Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. Pekošak, U. Filp, J. Škrinjar, A. J. Poot and A. D. Windhorst, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB02633H.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C6OB02633H

Journal Name

COMMUNICATION

A Rapid and Highly Enantioselective C-^{11}C Bond Formation of L-[^{11}C]Phenylalanine via Chiral Phase-Transfer Catalysis

tge Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Aleksandra Pekošak[a], Ulrike Filp[a], Janja Škrinjar[a,b], Alex J. Poot[a] and Albert D. Windhorst[a]

A rapid method for the synthesis of carbon-11 radiolabeled phenyalanine was developed using a chiral phase-transfer catalyst and sub-nanomolar quantity of [^{11}C]benzyl iodide as radio-precursor. Based upon a reported synthesis of [^{11}C]benzyl iodide, a Schiff base precursor was evaluated for stereoselective [^{11}C]benzylation. Extensive and interactive screening of precursor, catalyst, base, stirring and temperature was required to achieve high stereoinduction. The result is an efficient 5-step radiolabeling method to reliably synthesize L- or D-[^{11}C]phenylalanine with an excellent enantiomeric excess of >90% and almost quantitative radiochemical conversion of >95% (n>5).

Additionally, a phase-transfer catalyzed alkylation was utilized on the preparative scale using automated platform. The application resulted in high specific activity ranging from 85-135 GBq·µmol^{-1} of the enantiomericaly pure [^{11}C]phenylalanine, showing the process is robust and amenable to broad use in PET.

Positron emission tomography (PET) is a non-invasive imaging technique used for clinical diagnostic applications in oncology, neurology and cardiology, as well as drug development. The radionuclide carbon-11 ($t_{1/2}$=20.4 min, 99% β+, 0.96 MeV) is commonly used in PET, since the ubiquity of carbon atoms in all naturally occurring organic compounds makes it an attractive isotope for radiolabeling.[1–4] The notable information PET can provide strongly depends on the development and availability of PET-tracers. Current tracer development remains challenging and still relies on the application of a very small number of radiochemistry methods, consequently limiting facile synthesis of novel radiopharmaceuticals.[3,5]

An important class of chiral PET radiopharmaceuticals are radiolabeled amino acids (AAs) used to image e.g. up-regulated AA metabolism that is described for cancer cells.[6,7] With variable successes, and often in an asymmetric manner, many carbon-11 AAs isotopologues have been accomplished,

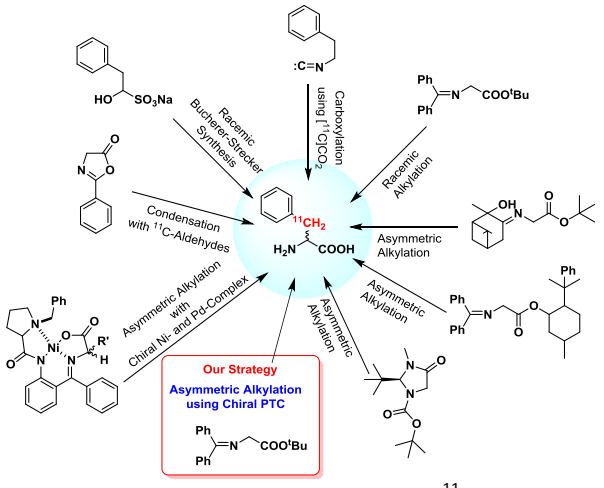


Figure 1: General synthetic routes to obtain [^{11}C]phenylalanine.[8,9]

where carbon-12 is substituted with radioactive carbon-11. The formidable challenge in the synthesis of ^{11}C-labeled AAs still lies in the stereoselective reaction on the α-carbon avoiding time consuming chiral separation via HPLC to ontain enantimoerically pure form[9], next to convenience and reliability of the radiolabeling process, limited by synthesis time and specific activity (SA) (GBq·µmol^{-1}), all important parameters that apply to radiopharmaceuticals.[1,5,8,10,11]

Our approach to synthesize chiral α-AAs utilizes the alkylation of an activated methylene group, the glycine Schiff base, in the presence of quaternary ammonium salts as chiral phase-transfer catalysts (PTCs).[12–15] To the extent of our knowledge, the use of chiral alkylation reactions in the presence of PTCs have not been described for the enantioselective radiolabeling of phenyalanine with carbon-11, as depicted in Figure 1.[8,16–20] Accordingly, asymmetric alkylation would be a powerful approach to overcome the mentioned limitations in ^{11}C-chemistry preserving the known properties, like target affinity, selectivity and specificity.

