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Efficient synthesis of ^{11}C-acrylesters, ^{11}C-acrylamides and their application in Michael addition reactions for PET tracer development.

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Abstract

Here we present the novel Michael addition reaction utilizing carbon-11 labeled acrylic esters and carbon-11 labeled amides. Subsequently, these synthons are reacted with commercially available Schiff base precursors to produce [^{11}C]glutamate and [^{11}C]glutamine. This methodology is especially useful for the development of positron emission tomography imaging agents as it opens up a new array of potential carbon-11 labeled compounds with this original ^{11}C-C bond forming strategy.

Keywords: ^{11}C-acrylester / Michael addition / Pd-catalyzed carbonylation / ^{11}C-labeled amino acids / Positron Emission Tomography

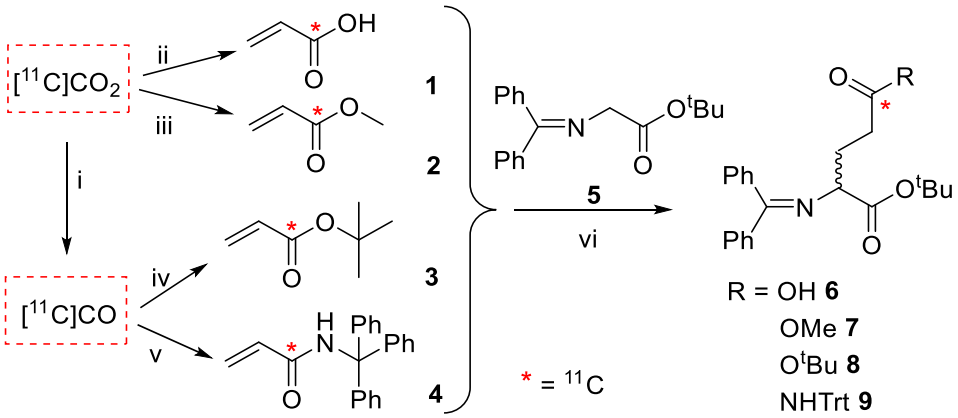
Introduction

Positron emission tomography[1] (PET) is an important technique that allows the study of biological and physiological processes at the molecular level *in vivo.* To perform PET imaging the availability of the desired PET tracers, compounds labeled with a positron emitting nuclide and administered in trace amounts to the study subject, is crucial. New radiochemistry methodology is needed to enable the development of novel PET imaging agents. Therefore, the development of synthesis methods for the introduction of positron-emitting radionuclides into molecules to yield PET agents is important and thus an active area of research. With respect to frequently used PET radionuclides, carbon-11 (100 % β^+, $t_{1/2}$ = 20.4 min)[2] is one of the most used for tracer development due to the ubiquity of carbon in all organic molecules. The challenge in working with carbon-11 is the short half-life and thus fast synthesis procedures are needed. The total synthesis time, including purification and formulation, should be limited to approximately 3 half-lives. Currently, most carbon-11 radiolabeling procedures performed are methylations by alkylation reactions with halogenated carbon-11 labeled reagents, or more activated [^{11}C]methyl triflate, further carboxylation reactions from [^{11}C]CO_2 or palladium-catalyzed [^{11}C]CO insertion reactions.[3–5] Other carbon-11 labeling reactions are known, but hardly applied for PET tracer development.[6]

In this paper we describe the potential of Michael addition reactions where the Michael acceptor is labeled with carbon-11. This reaction has been proposed by Antoni *et al.*, however its potential in radiosynthesis has not been further demonstrated.[7] To this end, we have synthesized functionalized ^{11}C-acrylesters and ^{11}C-acrylamides as versatile radiolabeling reagents and investigated their subsequent use as Michael acceptors, a novel radiochemical methodology to form ^{11}C-C bonds and potentially novel PET imaging agents. Moreover, by the formation of a ^{11}C-C bond, this reaction has the potential to form novel chiral centers, which is a unique challenge for radiochemistry development. As proof-of-concept, the focus was laid on the radiosyntheses of the amino acids (AAs) [^{11}C]glutamate and [^{11}C]glutamine by making use of the Michael addition with the corresponding ^{11}C-acrylester and an activated glycine Schiff base precursor.

To synthesize the desired ^{11}C-labeled synthons for the Michael additions, two methods have been investigated. The first approach to develop ^{11}C-acrylesters made use of Grignard reactions between different vinyl magnesium halides and [^{11}C]CO_2, followed by quenching with a nucleophile to obtain the Michael acceptor acrylic acid **1**[8] or the methyl acrylate **2** for further synthesis. Carbon-11 labeled acrylic acid and its methyl ester, **1** and **2,** have been reported

before, however only in low molar activity[1] (A_M). Furthermore, the application of these reagents was limited to 1,2-additions. The second approach implemented here is a Pd-mediated carbonylation reaction with [^{11}C]CO to obtain acrylester **3** and acrylamide **4**.[9,10] Another advantage, when applying the second methodology is the low isotopic dilution when making use of [^{11}C]CO compared to [^{11}C]CO_2, which in general yields higher A_M. The more widespread application of [^{11}C]CO became available in 2013 when Eriksson *et al.* published a simplified procedure for the transfer of [^{11}C]CO making use of xenon gas as well as Dahl *et al*. introducing xanthpos as trapping support agent, which caused a major breakthrough.[10,11] Moreover, nowadays also alternative procedures have been published to obtain [^{11}C]CO from [^{11}C]CO_2 using simplified and straightforward methodologies.[5,12–14]



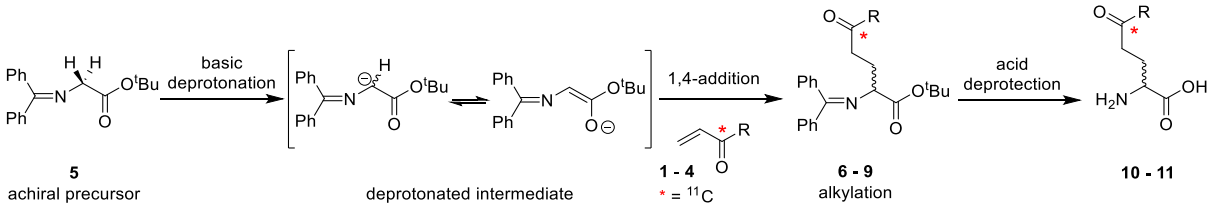
Scheme 1. Online transformations possible in carbon-11 chemistry: i) Reduction with molybdenum at 850 °C; ii) Coupling of [^{11}C]CO_2 with Vinyl-MgBr and quenching with water; iii) Coupling of [^{11}C]CO_2 with Vinyl-MgBr, after addition of sulfuric acid and methanol; iv) Coupling of [^{11}C]CO with Vinyl-I and Pd-xantphos with *tert*-butanol; v) Coupling of [^{11}C]CO with Vinyl-I and Pd-xantphos with tritylamine, vi) Michael addition with base.

