Optimization of Carbon-11-Carboxylate Exchange of α-Amino Acids

Braeden A. Mair,[1,2] Maxime Munch,[2,3] Abhishek P. Patel,[1,2] Ariel Buchler,[1,2] and Benjamin H. Rotstein[1,2,3]

Corresponding Author: Benjamin H. Rotstein, benjamin.rotstein@uottawa.ca

[1]Department of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada
[2]University of Ottawa Heart Institute, Ottawa, Ontario, Canada
[3]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada

1. Abstract

Radiolabeled amino acids offer a broad spectrum of applications in clinical care and pharmaceutical development. Traditional methods of labelling are limited in their availability, requiring specialized equipment and reagents, and in their scope, addressing only select amino acids. We discovered a simple and efficient approach using aldehyde-catalysed carboxylate exchange to ^{11}C-amino acids. Seeking enrichment of the carbon-11 methodology and the preparation of radiotracers suitable for animal imaging, we explored further optimization and probe development. We detail herein method development, including evaluations of aldehyde catalysts, discovering optimal reaction conditions, and the production of enantiopure radiolabelled amino acids.

Keywords: radiochemistry, positron emission tomography, carbon-11, carbon dioxide, carbon isotope exchange, amino acids

2. Introduction

Positron emission tomography (PET) is a non-invasive nuclear medicine technology for *in vivo* molecular imaging. Carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) is a short-lived PET nuclide commonly used for labelling small molecules and peptides; carbon's presence in all organic molecules presents the opportunity for isotopologue labelling without introducing structural modifications. ^{11}C-Labelled amino acids (AAs) offer potential as PET imaging agents, to be used for disease monitoring, prognostication and therapeutic evaluation, and for biochemical profiling of pharmacodynamics and pharmacokinetics of potential drug candidates.[1] AA-based radiotracers have become especially valuable for the study of cancer biology due to high uptake, and aromatic AAs have found a place in the evaluation and diagnosis of neurological disorders.[2–5]

The leading strategies for labelling AAs use either the Strecker reaction with $[^{11}C]HCN$,[6–10] which many cyclotrons and radiosynthesis units are not equipped to deliver, or methylation with $[^{11}C]CH_3I$, albeit only in appropriate cases (such as with [^{11}C]methionine). Alternative approaches harness ^{11}C-carboxylations using activated lithiated precursors;[11] these can provide several essential amino acids but require tedious organic syntheses to prepare and often post-labelling transformations to achieve the desired product.[12–14] Specific syntheses for labelling AA side chains exist, but are not widely applicable to all amino acid targets.[15] Furthermore with a short physical half-life, ^{11}C necessitates rapid, late-stage label-incorporation often incompatible with traditional literature methodologies.

Appreciating a need for a general and efficient approach to ^{11}C-AAs, we reported an isotopic exchange reaction with labelled CO_2 (Figure 1).[16,17] This process can be realized with the use of simple aldehyde catalysts to form Schiff base intermediates and can access most proteinogenic AAs in molar activities suitable for *in vivo* imaging. This method was developed for the use of carbon-13 and carbon-14, as well as for carbon-11 using [^{11}C]CO_2 produced directly from the cyclotron. As the ^{11}C-labelling reaction occurs under conditions developed from those using longer-lived isotopes, we considered that further modification to our previously reported protocol may elicit greater reactivity. In addition, enantiomeric resolution techniques that proved useful for carbon-13 labelling have yet to be translated to the ^{11}C CIE (carbon isotope exchange) process.

With that consideration, we sought to improve the labelling methodology to be amenable to conditions that suit ^{11}C, its handling, and its short half-life. We also wished to identify an approach to enantiopure ^{11}C-AAs. We herein detail the optimization of ^{11}C carboxylate exchange to access labelled α-amino acids.

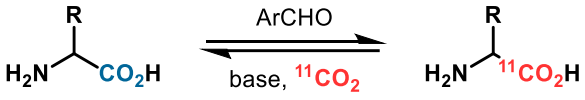


Figure 1. Carbon-11 carbon isotope exchange to prepare ^{11}C-amino acids. Stable amino acids are condensed into Schiff bases before subsequent addition of [^{11}C]CO_2 to achieve isotopic exchange.