The importance of enantiopurity of radiopharmaceuticals is paramount for radiolabeled AAs where stereochemistry influences the rate and selectivity of AA transport, preferential for L-enantiomers in mammalian cells.[21] Demonstrated by the application of L- and D-[^{11}C]phenylalanine, synthesized using enzymatic separation, where the L-enantiomer of

[a] Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, the Netherlands. E-mail: a.pekosak@vumc.nl
[b] Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia.
† Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/x0xx00000x

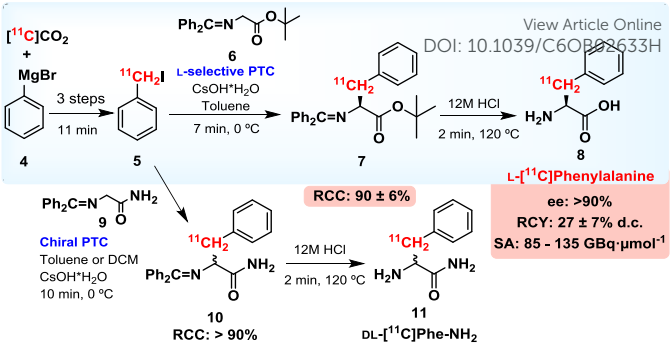
[^{11}C]phenylalanine showed better pancreas-to-liver ratios.[22] This was even further proven by the better imaging properties of L-[^{18}F]-labeled fluoroalkyl phenylalanine analogues, all demonstrating high uptake in tumor compared to surrounding tissues. These studies, not mentioning the gold standards L-[^{11}C]methionine and L-[^{18}F]-fluoroethyl tyrosine, thus emphasize the need for methods to synthesize enantiomerically pure AAs as PET tracers.[23–25]

In this communication we describe a new and generally applicable radiosynthetic method for the enantioselective synthesis of carbon-11 labeled L- and D-AAs by employing chiral PTC. This method is applied to synthesize L- and D-[^{11}C]phenylalanine, an essential aromatic AA used for tumor imaging, and its unnatural analogue phenylalanine amide.[26] The methodology described was translated from manual proof-of-concept radiosynthesis to a preparative scale on an automated platform in a GMP compliant laboratory. Furthermore, the here described rapid and robust radiolabeling might enable unprecedented native ^{11}C-labeling of peptides by alkylating a prochiral Schiff base-activated glycine residue.

The enantioselective synthesis of L- and D-[^{11}C]phenylalanine was achieved in 5 steps starting from cyclotron produced [^{11}C]CO_2, as depicted in Scheme 1. The first 3 steps involved a one-pot Grignard reaction to obtain [^{11}C]benzyl iodide **5**,[26] as alkylating reagent followed by subsequent asymmetric [^{11}C]benzylation on the commercially available Schiff base precursor **6**[15] with the aid of a commercially available chiral PTC. Acidic deprotection of the alkylated intermediate yielded enantiopure [^{11}C]phenylalanine, the desired product.

A major challenge in translating the mild phase-transfer conditions from successful organic to carbon-11 radiochemistry is the reaction time and the distorted stoichiometric condition in radiochemistry. Where in organic chemistry, reactions are allowed for several hours, in carbon-11 radiochemistry only a few minutes are acceptable. In addition, one is limited in radiochemistry by the low amount of carbon-11 labelled reagent, typically between 50-100 nmoles, resulting in large excess of non-radiolabelled reagents which are typically in the mmol range, influencing the reaction kinetics dramatically. Furthermore, small contaminants present in the reaction mixture might destroy the low amounts of carbon-11 labeled reagent easily.