As exemplified in Scheme 1, for the Michael addition with ^{11}C-acrylesters, the reactivity and thus the versatility of these reagents was investigated by reaction with Schiff base glycine derivatives (**5**) as Michael donor. A functional AA is created being [^{11}C]glutamate, [^{11}C]glutamine or derivatives thereof by exploiting this Michael addition to the Schiff base. Michael addition reactions are also known as 1,4-additions, where the C-C bond-forming ability is employed traditionally by an enolate that reacts with an α,β-unsaturated carbonyl compound (Scheme 2). An additional challenge for the Michael reactions explored in this paper is that the AAs formed are chiral molecules. For this reason the chiral induction during the Michael

[1] Molar activity: measured radioactivity per mole of compound (GBq·μmol^{-1}) readjusted from specific activiy.

addition is explored by using phase-transfer catalysis (PTC). The asymmetric radiolabeling approach with highly specialized chiral catalysts is unique and highly valuable to radiolabel chiral compounds. To date, this methodology has been successfully described in radiosynthesis of [^{11}C]alanine[15] and [^{11}C]phenylalanine[16], as well as for dipeptides (EurJOC, submitted) and tetrapeptides[17]. In addition, the asymmetric Michael addition[18,19] has been explored in ^{12}C-organic chemistry, however this challenging radiosynthesis method is unprecedented in radiochemistry thus far.

In this paper we will describe the syntheses, optimization and application of ^{11}C-acrylesters and ^{11}C-acrylamides **1** – **4** as reagents to be applied in Michael addition reactions for the development of PET imaging agents as exemplified by products **6** – **11**.



Scheme 2. Proposed mechanism of a racemic alkylation of a Schiff base for AA synthesis.

Results & Discussion

Radiosynthesis of ^{11}C-acrylesters using a Grignard reaction

First focus was to obtain ^{11}C-acrylesters by performing a Grignard reaction between vinyl magnesium bromide, which is reacted with cyclotron produced [^{11}C]CO_2 followed by quenching with a nucleophile to obtain [^{11}C]acrylic acid or [^{11}C]methyl acrylate.[8,20] The optimization led to quantitative trapping of [^{11}C]CO_2 from the transfer lines in a solution of vinyl magnesium bromide as reagent in THF at low temperatures. A reaction was achieved by increasing the temperature to room temperature (rt) over a period of 2 min with a constant He-flow of 10 mL·min^{-1}. The reaction mixture was quenched with 2M HCl and this resulted in the radiosynthesis of [^{11}C]**1** as reagent to be used in Michael addition reactions. The radiochemical conversion to product in the crude reaction mixture, determined by analytical HPLC and defined as radiochemical purity (RCP) to compound [^{11}C]**1** was satisfying 50-70 %.

In addition to the radiosynthesis of [^{11}C]**1**, the reaction conditions have been modified as such that acrylic esters could be formed as well. Therefore, the magnesium acrylic acid formed in

the Grignard reaction between vinyl magnesium bromide and [^{11}C]CO_2, was quenched with methanol and sulfuric acid and allowed the esterification of the product to obtain [^{11}C]**2** with a RCP between 65-78 % determined by analytical HPLC. Purification from the crude reaction mixture was achieved by distillation at 90 ºC into a cooled second reaction vial yielding highly purified [^{11}C]**2**. The average isolated radiochemical decay corrected (d.c.) yield obtained for this two-step reaction was 21-23 %, resulting in 0.43-0.47 GBq of product after 15 min synthesis time starting from 2.0 GBq [^{11}C]CO_2 (N=5).

Radiosynthesis to obtain [^{11}C]*tert*-butylacrylate and [^{11}C]*N*-tritylacrylamide

To investigate the radiosynthesis of other functionalized ^{11}C-acrylesters and to be able to obtain ^{11}C-acrylamides, the focus shifted to Pd-catalyzed carbonylation reactions with [^{11}C]CO. To be able to perform these reactions, first the reduction from [^{11}C]CO_2 to [^{11}C]CO was performed according to the procedures described by Eriksson *et al.* and Van der Wildt *et al*.[11,21] Here [^{11}C]CO_2 was reduced to [^{11}C]CO by passing it online through a molybdenum filled column heated to 850 °C. The product was collected on a silica trap that was cooled in liquid N_2. Unreacted [^{11}C]CO_2 was removed by trapping it on an ascarite trap. For optimal transfer of [^{11}C]CO to the reaction vial, the silica trap was heated to release the [^{11}C]CO and with a gentle flow of xenon (3.0 mL·min^{-1}) the [^{11}C]CO was efficiently transferred to the previously charged and sealed reagent vial for carbonylation. Making use of the Pd-catalyzed carbonylation reactions with [^{11}C]CO, the radiosyntheses of [^{11}C]*tert*-butylacrylate **3** and [^{11}C]*trityl*-acrylamide **4** were investigated.[9]

As summarized in Table 1, initially the synthesis of acrylester [^{11}C]**3** and acrylamide [^{11}C]**4** were examined making use of $Pd_2(dba)_3$ as a catalyst in the presence of PPh_3 as supporting ligand. However, only low conversions were observed using this strategy (Table 1: Entry 1-3, 6). The trapping efficacy of [^{11}C]CO in THF supported with xantphos was more successful.[10] The optimal radiochemical conversion obtained to synthesize acrylester [^{11}C]**3** and acrylamide [^{11}C]**4** were established using $[(Cinnamyl)PdCl]_2$ as a catalyst[22] (Table 1: Entry 4-5, 9) and the RCP for either synthon was >75 % and amounted to isolated radiochemical yield of [^{11}C]**3** to 0.41-0.45 GBq (18-20 % d.c. yield, 25 min, N=2) and 0.42-0.44 GBq of [^{11}C]**4** (22-23 % d.c. yield, 25 min, N=3) from 2.5 GBq of [^{11}C]CO_2.

Table 1. RCPs for the synthesis of **[^{11}C]3** and **[^{11}C]4** with [^{11}C]CO.

#[a]	Product	Vinyl halide (µmol)	Pd-source (µmol)	Ligand (µmol)	RCP ± SD (%)
1[b]	[^{11}C]**3**	Vinyl bromide (20)	[$Pd_2(dba)_3$] (2.4)	PPh_3 (20)	45.0 ± 5.1 (N=2)
2		Vinyl bromide (65)	[$Pd_2(dba)_3$] (10)	PPh_3 (20)	11.2
3		Vinyl bromide (10)	[$Pd_2(dba)_3$] (1.2)	PPh_3 (10)	2.0
4		Vinyl iodide (10)	[(Cinnamyl)PdCl]$_2$ (7)	$AsPh_3$ (56)	80.2 ± 5.2 (N=2)
5			[(Cinnamyl)PdCl]$_2$ (7)	Xanthpos (7)	79.0 ± 10.0 (N=15)
6[c]	[^{11}C]**4**	Vinyl bromide (20)	$Pd_2(dba)_3$ (2.4)	PPh_3 (20)	14.3 ± 2.1 (N=2)
7[d]		Vinyl iodide (10)	[(Cinnamyl)PdCl]$_2$ (7)	$AsPh_3$ (56)	75.1 ± 1.2 (N=2)
8[c]			[(Cinnamyl)PdCl]$_2$ (7)	Xanthpos (7)	9.0 ± 6.2 (N=2)
9[d]					73.0 ± 5.0 (N=10)

[a]Reaction performed in THF 450 µL for 3-5 min at 100 ºC; [b]*t*-BuOH: Entry 1-3 2600 µmol; 4-5: 2100 µmol; [c]Tritylamine 20 µmol; [d]Tritylamine 96 µmol.