3. Results and Discussion

3.1. Imine Preparation

Reactions were first completed with *in situ* formation of the reactive intermediate, a Schiff base capable of undergoing carboxylation with [^{11}C]CO_2, followed by spontaneous decarboxylation to yield the desired labelled amino acid. Initial attempts with phenylalanine provided the product in 12% radiochemical yield (RCY) (Figure 2). The multi-step reaction requires (a) aldehyde condensation with the amino acid to form the reactive imine, (b) ^{11}C-carboxylation forming an aminomalonate intermediate, (c) spontaneous decarboxylation, and (d) conversion of the imine back to an amino acid with acid-promoted hydrolysis. Given time constraints of ^{11}C-syntheses and in the interest of eliminating a step in our radiolabelling, we sought to compare this method with one using pre-formed Schiff bases. Individual precursor batches of phenylalanine benzaldehyde imine were prepared and provided 24% RCY in the subsequent radiolabelling. Attempts to prepare a large batch of precursor from which aliquots were taken for individual CIE reactions proved ineffective due to poor solubility and their instability. Using small scale, individually prepared imines, we observed that the condensed product should be kept for no longer than a week, with degradation observed at that time. We evaluated the stability of the imines to the reaction conditions with stable isotope-containing CO_2. ^{1}H NMR spectroscopy revealed that imines derived from electron-neutral benzaldehyde and electron-deficient 4-fluorobenzaldehyde are stable to labeling conditions, while an electron-rich imine released >10% of the parent 4-methoxybenzaldehyde (Supplemental Figure S1–S3).

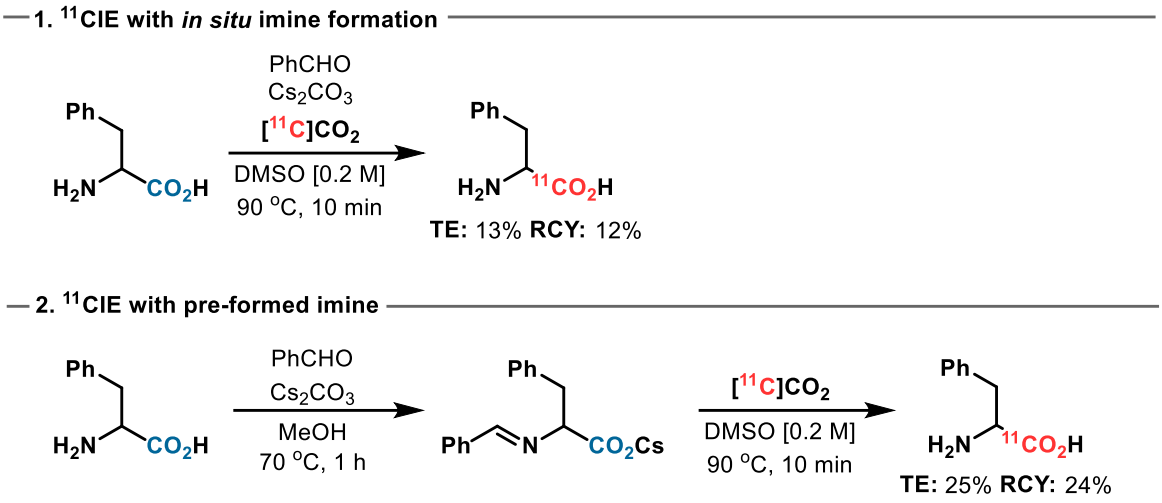


Figure 2. Imines were first prepared *in situ*, providing moderate results for labelling. Pre-formation of the imine intermediate simplified the radiochemical step and improved radiochemical yields.

3.2. ^{11}C-Carbon Isotope Exchange Optimization

Conditions for the CIE reaction were evaluated using benzaldehyde as the aldehyde catalyst (Figure 3). As discussed, initial translation of the *in situ* imine formation and subsequent labelling conditions provided 12% RCY (Figure 4, entry 1). Pre-formed imines presented a doubling in the yield, providing the desired product in 24% RCY (entry 2). Attempts to lower the precursor loading resulted in reduced reaction efficiency (entries 3, 4). A shorter reaction time with elevated temperatures lead to a minor decrease in product, whilst a doubling in reaction time yielded similar results with 22% RCY (entries 5, 6). A modest reduction of the base loading did not impact RCY, while increased amounts of Cs_2CO_3 cut the yields, perhaps due to competition with non-radioactive CO_2 released from this reagent (entries 7–

9). One alternative, K_3PO_4, facilitated CIE in diminished yield (entry 10) while Li_2CO_3 proved too insoluble to assist in isotopic exchange.