We first engaged in the S_N2 alkylation to obtain high radiochemical conversion (RCC) into the intermediate **7** by controlling the following parameters: order of addition, mixing of the reaction, amount of precursor **6** and precursor concentration, reaction time, base, amount of base, solvent and temperature (*T*) (Table 2, ESI†). As a proof-of-principle, we initially investigated reaction conditions in presence of a strong base, *tetra-n*-butylammonium fluoride (TBAF).[27] At this stage, we speculated that it was necessary to carefully examine the precursor concentration in order out-compete an undesired side effect during the radiolabeling, namely cleavage of the diphenylmethylene group on *N*-terminus[27] to benzophenone and glycine *tert*-butylester, crucial for activation of **6**, and provide a sufficinet amount of **6** for the [^{11}C]benzylation. An increased amount of **6** (17 µmol per alkylation reaction), gave indeed high RCC and further experiments confirmed that precursor concentration can



Scheme 1: Radiosynthesis of L-[^{11}C]phenylalanine **8** and DL-[^{11}C]phenylalanine amide **11.**

range form 55-60 mM. The radio-HPLC analysis was very encouraging and proved 85±6% RCC (of **5** to racemic **7**) after 10 min at 45 °C in presence of DCM and DMSO as a solvent[§§].

Encouraged by the rapid and near quantitative [^{11}C]benzylation, we turned our attention to five commercially available chiral PTCs and their influence on stereoinduction (Figure 2). Adapting the conditions from sucessful organic chemistry, we envisioned that high excess of hydroxide base $CsOH{\cdot}H_2O$, namely 150 eq compared to precursor **6**, toluene as solvent at 0 °C provided us almost quantitative RCC with moderate stereoselectivity (enantiomeric excess (ee) of 46±2%) for L-[^{11}C]phenylalanine **8** in presence of 10 mol%[‡‡] Corey's[28] **Cat 1** (Table 1, Entry 9). Large excess of base provided suficcient interfacial area between the two phases for this solid-liquid PTC. The ee was further increased to 75% by cooling the [^{11}C]benzyl iodide solution **5** to 0 °C prior to the addition of **6** (Table 1, Entry 11). These series of experiments also revealed new optimized reaction conditions, 170 eq[‡‡] of $CsOH{\cdot}H_2O$ for 7 min at 0 °C, where precursor concentration could even ranged between 20-90 mM.

Table 1: Screening the [^{11}C]alkylation conditions for **Cat 1**.

Entry	c of 6 [mM]	Base	Eq of base[a]	Solvent	*T* [°C]	RCC 7 [%][b]	ee 8 [%][c]
1	55-60	KOH	10	PhMe+DCM	-5	**5**	/
2	55	KOH	20	PhMe+DCM	-5	**<1**	/
3	55	KOH	30	PhMe+DCM	-5	**4±2**	/
4	55-60	KOH	35	PhMe+DCM	-5	**4±0**	/
5	55	KOH	40	PhMe+DCM	RT	**10**	/
6	60	$CsOH{\cdot}H_2O$	10	PhMe+DCM	-5	**4**	/
7	60	$CsOH{\cdot}H_2O$	10	PhMe+DCM	RT	**2**	/
8	60	CsOH·HO	10	PhMe	RT	**6**	/
9	40	$CsOH{\cdot}H_2O$	150	PhMe	-5	**92±1**	**46±2**
10	20	$CsOH{\cdot}H_2O$	150	PhMe	0	**83±8**	/
14	90	$CsOH{\cdot}H_2O$	170	PhMe	0*	**91±1**	**75±2**

All reactions were conducted with 17 µmol **6** and 0.1 eq of **Cat 1** in 10 min. PhMe stands for toluene and DCM for dichloromethane. [a]Compared to **6**. [b]Radiochemical conversions were determined by HPLC. [c]Enantiomeric excess was determined by chiral HPLC. *Reaction was performed for 7 min.