Successful [^{11}C]CO insertion reactions are dependent on the use of high concentrations of the nucleophile, *tert*-butanol (*t*-BuOH) for the radiosynthesis of [^{11}C]**3** and tritylamine for [^{11}C]**4**. The high amount of *t*-BuOH used is due to its technical handling losses, and its ability as solvent. For the radiosynthesis of acryl amides, solid tritylamine was used. Since this cannot be added in such great excess, lower quantities (Table 1: Entry 6; 8) were used but proved to be low yielding, therefore minimal amount of 96 µmol was found to be required in the reaction.

The A_M of product [^{11}C]**4** determined after preparative purification was high and ranged from 86-170 GBq·µmol^{-1} starting with an activity of approximately 2.5 GBq of [^{11}C]CO_2. Also [^{11}C]**3** was isolated on preparative scale with a minimum calculated A_M of 53.4 GBq·µmol^{-1}; however, due to the low UV absorbance of [^{11}C]**3** no A_M with acceptable precision could be determined experimentally.

^{11}C-acrylates, however proved to be unstable, which was investigated by radioHPLC while mimicking the reaction conditions of the Michael addition in the presence of high

amounts of base like $CsOH \cdot H_2O$.[15,23] The radiosynthesis of synthons [^{11}C]**3** and [^{11}C]**4** was performed according to the optimized procedure and subsequently the synthons were added to various amounts of $CsOH \cdot H_2O$ (2.0-8.9 M) in toluene. The samples were left for 5 min at rt and at 100 ºC before the analysis, results are listed in Table 2.

Table 2. Stability of [^{11}C]**3** and [^{11}C]**4** with $CsOH \cdot H_2O$ at rt and 100 ºC.

#[a]	T (ºC)	$CsOH \cdot H_2O$ (M)	[^{11}C]**3** (% intact)	[^{11}C]**4** (% intact)
1	20	2.0	71.6 ± 4.5	82.0 ± 2.0
2		8.9	31.0 ± 3.2	79.5 ± 6.5
3		/	79.0 ± 10.0	73.0 ± 5.0
4	100	2.0 or 8.9	0	43.0
5		/	76.2 ± 3.0	72.5 ± 3.0

[a]Reaction performed in 100 µL of toluene; N=2.

The major decomposition product of [^{11}C]**3** is [^{11}C]acrylic acid, which was confirmed by HPLC (see Supporting Information). If the solution was heated to 100 ºC for 5 min no [^{11}C]**3** could be detected at the end of the reaction. In contrast, [^{11}C]**4** showed minimal decomposition at rt, also in the presence of high amounts of $CsOH \cdot H_2O$. The stability, even at higher temperatures, is better compared to [^{11}C]**3** and still 43 % were intact after 5 min. This can be explained by the resonance stability of the amide which is stronger compared to esters. Notwithstanding these limitations, with the carbon-11 labeled acrylates **1** – **4** in hand the potential of these reagents was explored in Michael addition reactions.

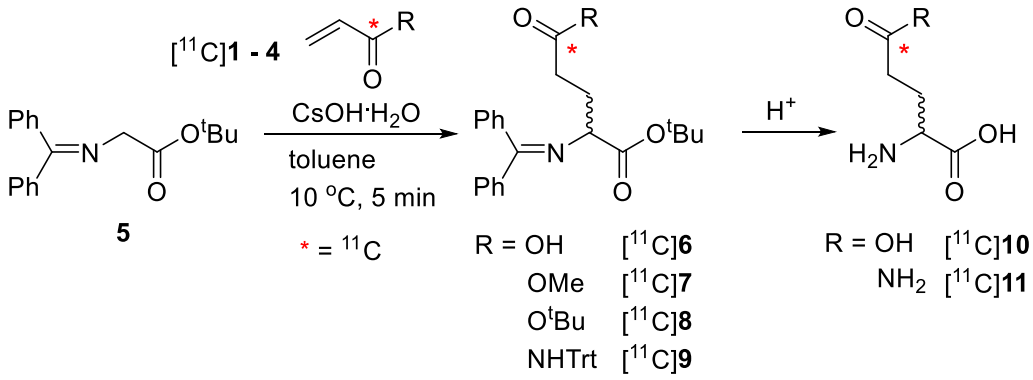
Michael addition reaction

Initially, the Michael reactions (Scheme 3) were performed without intermediate purification of the carbon-11 labeled acrylic derivatives; however, no conversion to Michael adducts was observed. Since it was expected that the impurities in the crude reaction mixture obstructed successful Michael additions, various purifications of the ^{11}C-acrylates were explored. Purification of [^{11}C]**2** was simply achieved by distillation. Unfortunately, this approach was not successful for [^{11}C]**1,** [^{11}C]**3** and [^{11}C]**4.** Solid-phase purification of the latter compounds were evaluated utilizing C18 and Alumina N SepPaks with a PTFE-filter, but were unsuccessful. Finally, passing the reaction mixture over custom made cartridge loaded with approximately 200 mg of Celite afforded [^{11}C]**3** and [^{11}C]**4** in sufficient purity to allow its use in Michael reactions.

Racemic Michael addition with synthons [^{11}C]1 and [^{11}C]2

After optimizing the radiosynthesis procedures to obtain the ^{11}C-acrylesters, [^{11}C]**1** was used as a Michael acceptor with the Schiff base precursor **5** as donor. Whereas acidic conditions were used for the hydrolysis of the magnesium-acrylester salts to obtain [^{11}C]**1**, an initial challenge was changing to basic conditions, which are needed for the second reaction, the C-C bond forming to the glycine moiety. In acidic reaction conditions, the Schiff base enolate cannot be formed and the reaction of the donor to the acceptor will not proceed. Likewise, no reaction occurred in highly basic conditions leaving unreacted **5**, which is likely to be caused by the low acceptor ability of [^{11}C]**1**.

However, utilizing distilled [^{11}C]**2**, the Michael addition reaction yielding [^{11}C]**7** was successful, as described in Scheme 3. For evaluation of the reactivity of [^{11}C]**2**, reactions were successfully performed with **5** in DMSO and TBAF (tetrabutyl ammonium fluoride) as base, reaction conditions that have also been used by Kato *et al.*[24] to alkylate **5**. The reaction was successful with overall conversion yields of up to 90 % determined by analytical radioHPLC. In addition to TBAF as an organic base, inorganic alkali-metal bases were explored to deprotonate **5** and perform the Michael additions. Alkali-metal bases were selected due to their widespread application in asymmetric syntheses.[23] However, hydrolysis of [^{11}C]**2** was mainly observed with $CsOH{\cdot}H_2O$ or KOH. Evidently, this competing reaction turned out to be faster than the Michael addition reaction, resulting in a drop in yields. Nonetheless, 10-15 % RCP of [^{11}C]**10** were obtained, assessed by chiral radioHPLC after the acidic deprotection of the imine and *tert*-butylester.