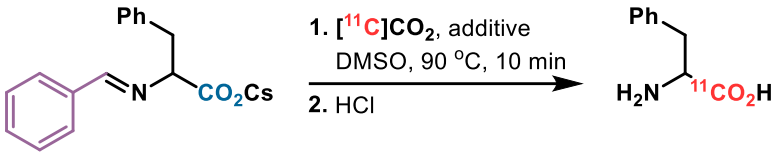
optimization results

Entry	[imine] (M)	Cs_2CO_3 (mol %)	Time (min)	Temp. (° C)	V_{DMSO} (mL)	TE (%)	RCC (%)	RCY (%)
1	0.2 [a]	50	10	90	0.75	13	90	12
2	0.2	50	10	90	0.75	25	95	24
3	0.1	50	10	90	0.50	15	99	14
4	0.1	50	10	70	0.50	13	74	10
5	0.2	50	5	110	0.75	19	97	18
6	0.2	50	20	90	0.75	22	99	22
7	0.2	40	10	90	0.75	28	94	26
8	**0.2**	**40**	**10**	**110**	**0.75**	**27**	**99**	**27**
9	0.2	100	10	90	0.75	10	95	10
10	0.2	0 [b]	10	90	0.75	17	97	16

[a] imines prepared *in situ* with 100% ArCHO and AA, [b] K_3PO_4 (50 mol %)

Figure 3. Evaluation of reaction conditions for the preparation of ^{11}C-amino acids.

We further evaluated the effects of additives on the reaction (Figure 4). The addition of trapping bases like DBU and DABCO did not improve the results; instead strong coordination with $[^{11}C]CO_2$ prevented interaction with the imine intermediate (Figure 4, entries 1, 2). Alternative bases TMEDA and NaOH did not impact the reaction (entries 3, 4). The crown ether 18-crown-6 and chelator 222-cryptand did not positively impact ^{11}C-labelled phenylalanine yields (entries 5, 6). Increased loading of base disabled the reaction entirely, only providing trapped $[^{11}C]CO_2$ (entries 7–9).



optimization results

Entry	Additive	TE (%)	RCC (%)	RCY (%)
1	DBU [a]	13	46	6
2	DABCO [a]	17	98	17
3	TMEDA [a]	21	99	21
4	NaOH [b]	20	95	19
5	18C6 [a]	23	97	22
6	K222 [a,c]	25	56	14
7	KOtBu [d]	12	0	0
8	DBU [e]	19	0	0
9	DABCO [e]	51	0	0

[a] 50 mol %, [b] 10 mol %, [c] K_2CO_3 (50 mol %) instead of Cs_2CO_3, [d] 100 mol %, [e] 200 mol %

Figure 4. Evaluation of reaction additives on ^{11}C-labelling.

3.3. Aldehyde Catalyst Evaluation

We next assessed the efficiency of alternative aldehyde catalysts (Figure 5). Given imine stability differences and the equilibrium between free amino acid and condensed Schiff base, changes in reaction success were expected with variation in the catalyst. Electronic substituents were evaluated in both the *ortho*- and *para*- positions with only moderate decreases in yield for 4-methoxybenzaldehyde, 4-dimethylaminobenzaldehyde, 4-fluorobenzaldehyde, 4-trifluoromethylbenzaldehyde, and 2-methoxybenzalehyde. The more strongly electron-withdrawing 4-nitrobenzaldehyde disabled the reaction, providing very low yield. Steric substituents appeared to offer improvements initially, with a minor increase using 2-methylbenzaldehyde, but did not stand further with the addition of bulkier

1-napthaldehyde, 2,6-dimethylbenzaldehyde, 2-phenylbenzaldehyde and the branched 2-*tert*-butylbenzaldehyde and 2-isopropylbenzaldehyde, all of which led to decreases in yield.

Heteroaromatic catalysts furfural, pyridinecarboxaldehydes could be similarly tolerated but did not offer improvements to the yield. Pyridine-3-carboxaldehyde led to a higher amount of trapped $[^{11}C]CO_2$, and thus is suspected to be acting simultaneously as a trapping base from which the $[^{11}C]CO_2$ is not being released. Alkyl aldehydes were also tested, including Garner's aldehyde, benzyloxyacetaldehyde, isobutyraldehyde and isovaleraldehyde, but did not improve reactivity. Ketones acetophenone and benzophenone were poorly tolerated, and volatile catalysts such as acetaldehyde and acetone were incompatible with the reaction. Ultimately, while several aldehyde catalysts are compatible and perform similarly under the conditions, the highest reaction yields can be approached using the simple benzaldehyde catalyst.