An enhanced enantioselective formation of L-[^{11}C]phenylalanine was observed by employing Maruoka's catalyst (*R*)-**Cat 3** to ee of 91%, without having an effect on the RCC (Table 2). Unfortunately, the combination of toluene and dichloromethane as solvent mixture resulted in a decrease of

enantioselectivity (ee of 78%). Employing a lower mol% of catalyst‡‡ was fruitless as well (ee of 78%), contrary to Kitamura.[29] However, a high ee could also be obtained at lower *T* of -20 °C (ee of 88%).

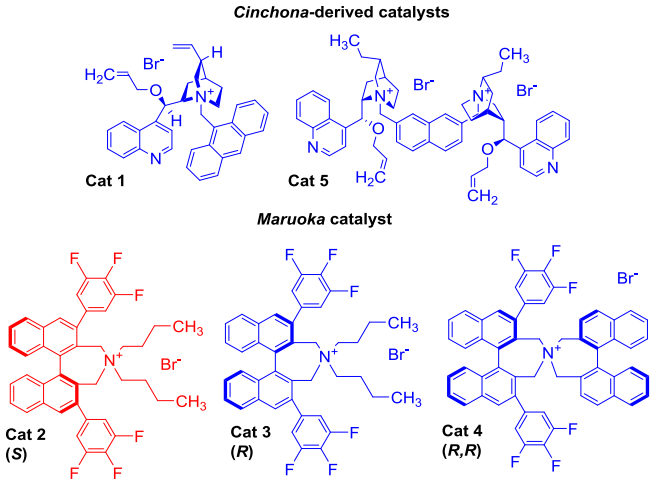


Figure 2: Chiral PTC explored for the radiosynthesis of L- and D-[^{11}C]phenylalanine and L- and D-[^{11}C]phenylalanine amide. Blue: catalysts yielding L-product; Red: catalyst yielding D-product.

Catalyst-controlled asymmetric induction of the [^{11}C]benzyl group was investigated when (*S*)-**Cat 2** was used to yield specifically D-[^{11}C]phenylalanine (Table 2). As depicted in Figure 2, **Cat 2** and **Cat 3** are enantiomers, therefore both chiral PTCs should yield comparable RCC and ee under the same reaction conditions, however with opposite enantiomers as product. Surprisingly, slightly lower enantioselectivity of ee up to 86%, relative to **Cat 3** was observed (ESI‡‡). In contrast, lower *T* of -20 °C this time gave rather disappointing results, decrease of enantioselectivity to 57%, next to a lower RCC. The lower RCC is explained by the lower *T* and consequently slower reaction kinetics, as **6** was still observed on HPLC.

Table 2: Screening the [^{11}C]alkylation conditions for **Cat 1**.

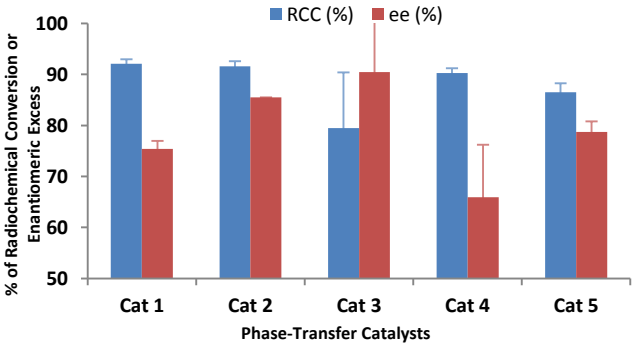
Entry	PTC [mol%][a]	Eq of base [a]	*T* [°C]	Time [min]	RCC 7 [±SD; %][b]	ee 8 [±SD; %][c]
1	**Cat 3** (10)	150	0	10	91	85
2	**Cat 3** (10)	150	0*	10	80±11	91±10
3	**Cat 3** (10)	170	0*	7	84±5	74±1
4	**Cat 3** (2.5)	170	0*	7	84	78
5[d]	**Cat 3** (10)	170	0*	7	84	78
6	**Cat 3** (10)	170	-20*	7	89	88±1
7	**Cat 2** (10)	150	0	10	53±2	72±4
8	**Cat 2** (10)	150	0*	10	74±12	83±5
9	**Cat 2** (10)	170	0*	7	92±1	85.5
10	**Cat 2** (10)	170	-20*	7	56±7	57±1
11	**Cat 2** (10)	40	0*	7	54±13	76±6
12	**Cat 4** (10)	150	0*	10	90±1	66±10
13	**Cat 5** (10)	170	0*	7	91±3	77±0
14	**Cat 5** (5)	170	0*	7	91±1	68±1
15	**Cat 5** (10)	170	-20*	7	87±2	79±2