Scheme 3. Michael addition reaction with synthon **1** - **4** to obtain Michael addition products.

These results further support the suitability of Michael addition reactions in the development of PET imaging agents for advanced carbon-11 labeled synthesis. The

applicability of this reaction has certain limitations. For instance, the reaction to obtain [^{11}C]**6** did not occur and the reaction to obtain [^{11}C]**7** was only possible with TBAF as a base. In order to overcome these issues, the research was further focused on the synthesis of [^{11}C]**8** and [^{11}C]**9**, utilizing [^{11}C]**3** and [^{11}C]**4** that are evidently more stable under previously described reaction conditions.

Racemic Michael addition with synthons [^{11}C]3 and [^{11}C]4

The concentration of precursor **5**, reaction time, type and amount of base and reaction temperature were initially optimized for [^{11}C]**8** and [^{11}C]**9** in order to obtain high ^{11}C-C addition yields. The effect of the precursor concentration was also investigated, using TBAF as a base. An increased amount of Schiff base **5** ranging between 170-330 mM was necessary to obtain higher RCPs. These high concentrations are attributed to the decomposition of **5** to benzophenone and glycine *tert*-butylester. Alkylation of **5** with [^{11}C]**3** according to procedures earlier described[24,25] was successful and yielded RCPs of 93.2 ± 5.7 % (N=5) and 78.1 ± 3.0 % (N=3) for [^{11}C]**8** and [^{11}C]**9** with TBAF (0.33 mM) in DMSO at 100 ºC for 5 min, respectively.

Solid inorganic bases for Michael reaction

As stated previously, alkali-metal bases are preferred in chiral PTC reactions, consequently various inorganic alkali-metal bases (Table 3), which are described in literature have been screened for their alkylation potential in toluene at 10 ºC, thus far optimal conditions for chiral reactions.[15] Generally, lower temperatures are favored in PTC reactions to enhance stereoselecitivity, therefore we focused with inorganic bases on lower temperatures. Due to a solid-liquid phase reaction taking place, a sufficient interfacial area between the two phases needs to be created by vigorous stirring.

Table 3. Michael alkylation reactions with different bases to obtain [^{11}C]**9**.

#[a]	Base	Equiv.[b]	RCP ± SD (%)	N
1	KOH	5.9	< 2	4
2	KOH	10.5	< 2	4
3	P1-*t*Bu	5.0	< 1	4
4	RbOH	9.8	< 2	2
5	RbOH	14.0-19.0	< 5	4
6	RbOH[c]	14.0-19.0	21.1 ± 5.8	2

7	$CsOH·H_2O$	10.5	51.2 ± 30.0	9

[a]Reaction performed with 170 mM **5** in toluene at 10 °C for 5 min; [b]Compared to **5**; [c]Reaction performed at 50 °C.

From these experiments it was concluded that $CsOH·H_2O$ as base in the reaction is superior over other alkali-metal bases investigated. Furthermore, the relative small variation in equivalents – also due to strong hygroscopicity of inorganic bases used, did not influence the outcome of the reaction to product (Table 3: Entry 1-2, 4-5). Remarkably, rather modest conversions were observed, in contrast to previously reported results in organic chemistry.[18,26,27] This is presumably caused by the reaction time, since in carbon-11 radiosynthesis only rapid reactions can be considered due to the half-life of 20 min, whereas in organic chemistry longer reaction times are feasible.

Kinetic analysis to obtain [^{11}C]9

To establish an improved procedure for the production of [^{11}C]**9**, a kinetic analysis was performed. Samples were taken from the start of reaction until 5 min, which was confirmed as optimal reaction time (Figure 1 A).

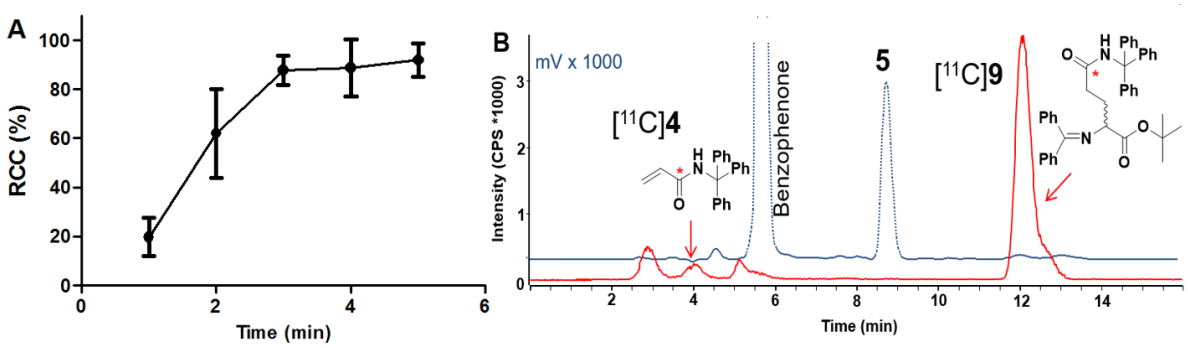


Figure 1. A) Kinetic analysis of the formation of [^{11}C]**9** as function of reaction time, assessed with HPLC; B) Exemplified radiochromatogram of the crude reaction mixture after 5 min.

By utilizing radio-TLC over HPLC we have monitored the entire reaction to overcome the breakdown of aqueous sensitive intermediates, thereby confirming the stability and availability of the Schiff base (see Supporting Information: Stability of **5**). We observed precursor **5** consistently during the reaction, however also the presence of the decomposition product benzophenone was detectable. Despite of the decomposition, seemingly there was enough precursor **5** available for the Michael addition and benzophenone did not disturb this reaction.

It was important to bear in mind to add precursor **5** as late as possible to the reaction mixture for the Michael addition. Furthermore, between 50-100 nmol (low μM) of labeling reagent is typically used, resulting in large excess of non-radiolabeled reagents which are typically in the μmol (mM) range. These non-stoichiometric reaction conditions can result in the operation of pseudo-first order kinetics with respect to the non-labeled reagents employed. In spite of the fact that the amount of ^{11}C-labeled reagent is fairly stable, the synthons were steadily decomposing as well, resulting in variations in RCP. However, once product [^{11}C]**8** or [^{11}C]**9** were formed, they were stable.

So far a 10-fold excess of base (CsOH·H_2O) to Schiff base precursor **5** was used in this type of reactions[15] and since [^{11}C]**4** is more stable with higher quantities of base, the Michael addition reactions were investigated with elevated base concentrations, see Table 4. Increasing the amount of base resulted in significantly lower yields which most probably is caused by decomposition of [^{11}C]**4**. Regarding the synthesis of [^{11}C]**8**, stability experiments already showed that higher amounts of base led to partial decomposition of reagent [^{11}C]**3**, so further experiments were abandoned. To conclude, 10.5 equivalents of base relative to **5** gave the best results.

Table 4. Radiosynthesis of [^{11}C]**9** with varying amounts of CsOH·H_2O.