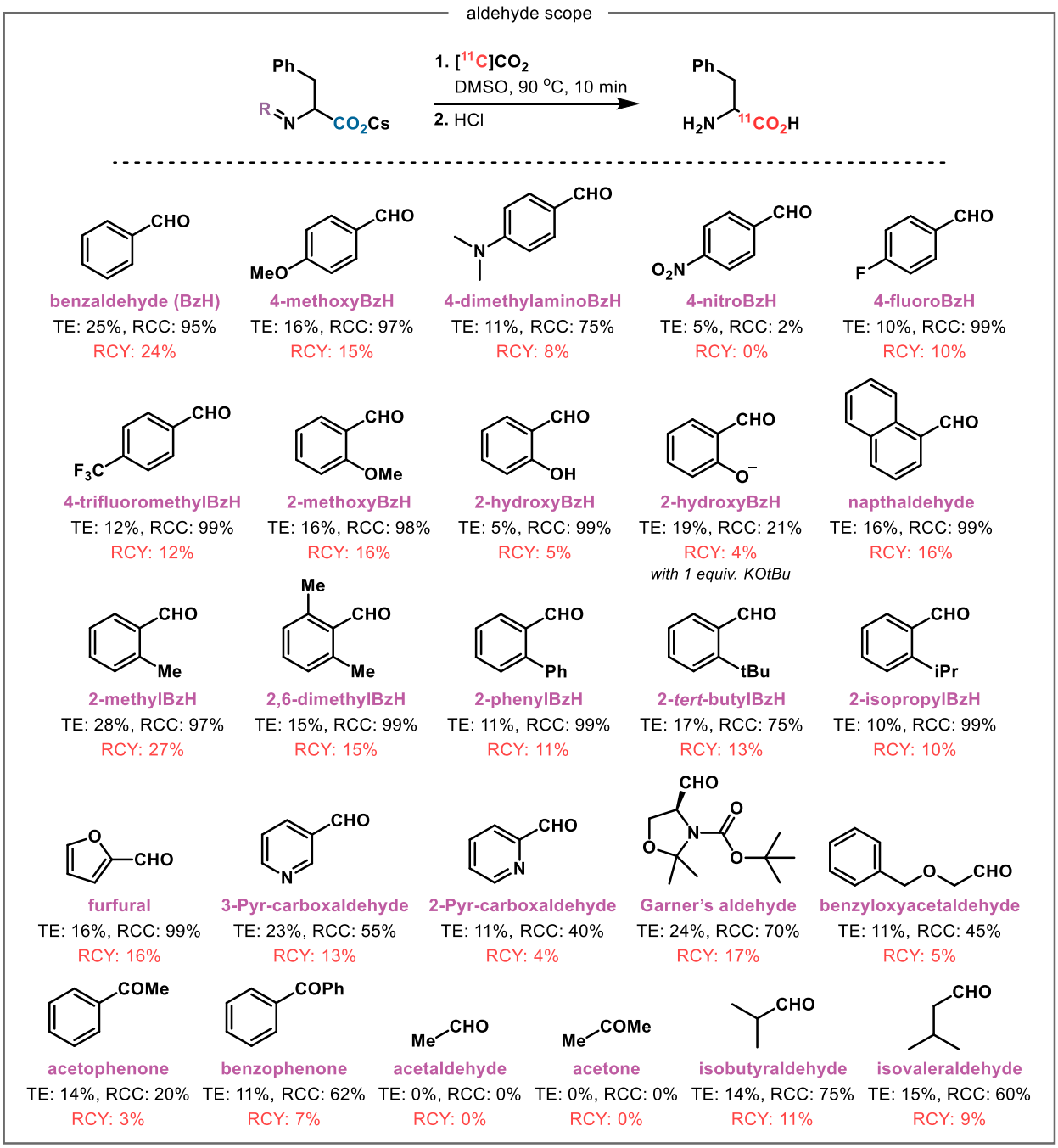
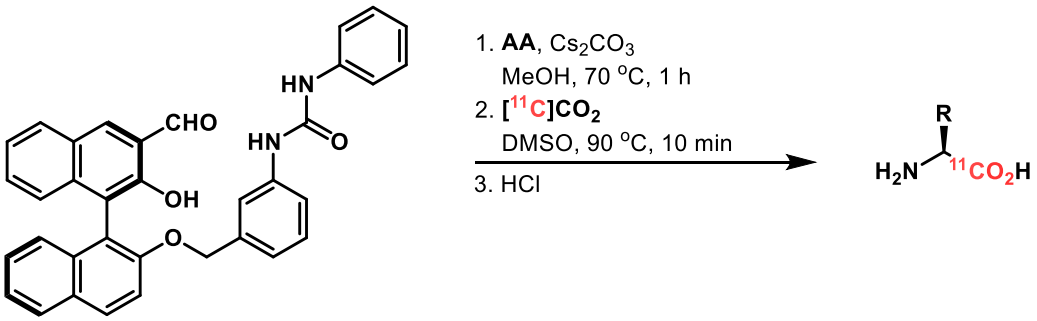