All reactions were conducted with 17 µmol **6** and 400 µL of toluene in 10 min. [a]% of catalyst and eq of base are compared to **6**. [b]Radiochemical conversions were determined by HPLC. [c]Enantiomeric excess was determined by chiral HPLC. *Precooled **5** to desired T. [d]Combination of toluene and DCM (400 µL; *v/v*=1/1).

Despite the success of *N*-spiro C_2-symmetric chiral **Cat 4**[14] in organic chemistry and also in the radiosynthesis of [^{18}F]FDOPA[30], this catalyst did not demonstrate desired enantioselectivity in the [^{11}C]benzylation reaction. Standard conditions, resulted in an excellent RCC of 90%, but undesired ee of only 66% for L-[^{11}C]phenylalanine (Table 2, Entry 12).

Lastly, the use of dimeric *Cinchona*-derived alkaloid **Cat 5** was investigated. The use of **Cat 5** resulted in a high RCC of the reaction, but unfortunately, a lower ee of the product of 79% towards L-[^{11}C]phenylalanine was obtained (Table 2). Experiments with lower mol%‡‡ of catalyst or lower *T* (-20 °C) were meaningless, contrary to remarkable catalytic and chiral efficiency in organic chemistry.[31] Introduction of a naphthalene ligand in **Cat 5**, compared to 9-anthracenylmethyl in **Cat 1**, resulted in enhancement in enantioselectivity.

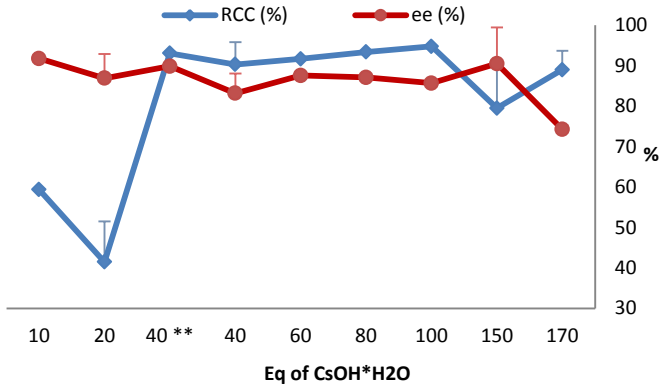
Unexpectedly, as can be concluded from the results obtained, slight reaction rate retardation in the enantiofacial differentiation compared to benzylation in organic chemistry seems inevitable. The excellent RCCs obtained can be explained by the effective surface area of solid base and nanomolar and sub-stoichiometric amounts of **5** that react instantly. On the other hand, latest advantage might serve as a drawback for enantioselectivity, since the alkylating agent should be longer exposed to the PTC conditions employing lower *T*s (-78 to -40 °C), which are regularly used in organic chemistry, to result in extremely high enantioselectivities.[13–15] Extrapolations of these conditions to radiochemistry, especially with short-lived isotopes like carbon-11, is not feasible as the synthesis time must be kept as short as possible in radiochemistry.



Graph 1: An overview of the screened PTC for the radiosynthesis of L- or D-[^{11}C]phenylalanine. All reactions were conducted with 17 µmol of **6**, 10% of catalyst, 170 eq of $CsOH{\cdot}H_2O_{(s)}$ and 400 µL of toluene for 7 min at 0 °C. ‡‡