#[a]	CsOH·H_2O equiv.[b]	RCP (%)	N
1	10.5	51.2 ± 30.0	9
2	15.3	34.4 ± 13.2	2
3	20.9	30.6 ± 12.7	2
4	105	33.8 ± 6.1	4

[a]Reaction performed with 170 mM of **5** in toluene at 10 °C for 5 min; [b]Compared to **5**.

Reactions of most suitable synthons with phase-transfer catalysts

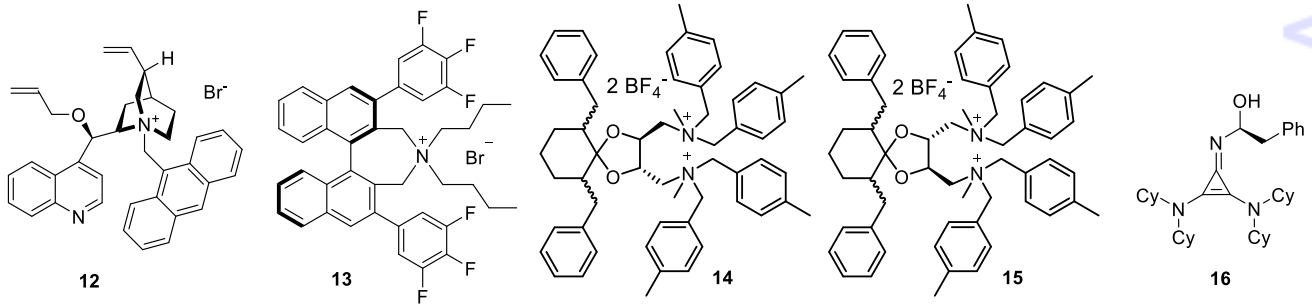
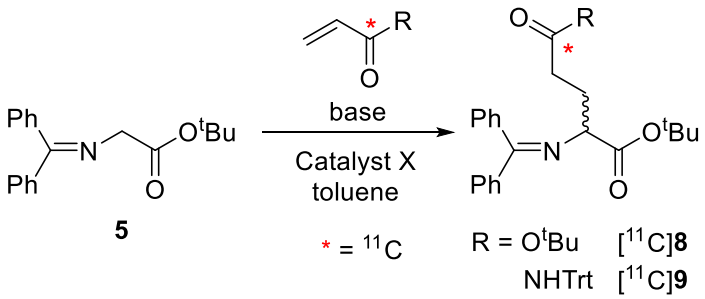


Figure 2. Chiral PTCs explored in PTC reactions for Michael additions: quaternary ammonium salt **12** and **13**; tartare-derived catalyst **14** and **15**; Brønsted base **16**.

In order to induce an enantioselective Michael addition reaction, the application of chiral PTCs was investigated as described in literature in organic chemistry.[18,23,28] With regard to the constraints presented in radiochemistry like time as limiting factor, as well as the non-catalytic reaction conditions in which the chiral catalysts are used in stoichiometric amounts compared to the precursor material and in excess of the ^{11}C-labeled reagent, the translation of PTC reaction conditions to radiochemistry has been challenging.[15–17]



Scheme 4. Asymmetric Synthesis of Michael addition products.

In Table 5, results are summarized of asymmetric synthesis with the various catalysts that were commercially available.[15,16]

Table 5. RCP (in % ± SD, N ≥ 2) of alkylation with synthons to obtain [^{11}C]**8** and [^{11}C]**9**.

#[a]	Product	Temp (°C)	Cat 12	Cat 13	Cat 14	Cat 15	Cat 16
1	[^{11}C]**8**	20	31.1 ± 29.1	n.d.	23.2 ± 16.5	1	n.d.[b]
2		10	32.1 ± 21.1	28.8 ± 0.4	44.1 ± 21.4	42.6 ± 6.7	
3	[^{11}C]**9**	20	31.0± 7.2	5.4 ± 2.8	37.6 ± 25.3	n.d.	2
4		15	18.4	16.5 ± 4.4	5.3 ± 2.9		n.d.
5		10	16.3 ± 13.3	33.8 ± 6.1	15.5 ± 13.4		0

[a]Reaction performed with 170 mM of **5**; 10.5 equiv. of $CsOH{\cdot}H_2O$ in toluene with 0.1 mol% of Cat at 10 ºC for 5 min with vigorous stirring; [b]n.d. not determined.

With RCPs not exceeding 50 % all reactions resulted in moderate conversions for both [^{11}C]**8** and [^{11}C]**9** (Table 5), however with lower temperature the conversions were slightly higher. Tartrate-derived catalysts **14** and **15** resulted in good enantiomeric ratios in Michael addition reactions in organic chemistry[19,29-30] and this was also observed under radiochemistry conditions. Catalysts **12** and **13** gave unsatisfactory results, hardly any enantiomeric enrichment was observed in contrary to results obtained for previous studies to obtain L-[^{11}C]alanine.[15] Furthermore, during the conduct of the study Bander *et al.* introduced the concept of using a

chiral Brønsted base **16** capable of catalyzing proton transfer reactions enantioselectively.[31] Unfortunately, it was not possible to reproduce these results under radiochemistry conditions. Ultimately, the difference in the asymmetric radiochemistry reactions presented so far in literature, is the formation of a new C-C bond, which is an alkylation reaction with a reactive alkylating agent and in the latter an 1,4-addition with constraints concerning availability of ^{11}C-reagent and stability issues.

The enantiomeric ratio obtained with catalyst **14** (Figure 3) is presented in Table 6. These were determined with chiral HPLC of the resulting AAs after complete deprotection with 0.1 mL of 6M HCl and heating to 100 ºC for 2 min.

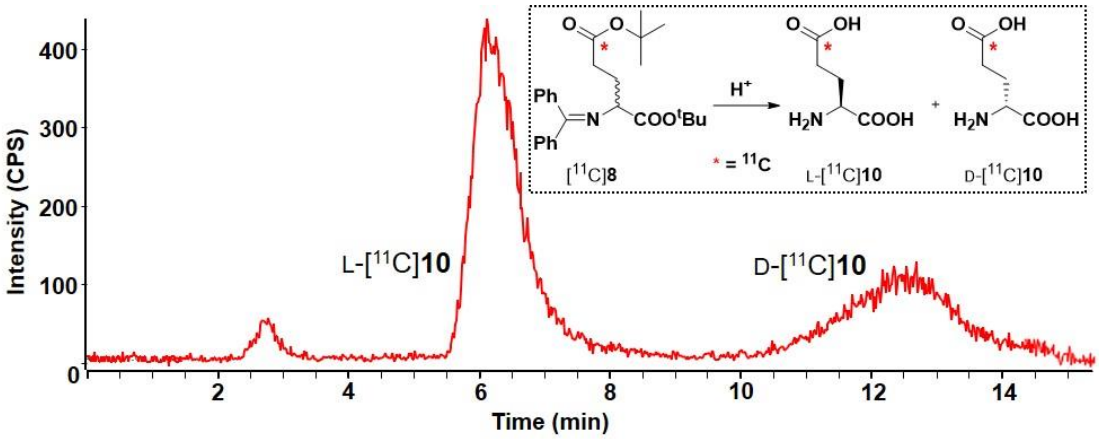


Figure 3. Analysis of L-and D-[^{11}C]**10** with chiral radioHPLC.