Figure 5. Aldehyde catalyst scope for ^{11}C-carbon isotope exchange reaction.

3.4. Asymmetric ^{11}C-Amino Acid Radiolabeling

An alternative use for the aldehyde catalyst is to impart stereoselectivity on the desired amino acid. Enantioselective CIE using chiral urea-tethered aldehyde catalysts developed by Kim and co-workers[18,19] has been reported with carbon-13 and carbon-14 conditions.[20,21] We tested the application of this axially chiral urea-tethered aldehyde for enantioselective radiosynthesis (Figure 6). The reaction only proceeded using phenylalanine and without base, unlike conditions for carbon-13 and carbon-14 labelling. Despite lower yields, the enantiomeric ratio was determined to be 67:33 (L:D), indicating minor enrichment of the desired enantiomer (Supplemental Figure S4). Restrictions in reaction time appear to limit the capacity for both complete deracemization and for elevated yields. Additionally, the essential use of base in the carbon-13 and carbon-14 conditions is incompatible with this approach to ^{11}C CIE, as trapping bases (e.g., DBU) sequester reactive [^{11}C]CO_2 and alternative bases lead to diminished radiochemical yields when used in excess.



optimization results

amino acid	base	TE (%)	RCC (%)	RCY (%)	er
Leu	DBU [a]	31	0	0	-
Leu	-	0	0	0	-
Phe	DBU [a]	36	0	0	-
Phe	-	5	38	2	67:33
Phe	DABCO [a]	15	0	0	-
Phe	KO*t*Bu [b]	12	0	0	-
Phe	KO*t*Bu [a]	21	0	0	-

[a] 2 equiv. [b] 1 equiv.

Figure 6. Chiral catalyst evaluation in the synthesis of L-leucine and L-phenylalanine.

In order to achieve enantiopure ^{11}C-amino acids, we instead developed an enantiomeric resolution using chromatographic separation with chiral recognition (Chirobiotic™ T). Optimization of the resolution of two enantiomers suggested 20% methanol in water as the ideal mobile phase; L- and D-leucine could be resolved on a preparative scale with a nearly 3-minute difference in their elution times (Supplemental Figure S5). Attempts to translate this method for ^{11}C applications proved difficult due to low residence time of the L-enantiomer on the column, causing partial co-elution with the similarly eluted unreactive [^{11}C]CO_2 and related adducts (Supplemental Figure S6). Given the poor solubility of leucine in organic solvents, subsequent the preparative injection the column was purged with 90% methanol in water to rapidly elute unreacted [^{11}C]CO_2 before

changing to the 20% mobile phase for resolution of the two enantiomers. This approach successfully provided L-[^{11}C]leucine sufficient for study (Supplemental Figure S7).

3.5. Pilot Evaluation of [^{11}C]Leucine in Mice

Researchers in our laboratories are studying branched-chain amino acid metabolism in cardiovascular disease. In parallel to the optimization efforts described above, we evaluated the feasibility of animal imaging studies with (±)-[^{11}C]leucine. Doses of 9.25 MBq in 200 µL of saline were injected into two C57BL/6 mice (1 M, 1 F) and imaged for 60 minutes (Figure 7). Radiotracer localization was visualized primarily in the liver, albeit with measurable uptake in the heart. Given the many roles AAs can play within the body as well as both their incorporation into proteins and degradation into amines that are reused in biochemical cycle, further analysis with compartmental modeling would be necessary to evaluate accurate tracer distribution.