After screening all selected chiral PTCs, **Cat 3** has been identified as a catalyst of choice for the preparation of L-[^{11}C]phenylalanine **8** (Graph 1). Further investigations therefore focused on decreasing the excess of base used, monitoring the effect on RCC and ee. With 40 eq‡‡ of $CsOH{\cdot}H_2O_{(s)}$ high conversion and enantioselectivity (RCC: 90±6%; ee: 83±5%) were still observed (Graph 2), and are consistent with results of other reports.[30–33] Recently Kano reported asymmetric solid-liquid phase-transfer benzylation on the **6** in organic chemistry using the homogenizer in 5 min.[34] Aiming to adapt these conditions we achieved RCC of 93±0% and ee of 90±3% in only 40 s using vortex mixing. Though the superfast ^{11}C-benzylation (from 7 min to 40s) provided slighly better results (Graph 2), the manual use of

Vortex mixer is not justified due to the radioation dose radiochemist is exposed during the experiment. Base upon, it was clear that vigorous stirring enlarges the interfacial contact between the two phases and results in considerable rate enhacement. At this stage, we could speculate that even lower amounts of base would attain a sufficient raction rate on Vortex mixer.



Graph 2: Effect of $CsOH{\cdot}H_2O$ on RCC [±SD;%] and ee [±SD;%] of **Cat 3**.

Having established an efficient enantioselective synthesis for L-[^{11}C]phenylalanine, we extended the PTC use and application to the asymmetric synthesis of unnatural α-AAs as well, since nonproteinogenic AAs play a special role in peptidomimetics. In order to explore the applicability of the developed method, achiral glycinamide precursor **9** has been studied (Scheme 1), since amides tend to be more stable under PTC conditions and *in vivo*.[35–37] As anticipated from initial experiments with TBAF for LD-[^{11}C]phenylalanine[§], this strong base appeared sufficient for [^{11}C]benzylation towards **10** (RCC up to 70%), while $Cs_2CO_{3(s)}$ or PTCs, like $TBAB_{(s)}$ and $TBAHS_{(s)}$‡, were ineffective (RCC of <5%). Aiming to achieve the enantioselective synthesis of unnatural L-[^{11}C]phenylalanine amide **11**, chiral PTC from Figure 2 demonstrated no stereocontrol, despite the superb incorporation (RCC up to 99%) of **5** and variations in the solvent and temperature (Table 3, ESI‡). Evidently, deprotonation of α-hydrogen of **9** does not generate the enolate to interact with the ammonium cation from chiral catalysts resulting in formation of lipophilic onium enolate, like **6** (Figure 15, ESI‡).[13,38,39]

Final step, removal of protecting groups has been achieved at elevated temperatures (120 °C for 2 min) and under acidic conditions by addition of 12M $HCl_{(aq)}$ (200 µL) resulting in a quantitative >96% conversion to product **8** or **11** (Table 4, ESI†). Afterwards, the exact stereochemical outcome was determined using chiral radioHPLC (ESI† and Figure 3).

In order to demonstrate the utility of the developed method in producing a novel PET-tracer, the total synthesis of L-[^{11}C]phenylalanine was scaled-up and fully automated with starting amounts of approximately 50 GBq of [^{11}C]CO_2 according to GMP† standards (ESI†). L-[^{11}C]Phenylalanine was synthesized within 24 minutes and yields were 5-7 GBq[§§] at the end of synthesis, corresponding to a decay-corrected radiochemical yield of 27±7%, calculated from the end of the production of [^{11}C]CO_2. Analysis showed an ee of >90% (Figure 2) and a SA of 85-135 GBq/µmol at the end of synthesis (EOS).

In summary, we successfully developed a novel, rapid and efficient multi-step synthesis to obtain enantiomerically pure L-[^{11}C]phenylalanine by applying a chiral PTC, so far unexplored in carbon-11 radiochemistry. Moreover, this methodology enables enantiomerically pure D-[^{11}C]phenylalanine, which cannot be obtained using well established enzyme-catalyzed synthesis. The overall process illustrates the challenges in determining optimal conditions for controling this [^{11}C]benzylation that yielded an enantiopure [^{11}C]phenylalanine. More specifically, an interactive systematic automation of all 5steps revealed the procedure is reliable and reproducible, and employs commercially available precursor **6** and **Cat 3**. Further research that is under investigation focuses on translating this powerful methodology towards carbon-11 labeling of peptides in an enantioselective manner.