Table 6. Enantiomeric ratio (in %, ± SD, N ≥ 2) of L-and D-[^{11}C]**10** with Cat **14**.

#[a]	Equiv. of 14	L-[^{11}C]Glu	D-[^{11}C]Glu
1	/	51 ± 3	49 ± 3
2	0.1	60 ± 5	40 ± 5
3	0.5	61 ± 4	39 ± 4

[a]Reactions performed with 170 mM of **5** in 100 µL of toluene with 12-14 equiv. $CsOH \cdot H_2O$ at 10 ºC for 5 min.

The enantiomeric ratios are lower compared to traditional ^{12}C-organic chemistry procedures, where longer reaction times are possible, furthermore lower temperatures are applied to obtain excellent enatiomeric ratios. From Table 6 it can be concluded that the catalyst positively influenced the ratio towards the desired enantiomer, compared to no catalyst in the reaction mixture (Table 6: Entry 1). Nevertheless, it was not possible to obtain satisfactory enantiomeric ratios for the synthesis of [^{11}C]**10**. Therefore, studies to obtain enantomerically enriched [^{11}C]**11** with synthon [^{11}C]**4** were not explored. Unarguably, the asymmetric syntheses

with presented catalysts have not been as successful and we believe the distorted conditions led to the catalyst-enolate complex not forming properly. Regardless, a new methodology for the formation of a covalent ^{11}C-C bond has been explored and presents new strategies for AA synthesis.

Furthermore, a reason for the variation in RCP might be the Pd-ligand complex, utilized in the [^{11}C]CO insertion reaction, which cannot be completely removed from the reaction via the celite purification. As a control experiment, we have synthesized [^{11}C]alanine[15] and added the same Pd-ligand complex to the phase-transfer catalyst alkylation reaction in approximately the same amount. The addition of the Pd-complex caused a complete depletion of yield compared to the original conditions, thereby proving the negative influence of the Pd-complex on the alkylation reaction (details in Supporting Information). Presumably the phase-transfer catalyst and the Pd-complex are not compatible and hindering the reaction by either not activating **5** to form the enolate or/and cause de-activation of catalyst.

Conclusion

Here we have demonstrated for the first time the feasibility of Michael addition reactions in radiochemistry, where the Michael acceptor was labeled with carbon-11 after reaction with an acrylate. The Michael addition creates new possibilities for the synthesis of carbon-11 labeled PET tracer candidates. Further research is ongoing for the enantioselective Michael addition radiosynthesis.

Acknowledgements

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Material & Methods

General

All chemicals were purchased from commercial sources (Sigma Aldrich (Zwijndrecht, The Netherlands), Bachem (Bubendorf, Switzerland), ABCR (Karlsruhe, Germany), Santa Cruz Biotechnology (Bio-Connect B.V., Huissen, the Netherlands)) and used without further purification. Solvents were purchased from Biosolve (Valkenswaard, the Netherlands) and used as received unless stated otherwise. Reactions were monitored by thin layer chromatography on pre-coated silica 60 F254 aluminum plates (Merck, Darmstadt, Germany). Spots on TLC were visualized by UV light and staining with ninhydrine and potassium permanganate solutions. Solvents were evaporated under reduced pressure using a rotary evaporator (Rotavapor® R II, Flawil, Switzerland). Flash chromatography purifications were performed on a Buchi operated by SepacoreControl system. Non-radioactive reference compounds were synthesized according to reported methods and were used to verify the identity of the radiolabeled products.

^{1}H and ^{13}C Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AC 500.23, 400.13 or 250.13 MHz (Billerica, USA) and chemical shifts (δ) were defined relative to the signal of the solvent (7.27 ppm for $CDCl_3$, 3.31 ppm for MeOH-*d4* , 2.50 ppm for DMSO-*d6*). High resolution mass spectra (HRMS) were carried out using a Bruker microTOF-Q instrument in positive or negative ion mode (capillary potential of 4500 V). Analytical HPLC systems used were equipped with: a Waters 600E pump, a manual Rheodyne injector (20-100 µL loop), a Waters PDA and GinaStar software from Raytest (Germany). The radioactive profile was monitored with a Raytest 2.5 inch radioactivity detector (Raytest, Germany). Small synthons [^{11}C]**1** - **4** were analyzed with a Grace Smart C18 HPLC column obtained from Grace Alltech (4.6 x 250 mm, 5 µm) with acetonitrile/sodiumformate 4 mM + 4 % DMF (buffer 1) (68/32, *v/v*) as eluent unless stated otherwise. Michael adducts [^{11}C]**6** - **9** were measured on a Great Smart (4.6 x 250 mm, 5 µm; formerly known as Grace Smart, Dr. Maisch, Ammerbuch, Germany) with acetonitrile/buffer 1 (65/35, *v/v*) or as stated otherwise, UV monitoring at 254 nm. Flow rates for all HPLC analysis were 1 $mL \cdot min^{-1}$ unless stated otherwise. HPLC preparative purification of synthons [^{11}C]**3** and [^{11}C]**4** was performed on Alltima C18 (22 x 250 mm, 10 µm) with acetonitrile/buffer 1 70/30 (*v/v*) with a flow of 4 $mL \cdot min^{-1}$. Enantiomeric purity of the products [^{11}C]**10 – 11** was determined using an analytical Reprosil chiral-AA (4.6 x 250 mm) from Dr. Maisch GmbH at 214 nm. The product was eluted with methanol/water (70/30 or 90/10, *v/v*).

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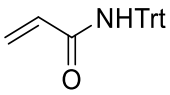
Radiochemical conversion was determined by HPLC analysis as the percentage of converted carbon-11 labeled reagent to the desired product in the crude reaction mixture, which is based on the AUC of the radioactivity profile, using analytical HPLC and expressed here as Radiochemical purity (RCP). Radiochemical yield (RCY) is the amount of radioactivity in the product expressed as the percentage of related starting radioactivity used in the corresponding synthesis. RCY was calculated as the quotient of measured activity of the isolated product at the end of synthesis (EOS) and the measured activity at the end of the cyclotron bombardment (EOB) in the vessel at the beginning of the synthesis, both measured in a dose calibrator, and expressed as a percentage. Radiochemical yield has been corrected for decay from EOB, no other corrections for radioactivity losses have been made.

Molar activity (A_M) of the radioactive intermediates (e.g. [^{11}C]**4**) after preparative HPLC purification was determined by measurement of the UV absorbance of a known amount of radioactivity under identical analytical HPLC conditions used to generate a molar calibration curve for the corresponding non-radioactive standard.