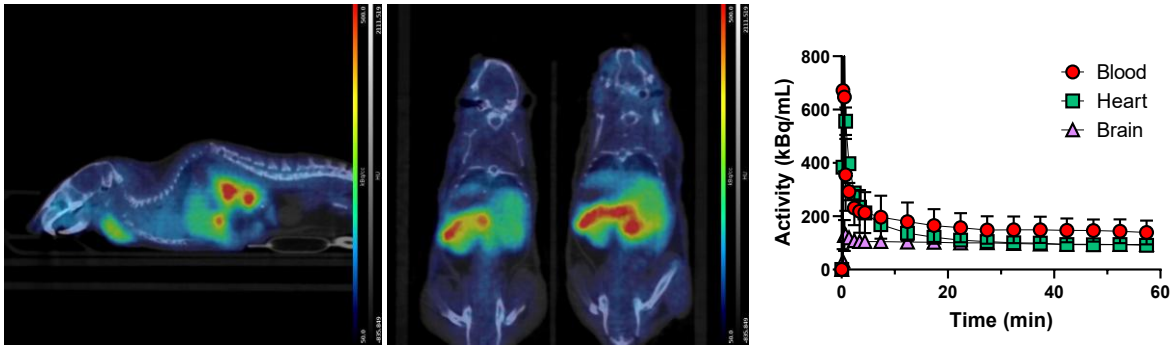


Figure 7. PET images following administration of (±)-[^{11}C]leucine in C57BL/6 mice (1 M, 1 F side-by-side, summed 60 min).

4. Conclusion

We evaluated an extensive scope of reaction conditions seeking an improved CIE methodology for labelling with ^{11}C. Our findings suggest the reaction to be robust to different aldehyde catalysts, and that they can be used to produce radiotracers suitable for imaging in animal models. We also set out to access enantiopure ^{11}C-amino acids, evaluating a chiral resolution to isolate L-[^{11}C]leucine for imaging. These approaches enable rapid and efficient labelling of ^{11}C-AAs and allow for further investigation into AA PET imaging.

5. Experimental

5.1. Imine Synthesis

Amino acid (0.15 mmol, 1 equiv.) and Cs_2CO_3 (0.075 mmol, 0.05 equiv.) were added to a 1-dram vial equipped with a stir bar. The vial was then sealed, equipped with an exhaust needle, and filled with argon by performing three vacuum/argon re-filling cycles. Anhydrous MeOH (750 μL) and aldehyde catalyst (0.15 mmol, 1 equiv.) were then added, and the reaction mixture was heated in an oil bath to 70 °C for 1 h while stirring. The vial was then equipped with an exhaust needle and the solvent was removed by flowing argon over the reaction mixture. The crude material was dried *in vacuo* for 1 h to produce a waxy solid that was either used directly for radiolabelling or stored for up to a week at -20 °C.

5.2. ^{11}C-Carbon Isotope Exchange

A Synthra MeIPlus Research module was used for all radiochemical syntheses. Imine precursor was dissolved in anhydrous DMSO (750 μL) and subsequently transferred to the

radiochemistry synthesis module reactor. The reactor was sealed and flushed with helium. After [^{11}C]CO_2 production and delivery to the reactor, it was then heated to 90 °C for 10 minutes while stirring. After, the reactor was cooled to 30 °C, then 1 M HCl (450 μL) was added to the vessel. Helium was then bubbled into the mixture for 1 minute to remove most of the unreacted [^{11}C]CO_2. The product was then either collected from the reactor for crude analysis by radio-HPLC or purified *via* in-line preparative HPLC. Details on calculations of TE, RCC, and RCY can be found in the supplementary materials.

6. Acknowledgements

The authors would like to acknowledge Dr. Rylan Lundgren, Dr. Michael Doyle, and Dr. Odey Bsharat for their insightful discussions and contributions.

6.1. Funding

This work was supported by Natural Sciences and Engineering Council of Canada (NSERC, RGPIN-2017-06167, 567606-2021), and Canadian Foundation for Innovation (CFI, JELF 36848, 39858) grants to B.H.R. B.A.M. was supported by NSERC and the University of Ottawa Heart Institute Endowed Program. A.P.P. was supported by a Mitacs Globalink Research Internship. A.B. was supported by a CIHR Canada Graduate Scholarship.