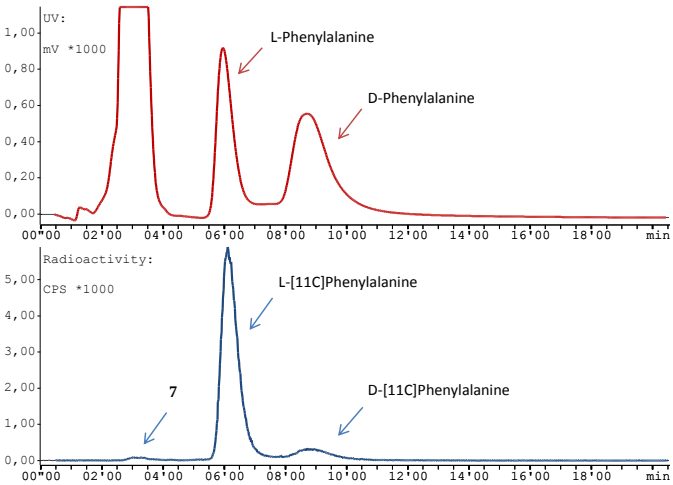


Figure 3: HPLC UV and radioactivity profile of the crude reaction mixture after automation procedure with co-injection of the cold standard L- and D-Phenylalanine: Separation of D- and L-[^{11}C]phenylalanine on chiral column to determine ee %.

The research leading to these results has been financially supported by the European Marie Curie Actions RADIOMI ITN (FP7-PEOPLE-2012-ITN; no. 316882). BV Cyclotron VU (Amsterdam) is acknowledged for providing [^{11}C]CO_2.

Notes and references

‡ Footnotes are explained in the ESI.
‡‡ mol% and equivalents (eq) compared to precursor **7** or **9**.
§ Reaction conditions: 1 eq of precursor **6,** 2 eq of TBAF, 100 µL of DCM, 300 µL of DMSO and *in situ* produced [^{11}C]benzyl iodide vigorously stirred for 10 min at 45 °C.
§§ Reaction conditions: 1 eq of precursor **6**, 0.1 eq of **Cat 3**, 40 eq of $CsOH{\cdot}H_2O$, 400 µL of toluene and *in situ* produced [^{11}C]benzyl iodide vigorously stirred for 7 min at 0 °C, followed by addition of 200 µL of 12M HCl for 2 min at 120 °C.

1 W. Wadsak and M. Mitterhauser, *Eur. J. Radiol.*, 2010, **73**, 461–469.
2 S. Vallabhajosula, L. Solnes and B. Vallabhajosula, *Semin. Nucl. Med.*, 2011, **41**, 246–264.
3 B. H. Rotstein, S. H. Liang, M. S. Placzek, J. M. Hooker, A. A. Wilson and N. Vasdev, *Chem. Soc. Rev.*, 2016, **in press**.