Synthesis of reference compounds

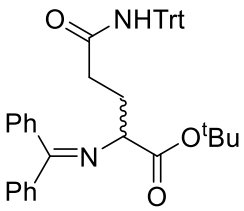
Tritylacrylamide **4**[32]



Acrylamide (500 mg, 7.030 mmol), triphenylmethanol (964 mg, 3.700 mmol) and *para*-toluenesulfonic acid monohydrate (444 mg, 2.330 mmol) were refluxed in 100 mL of toluene. After 4 hours, the solution was cooled to room temperature and quenched with 50 mL of 2 % aqueous sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with water and brine. After drying over sodium sulfate (Na_2SO_4) and evaporating the solvent, the product was purified on a silica column (hexane/ethyl acetate, first 5:1 then 1:1) affording 935 mg (2.980 mmol, 81 %) of colorless crystals.

^{1}H-NMR (500.13 MHz, $CDCl_3$): δ = 7.34-7.23 (m, 15H, 3x –Ph), 6.27 (dd, 2H, *J*=5.0, 2.5 Hz, =CH_2), 5.67 (dd, 1H, *J*=5.0, 2.5 Hz, –CH) ppm; ^{13}C-NMR (125.62 MHz, $CDCl_3$): δ = 164.45, 144.55, 131.43, 128.72, 128.03, 127.13, 70.66 ppm; HRMS (ESI) calculated for $C_{22}H_{19}NO$: 314.1545 $[(M+H)]^+$, found: 314.1520 $[(M+H)]^+$, 336.1343 $[(M+Na)]^+$.

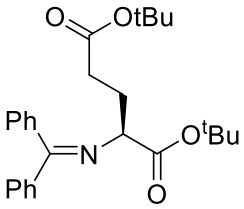
Tert-butyl 2-((diphenylmethylene)amino)-5-oxo-5-(tritylamino)pentanoate



N-(Diphenylmethylene)glycine *tert*-butylester (100 mg, 0.340 mmol) and N-tritylacrylamide (300 mg, 0.960 mmol) were dissolved in 3 mL of dimethylsulfoxide (DMSO). Additionally, 1 mL of 1 M solution of TBAF in tetrahydrofuran (THF) was added and the dark red solution was stirred for two hours at room temperature. After being diluted with 60 mL of diethyl ether, the organic phase was washed with H_2O (2 x 20 mL), brine (40 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica chromatography twice (1) 5-16 % ethyl acetate/hexane, (2) 0-15 % MeOH/DCM in 20 min, which afforded 48.0 mg of a light yellow solid (0.080 mmol, 23 %).

^{1}H-NMR (400.13 MHz, $CDCl_3$): δ = 7.67 (d, 2H, *J*=8.0 Hz, –Ph), 7.35-7.23 (m, 15H, 3x –Ph), 7.20-7.16 (m, 8H, 2x –Ph), 4.03 (t, 1H, *J*=8.0 Hz, –CH), 2.40-2.36 (m, 2H, $–CH_2$), 2.29-2.25 (m, 2H, $–CH_2$), 1.44 (s, 9H, 3x $–CH_3$) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ = 171.36, 170.87, 144.77, 139.50, 136.44, 132.40, 130.33, 128.78, 128.69, 127.90, 126.94, 81.24, 65.06, 34.20, 29.58, 28.05 ppm; HRMS (ESI) calculated for $C_{41}H_{40}N_2O_3$ 609.3117 $[(M+H)]^+$, found: 609.3046 $[(M+H)]^+$.

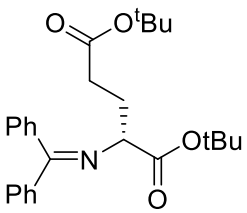
(S)-Di-*tert*-butyl 2-((diphenylmethylene)amino)pentanedioate



N-(Diphenylmethylene)glycine *tert*-butylester (200 mg, 0.680 mmol) and the phase transfer catalyst **12** (40 mg, 0.030 mmol) were dissolved in 2 mL DCM and 0.4 mL of 50 % (w/w) potassium hydroxide solution was added. *Tert*-butyl acrylate (87 mg, 0.677 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature. After dilution with 120 mL of ethyl acetate the organic phase was washed with H_2O (2 x 40 mL), brine (80 mL), dried over Na_2SO_4 and concentrated in vacuo. By purification of the residue by silica chromatography (20:1 to 5:1 hexane/ethyl acetate) 196 mg (0.463 mmol, 68 %) of a colorless oil could be obtained.

^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 2H, –Ph), 7.45-7.33 (m, 6H, –Ph), 7.21-7.18 (m, 2H, –Ph), 3.98 (t, 1H, *J*=2.5 Hz, –CH), 2.27-2.21 (m, 4H, 2x $–CH_2$), 1.46 (s, 9H, 3x $–CH_3$), 1.41 (s, 9H, 3x $–CH_3$) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ = 170.90, 170.59, 139.55, 132.42, 130.06, 128.81, 127.99, 127.81, 80.17, 64.98, 32.01, 28.89, 28.07 ppm; HRMS (ESI) calculated for $C_{26}H_{33}NO_4$: 424.2488 $[(M+H)]^+$, found: 424.2388 $[(M+H)]^+$, 446.2208 $[(M+Na)]^+$.

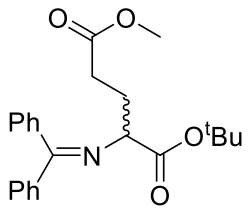
(R)-Di-*tert*-butyl 2-((diphenylmethylene)amino)pentanedioate



(R)-Di-*tert*-butyl 2-aminopentanedioate (200 mg, 0.770 mmol) was stirred overnight at rt with benzophenone imine (129 µL, 0.770 mmol) in DCM (5 mL). The solvent was evaporated and the mixture purified by flash chromatography (20:1 to 5:1 hexane/ethyl acetate) resulting in 308 mg of a colorless oil (0.730 mmol, 94 %).

^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 7.70-7.64 (m, 2H, –Ph), 7.46-7.38 (m, 6H, –Ph), 7.22-7.18 (m, 2H, –Ph), 4.00 (t, 1H, *J*=5.0 Hz, –CH), 2.31-2.21 (m, 4H, 2x – CH_2), 1.46 (s, 9H, 3x –CH_3), 1.41 (s, 9H, 3x –CH_3) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ = 172.47, 170.88, 139.58, 136.55, 130.24, 128.80, 127.98, 127.81, 80.06, 64.99, 32.01, 32.01, 28.91, 28.07 ppm; HRMS (ESI) calculated for $C_{26}H_{33}NO_4$: 424.2488 $[(M+H)]^+$, found: 424.2482 $[(M+H)]^+$.

1-(*Tert*-butyl)5-methyl 2-((diphenylmethylene)amino)pentanedioate



N-(Diphenylmethylene)glycine *tert*-butylester (100 mg, 0.340 mmol) and the catalyst **12** (20 mg, 0.030 mmol) were dissolved in 1 mL of DCM, then 0.2 mL of 50 % (*w/w*) aqueous potassium hydroxide solution was added dropwise and the mixture was cooled to -50 °C. A solution of methyl acrylate (0.1 mL, 1.097 mmol) in 0.2 mL DCM was added dropwise and stirred for 4 hours at -50 °C. After being diluted with 60 mL of diethyl ether, the organic phase was washed with H_2O (2 x 20 mL), brine (40 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica chromatography (hexane/ethyl acetate 20:1 to 5:1), which afforded the product as colorless oil (87.0 mg, 67 %).