7. Author Information

7.1. Author ORCIDs

Braeden A. Mair – 0000-0002-9180-8907

Maxime Munch – 0000-0002-3552-0538

Abhishek P. Patel – 0009-0000-6119-6068

Ariel Buchler – 0000-0002-4016-032X

Benjamin H. Rotstein – 0000-0001-9707-9357

7.2. Author Contributions

Conceptualization: BAM, MM, BHR; Formal analysis: BAM, MM, APP, BHR; Funding acquisition: BHR; Investigation: BAM, MM, APP, AB; Methodology: BAM, MM, APP, AB, BHR; Supervision: BHR; Writing – original draft: BAM; Writing – review & editing: MM, APP, AB, BHR.

7.3. Competing Interests

The authors declare that there are no competing interests with this work.

8. Supplementary Materials

Supplementary materials are available: NMR spectra and HPLC chromatograms.

8.1. Data Availability

Data generated or analyzed during this study are available from the corresponding author upon reasonable request.

9. References

(1) Pekošak, A.; Filp, U.; Poot, A. J.; Windhorst, A. D. From Carbon-11-Labeled Amino Acids to Peptides in Positron Emission Tomography: The Synthesis and Clinical

Application. *Mol Imaging Biol* **2018**, *20* (4), 510–532. https://doi.org/10.1007/s11307-018-1163-5.

(2) Huang, C.; McConathy, J. Radiolabeled Amino Acids for Oncologic Imaging. *J Nucl Med* **2013**, *54* (7), 1007–1010. https://doi.org/10.2967/jnumed.112.113100.

(3) Sun, A.; Liu, X.; Tang, G. Carbon-11 and Fluorine-18 Labeled Amino Acid Tracers for Positron Emission Tomography Imaging of Tumors. *Front. Chem.* **2018**, *5*. https://doi.org/10.3389/fchem.2017.00124.

(4) Galldiks, N.; Lohmann, P.; Fink, G. R.; Langen, K.-J. Amino Acid PET in Neurooncology. *J Nucl Med* **2023**, *64* (5), 693–700. https://doi.org/10.2967/jnumed.122.264859.

(5) Herholz, K.; McMahon, A.; Thompson, J. C.; Jones, M.; Boutin, H.; Gregory, J.; Parker, C. A.; Hinz, R. Quantitative Imaging of Regional Cerebral Protein Synthesis in Clinical Alzheimer's Disease by [^{11}C]Leucine PET. *Mol Imaging Biol* **2024**, *26* (6), 977–985. https://doi.org/10.1007/s11307-024-01965-3.

(6) Hayes, R. L.; Washburn, L. C.; Wieland, B. W.; Sun, T. T.; Turtle, R. R.; Butler, T. A. Carboxyl-Labeled ^{11}C-1-Aminocyclopentanecarboxylic Acid, a Potential Agent for Cancer Detection. *J Nucl Med* **1976**, *17* (8), 748–751.

(7) Washburn, L. C.; Wieland, B. W.; Sun, T. T.; Hayes, R. L.; Butler, T. A. [1-^{11}C] DL-Valine, A Potential Pancreas-Imaging Agent. *J Nucl Med* **1978**, *19* (1), 77–83.

(8) Hayes, R. L.; Washburn, L. C.; Wieland, B. W.; Sun, T. T.; Anon, J. B.; Butler, T. A.; Callahan, A. P. Synthesis and Purification of ^{11}C-Carboxyl-Labeled Amino Acids. *Int J Appl Radiat Isot* **1978**, *29* (3), 186–187. https://doi.org/10.1016/0020-708X(78)90142-4.

(9) Studenov, A. R.; Szalda, D. E.; Ding, Y.-S. Synthesis of No-Carrier-Added C-11 Labeled D- and L-Enantiomers of Phenylalanine and Tyrosine for Comparative PET Studies. *Nucl Med Biol* **2003**, *30* (1), 39–44. https://doi.org/10.1016/S0969-8051(02)00349-9.

(10) Xing, J.; Brooks, A. F.; Fink, D.; Zhang, H.; Piert, M. R.; Scott, P. J. H.; Shao, X. High-Yielding Automated Convergent Synthesis of No-Carrier-Added [^{11}C-*Carbonyl*]-Labeled Amino Acids Using the Strecker Reaction. *Synlett* **2016**, *28*, 371–375. https://doi.org/10.1055/s-0036-1588638.

