]phenylalanine in 24% radiochemical yield (RCY). Reactions of the imine carboxylate salt were superior to those using catalytic amounts of aldehyde under $^{11}CO_2$ conditions (Extended Data Fig 1b). The ^{11}C radiolabeling of α-amino acids is general to aromatic, aliphatic, polar sidechain containing products including tyrosine, tryptophan, leucine, methionine, lysine, glutamine, as well as non-proteinogenic substrates thyroxine, and glutathione (Fig 3c). The speed and operational simplicity of the ^{11}C isotope exchange reaction provides opportunities for use in positron emission tomography.

The mechanism for carboxylate exchange likely occurs by the carboxylation of imino-enol or imino dienolate intermediates[48] followed by decarboxylation[10] (Fig 4a, **i-1** to **1**), rather than by trapping from an aza-allyl anion formed by an initial decarboxylation (Fig 4a, **i-3**).[49] When D_2O is added to a reaction conducted under otherwise standard conditions using **1**, products arising from both H/D and $^{12}C/^{13}C$ exchange are observed (Fig 4a).[50] The presence of D_2O slows the rate of carboxylate exchange, however the amount of proto- or deuterodecarboxylation product **38** remains low (<1%). Assuming the exchange processes occur from a common intermediate, these results suggest an aza-allyl anion is not an intermediate formed during the reaction. Electrophilic catalysis is established to promote the fast monodecarboxylation of aminomalonates,[10, 51] however, attempts to determine the rate of decarboxylation of **i-2** under the standard conditions were thwarted by a lack of solubility. Any amine generated from α-amino acid protodecarboxylation is unable to re-enter the exchange pathway via carboxylation (Fig 4b).[49, 52] Acetone catalyzes the carboxylate exchange, leading to 14% exchange in **1**, while non-enolizable α-amino acid 2-aminoisobutyric acid (**39**) was unreactive to carboxylate exchange despite the ability to form a benzylic stabilized aza-allyl anion by decarboxylation of imine **i-4** (Fig 4c). The positional selectivity of carboxylation from pseudo-symmetrical intermediates generated by condensation between 4-bromophenylalanine (**22**) and phenylacetaldehyde also supports the formation of a malonate intermediate **i-6** rather than an aza-allyl intermediate **i-7** that would generate some amount of phenylalanine (Fig 4d). When conducting carboxylate exchange reactions, the corresponding arylglycine regioisomers were not observed at various aldehyde loadings, further suggesting an aza-allyl nucleophile like **i-3** is not generated (see the SI for details). An aminomalonate mechanism for carboxylate exchange helps to explain the relative mildness in conditions compared to non-enzymatic

protodecarboxylation reactions[38] and may aid in the development of related α-amino acid functionalization reactions.