4 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chemie Int. Ed.*, 2008, **47**, 8998–9033.
5 Z. Li and P. S. Conti, *Adv. Drug Deliv. Rev.*, 2010, **62**, 1031–1051.
6 C. Huang and J. McConathy, *J. Nucl. Med.*, 2013, **54**, 1007–1010.
7 P. L. Jager, W. Vaalburg, J. Pruim, E. G. de Vries, K. J. Langen and D. a Piers, *J. Nucl. Med.*, 2001, **42**, 432–445.
8 A. Popkov and P. H. Elsinga, *Curr. Org. Chem.*, 2013, **17**, 2127–2137.
9 J. Ermert and H. H. Coenen, *J. Labelled Comp. Radiopharm.*, 2013, **56**, 225–36.
10 G. Antoni, T. Kihlberg and B. Långström, *Handbook of Nuclear Chemistry; 11C: Labeling Chemistry and Labeled Compounds*, 2011.
11 F. Buckingham and V. Gouverneur, *Chem. Sci.*, 2016, **7**, 1645–1652.
12 M. J. O'Donnell and R. L. Polt, *J. Org. Chem.*, 1982, 47, 2663–2666.
13 K. Brak and E. N. Jacobsen, *Angew. Chemie Int. Ed.*, 2013, **52**, 534–561.
14 S. Shirakawa and K. Maruoka, *Angew. Chemie Int. Ed.*, 2013, **52**, 4312–4348.
15 T. Ooi and K. Maruoka, *Angew. Chemie - Int. Ed.*, 2007, **46**, 4222–4266.
16 R. M. Kilbourn, D. D. Dischino and J. M. Welch, *Int. J. Appl. Radiat. Isot.*, 1984, **35**, 603–605.
17 G. Antoni and B. Långström, *J. Label. Compd. Radiopharm.*, 1987, 24, 125–143.
18 C. Halldin and B. Laangström, *Int. J. Appl. Radiat. Isot.*, 1984, **35**, 945–948.
19 C. Halldin and B. Langstrom, *Int J Appl Radiat Isot.*, 1984, **35**, 779–782.
20 K. Fasth, G. Antoni and B. Langstrom, *J.Chem.Soc.*, 1988, **I**, 3081–3084.
21 J. McConathy and M. M. Goodman, *Cancer Metastasis Rev.*, 2008, **27**, 555–573.
22 D. L. Casey, G. a Digenis, D. a Wesner, L. C. Washburn, J. E. Chaney, R. L. Hayes and a P. Callahan, *Int. J. Appl. Radiat. Isot.*, 1981, **32**, 325–330.
23 L. Wang, W. Qu, B. P. Lieberman, K. Plössl and H. F. Kung, *Nucl. Med. Biol.*, 2011, **38**, 53–62.
24 L. Wang, B. P. Lieberman, K. Plössl, W. Qu and H. F. Kung, *Nucl. Med. Biol.*, 2011, **38**, 301–312.
25 K. Kubota, K. Yamada, H. Fukada, S. Endo, M. Ito, Y. Abe, T. Yamaguchi, T. Fujiwara, T. Sato, K. Ito, S. Yoshioka, J. Hatazawa, T. Matsuzawa, R. Iwata and T. Ido, *Eur. J. Nucl. Med.*, 1984, **9**, 136–140.
26 A. Pekošak, U. Filp, L. Rotteveel, A. J. Poot and A. D. Windhorst, *J. Label. Compd. Radiopharm.*, 2015, **58**, 342–348.
27 K. Kato, A. B. Tsuji, T. Saga and M.-R. Zhang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2437–2440.
28 E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **2400**, 12414–12415.
29 M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chemie - Int. Ed.*, 2005, **44**, 1549–1551.
30 L. C. Libert, X. Franci, A. R. Plenevaux, T. Ooi, K. Maruoka, A. J. Luxen and C. F. Lemaire, *J. Nucl. Med.*, 2013, **54**, 1154–61.
31 H. Park, B. Jeong, S. Yoo, J. Lee, M. Park, J. Lee, M. Kim and S. Jew, *Angew. Chemie*, 2002, **114**, 3162–3164.
32 C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts and A. Luxen, *European J. Org. Chem.*, 2004, **13**, 2899–2904.
33 C. Lemaire, L. Libert, X. Franci, J.-L. Genon, S. Kuci, F. Giacomelli and A. Luxen, *J. Label. Compd. Radiopharm.*, 2015, **58**, 281–290.
34 T. Kano, Y. Aota and K. Maruoka, *Adv. Synth. Catal.*, 2016, 2996–2999.
35 Y. S. Park, H. J. Kim and D. Lim, *Bull. Korean Chem. Soc.*, 2001, **22**, 958–962.
36 D. J. Hyett, M. Didonè, T. J. a Milcent, Q. B. Broxterman and B. Kaptein, *Tetrahedron Lett.*, 2006, **47**, 7771–7774.
37 M. J. O'Donnell, J. D. Keeton, V. Van Khau and C. J. Bollinger, *Can. J. Chem.*, 2006, **84**, 1301–1312.
38 E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **119**, 12414–12415.
39 G. P. Petrova, H. B. Li, K. Maruoka and K. Morokuma, *J. Phys. Chem. B*, 2014, **118**, 5154–5167.
40 S. H. Liang and N. Vasdev, *Aust. J. Chem.*, 2015, **68**, 1319–1328.