(11) Vaalburg, W.; Beerling-van der Molen, H. D.; Reiffers, S.; Rijskamp, A.; Woldring, M. G.; Wynberg, H. Preparation of Carbon-11 Labelled Phenylalanine and Phenylglycine by a New Amino Acid Synthesis. *Int J Appl Radiat Isot* **1976**, *27* (3), 153–157. https://doi.org/10.1016/0020-708X(76)90126-5.

(12) Bolster, J. M.; Vaalburg, W.; Van Veen, W.; Van Dijk, Th.; Van der Molen, H. D.; Wynberg, H.; Woldring, M. G. Synthesis of No-Carrier-Added L- and D-[1-^{11}C]-DOPA. *Int J Appl Radiat Isot* **1983**, *34* (12), 1650–1652. https://doi.org/10.1016/0020-708X(83)90019-4.

(13) Bolster, J. M.; Vaalburg, W.; Paans, A. M. J.; van Dijk, T. H.; Elsinga, P. H.; Zijlstra, J. B.; Piers, D. A.; Mulder, N. H.; Woldring, M. G.; Wynberg, H. Carbon-11 Labelled Tyrosine to Study Tumor Metabolism by Positron Emission Tomography (PET). *Eur J Nucl Med* **1986**, *12* (7), 321–324. https://doi.org/10.1007/BF00263811.

(14) Bolster, J. M.; Vaalburg, W.; Elsinga, Ph. H.; Wynberg, H.; Woldring, M. G. Synthesis of DL-[1-^{11}C]Methionine. *Int J Radiat Appl Radiat Isot* **1986**, *37* (10), 1069–1070. https://doi.org/10.1016/0883-2889(86)90047-X.

(15) Antoni, G.; Kihlberg, T.; Långström, B. ^{11}C: Labeling Chemistry and Labeled Compounds. In *Handbook of Nuclear Chemistry*; Vértes, A., Nagy, S., Klencsár, Z., Lovas, R. G., Rösch, F., Eds.; Springer US: Boston, MA, 2011; pp 1977–2019. https://doi.org/10.1007/978-1-4419-0720-2_41.
(16) Bsharat, O.; Doyle, M. G. J.; Munch, M.; Mair, B. A.; Cooze, C. J. C.; Derdau, V.; Bauer, A.; Kong, D.; Rotstein, B. H.; Lundgren, R. J. Aldehyde-Catalysed Carboxylate Exchange in α-Amino Acids with Isotopically Labelled CO_2. *Nat. Chem.* **2022**, *14* (12), 1367–1374. https://doi.org/10.1038/s41557-022-01074-0.
(17) Doyle, M. G. J.; Mair, B. A.; Sib, A.; Bsharat, O.; Munch, M.; Derdau, V.; Rotstein, B. H.; Lundgren, R. J. A Practical Guide for the Preparation of C1-Labeled α-Amino Acids Using Aldehyde Catalysis with Isotopically Labeled CO_2. *Nat Protoc* **2024**, 1–33. https://doi.org/10.1038/s41596-024-00974-4.
(18) Park, H.; Kim, K. M.; Lee, A.; Ham, S.; Nam, W.; Chin, J. *J. Am. Chem. Soc.* **2007**, *129* (6), 1518.
(19) Park, H.; Nandhakumar, R.; Hong, J.; Ham, S.; Chin, J.; Kim, K. M. *Chem. Eur. J.* **2008**, *14* (32), 9935.
(20) Doyle, M. G. J.; Bsharat, O.; Sib, A.; Derdau, V.; Lundgren, R. J. Enantioselective Carbon Isotope Exchange. *J. Am. Chem. Soc.* **2024**. https://doi.org/10.1021/jacs.4c03685.
(21) Bsharat, O. ^{12}C/^{13}C Isotope Exchange for the Synthesis of D-[^{13}C]Phenylalanine by Using [^{13}C]CO_2 and Binol Chiral Aldehyde Receptor. *J Radioanal Nucl Chem* **2025**. https://doi.org/10.1007/s10967-025-10073-7.

10. Version of Record:

Mair, B. A.; Munch, M.; Patel, A. P.; Buchler, A.; Rotstein, B. *Can. J. Chem.* https://doi.org/10.1139/cjc-2025-0190