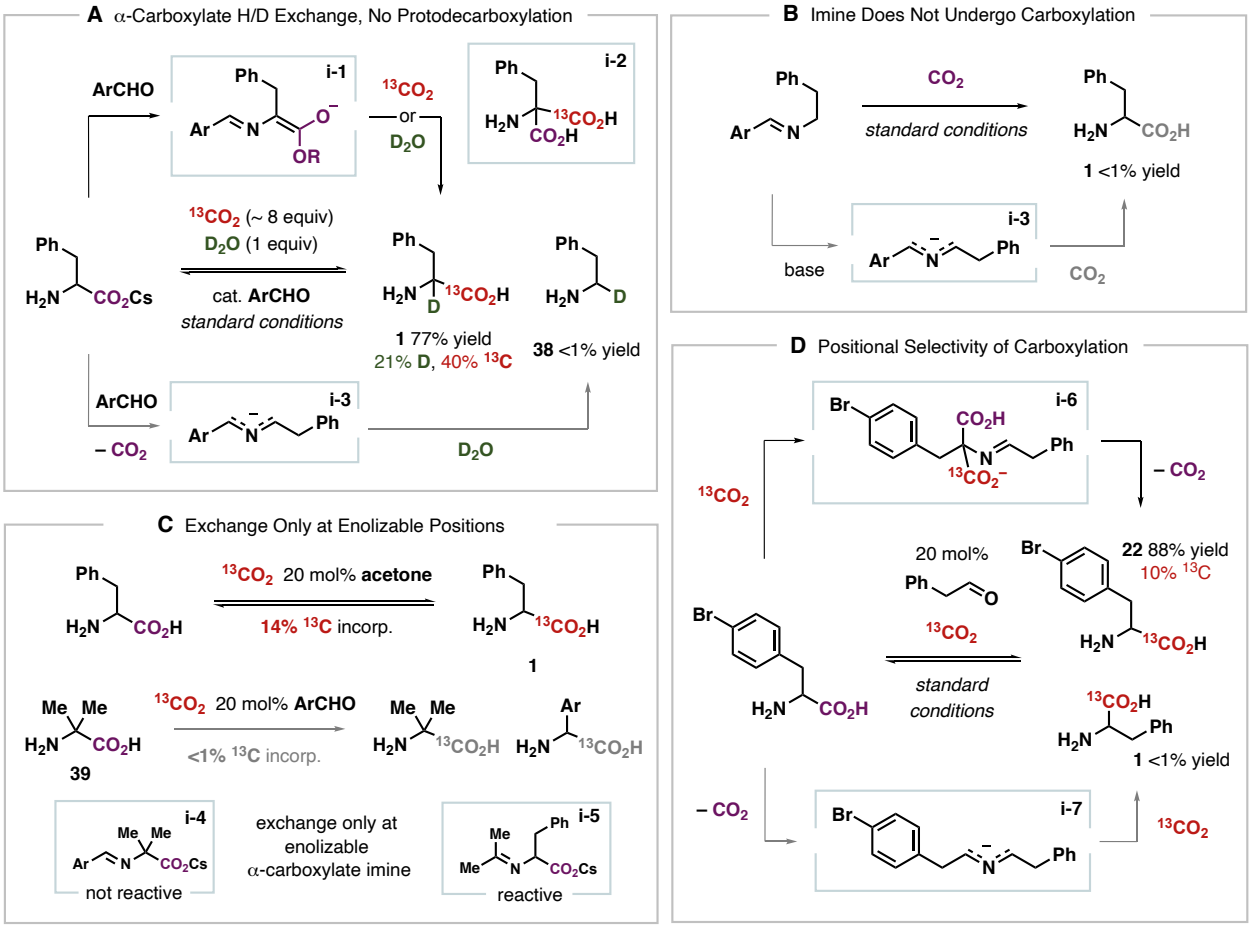

Figure 4 Mechanistic studies probing the nature of isotopic carboxylate exchange. **A** Concurrent H/D exchange under carboxylate exchange conditions. **B** Imine substrates do not carboxylate under the standard conditions. **C** Carboxylate exchange occurs only at the enolizable α-carboxylate. **D** Generation of Phe (**1**) is not observed in potential crossover studies. All reactions conducted in DMSO with Cs_2CO_3, protonation steps omitted for clarity, Ar = 4-OMe-C_6H_4.

In conclusion, the carboxylate exchange of α-amino acids with *CO_2 can be catalyzed by aryl aldehydes to give general access to C1-labeled products in a direct and operationally trivial manner. Productive catalysts must have balanced electrophilicity to enable carboxylate exchange without being irreversibly consumed in the process. Given the widespread use of labeled α-amino acids in discovery science, drug development, and medical imaging, we expect this finding to have immediate application.

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Competing Interests R.J.L. and the University of Alberta have filed a provisional patent on the reported technology, V.D. and A.B. are employees of Sanofi and may hold shares or options of the company.

Author Contributions O.B., M.G.J.D., and C.J.C.C. designed and performed experiments and analyzed data related to studies involving ^{13}C. D.K. conducted selected ^{13}C scope studies. M.M. and B.A.M. designed and performed experiments and analyzed data related to studies involving ^{11}C. A.B. and V.D. designed and performed experiments and analyzed data related to studies involving ^{14}C. R.J.L. and B.H.R. directed the research, R.J.L. conceived the project and prepared the manuscript, all authors contributed to discussion.

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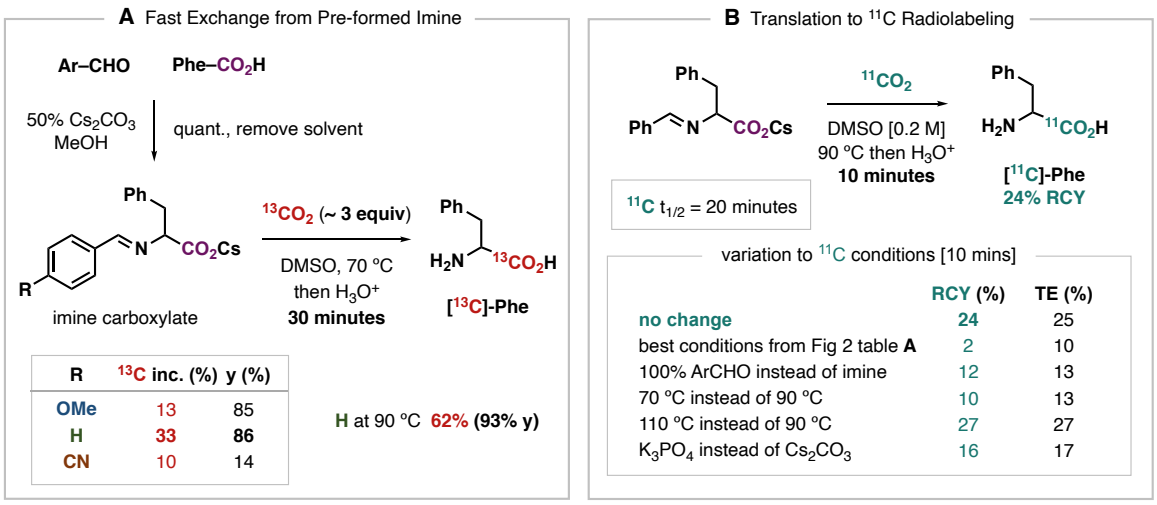

Extended Data Figure 1 A Development of fast conditions for carboxylate exchange. **B** Translation of the reaction to radiolabeling with $^{11}CO_2$.