^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 7.55-7.60 (m, 2H, –Ph), 7.21-7.40 (m, 6H, –Ph), 7.07-7.15 (m, 2H, –Ph), 3.90 (t, 1H, *J*=6.3 Hz, –CH), 3.52 (s, 3H, –OCH_3), 2.25-2.35 (m, 2H, –CH_2), 2.09-2.20 (m, 2H, –CH_2), 1.37 (s, 9H, 3x –CH_3) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ = 173.57, 170.68, 139.45, 136.45, 132.42, 130.32, 128.8, 128.44, 81.19, 64.79, 51.51, 30.51, 28.65, 28.04 ppm; HRMS (ESI) calculated for $C_{23}H_{27}NO_4$: 382.2018 $[(M+H)]^+$, found: 382.1967 $[(M+H)]^+$, 404.1788 $[(M+Na)]^+$.

Radiochemistry

[^{11}C]Acrylic acid 1

[^{11}C]CO_2 was transferred from the cooling trap to the reaction vessel with a helium flow of 10 mL·min^{-1}and trapped in 100 µL of a 0.2 M solution of vinyl magnesium bromide in THF, which was cooled to 7 °C. After 1 min, the temperature of the reaction vessel was raised to 25 °C and maintained for 2 min. The intermediate was hydrolyzed by adding 100 µL of 2 M HCl and a sample was taken from the solution for reverse phase HPLC analysis. RCPs were obtained in the range of 50-70 %. The identity of the labeled compound was confirmed by co-injection with the reference. [R_t(Grace Smart RP-18, MeCN/acetate buffer (pH 3.8) 96/4, 1 mL·min^{-1}, 254 nm) = 13.5 min]

[^{11}C]Methyl acrylate 2

The [^{11}C]CO_2 transfer and synthesis of the Grignard intermediate were conducted as described above. Hydrolysis was performed with 50 µL conc. sulfuric acid and 100 µL methanol were added. The vessel was heated to 70 °C and this temperature was maintained for 5 min while using a helium flow of 10 mL·min^{-1}. Then the temperature was raised to 90 °C and for a duration of 5 min the methyl ester was distilled in a second reaction vessel cooled to -10 °C. The distillate was diluted with 100 µL DMSO and a sample taken from the solution was analyzed by reverse phase HPLC. The distillate was obtained in RCP range of 65-78 %. The identity of the labeled compound was confirmed by co-injection with the cold reference. RCY obtained for this two-step reaction is based on the quality of the first reaction and starting from approximately 2.5 GBq a d.c. isolated yield of 19 % (0.47 GBq) was accomplished with a RCP of 98 % within 20 min [R_t(Grace Smart RP-18, MeCN/water 50/50, 1 mL·min^{-1}, 254 nm) = 4.0 min].

[^{11}C]*Tert*-Butyl acrylate 3

[^{11}C]CO_2 was converted to [^{11}C]CO on-line through reduction with molybdenum at 850 °C. The [^{11}C]CO was concentrated in a cold trap after removing remaining CO_2 by an Ascarite column. It was transferred with a xenon flow to a sealed reaction vial containing a solution of Pd_2[π-cinnamyl]Cl_2 (3.6 mg, 7.0 µmol), xantphos (4.1 mg, 7.0 µmol), 250 µL *tert*-butanol and vinyliodie (1.0 µL, 10.0 µmol) in 300 µL THF. The vial was heated for 3-5 min to 100 °C. After cooling down, a sample was diluted with MeCN and analyzed by HPLC [R_t(Grace Smart RP-18, MeCN/buffer 1 68/32, 1 mL·min^{-1}, 254 nm) = 4.4 min]. The identity of the labeled compound was confirmed by co-injection with the unlabeled *tert*-butyl acrylate. RCP of 70-80

% were determined with a d.c. RCY of 18 % (0.41 GBq) starting from approximately 2.5 GBq of [^{11}C]CO_2 (A_M could not be determined). [HPLC prep purification: Alltima C18 MeCN/buffer 1 70/30, 4 mL·min^{-1}, 254 nm, R_t = 14.3 min].

[^{11}C]*N*-Tritylacrylamide 4

[^{11}C]CO was produced as described above and xenon gas was used to transfer it in a sealed reaction vial containing a solution of Pd_2[π-cinnamyl]Cl_2 (3.6 mg, 7.0 μmol), xantphos (4.1 mg, 7.0 μmol), triphenylmethylamine (25 mg, 96 μmol) and vinyl iodide (1.0 μL, 10.0 μmol) in 600 μL THF. The vial was heated for 3-5 minutes to 100 °C. After it had cooled down, a sample was taken and analyzed with HPLC [R_t(Grace Smart RP-18, MeCN/buffer 1 68/32, 1 mL·min^{-1}, 254 nm) = 4.5 min]. The identity of the labeled compound was confirmed by co-injection with the cold reference compound. RCP within 75-85 % were determined with RCY of 22 % (0.42 GBq) starting from approximately 2.5 GBq of [^{11}C]CO_2 with A_M of 86-170 GBq·μmol^{-1}. [HPLC prep purification: Alltima C18 MeCN/buffer 1 70/30, 4 mL·min^{-1}, 254 nm, R_t = 9.8 min]

[^{11}C]1-*Tert*-butyl 5-methyl 2-((diphenylmethylene)amino)pentanedioate 7 followed by [^{11}C]10

[^{11}C]Methyl acrylate was obtained like described above. To this solution in DMSO a solution of **5** mg (17 μmol) Schiff base precursor in 100 μL DMSO and 100 μL of a 0.1 M solution of TBAF were added. After 5 min a sample was taken. Analysis by reverse phase HPLC and co-injection with the cold standard confirmed product formation [R_t(Grace Smart C18, MeCN/water 50/50, 1 mL·min^{-1}, 254 nm) = 17.5]. For the deprotection, 50 μL of 50 % aq KOH were added to a solution of [^{11}C]**7** in DMSO. After a couple of minutes, 200 μL concentrated HCl were added to the vessel and the temperature was raised to 100 °C for 2 min. A sample taken from the solution was analyzed by reverse phase HPLC (C18) as well as by chiral HPLC [Reprosil chiral-aa, MeOH/water 70/30, 1 mL·min^{-1}, R_t= L-Glu 7.1 min & D-Glu 11.1 min].

General procedure for the synthesis of [^{11}C]8 and[^{11}C]9

Synthons [^{11}C]**3** and [^{11}C]**4** were synthesized as described above. For both, the reaction mixture in toluene was eluted through a custom made disposable celite cartridge containing approximately 200 mg of celite, into a reaction vial containing **5** (5-10 mg, 17-33 μmol) and 10.5 equiv. of CsOH·H_2O. The reaction was vigorously stirred for 5 min at 10 °C prior to analysis. HPLC samples were taken by diluting a sample of the reaction mixture in MeCN

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followed by the injection of 20 µl on the column. [R_t(Grace Smart RP-18, MeCN/buffer 1 68/32, 1 mL·min^{-1}, 254 nm) = 10.3 min for **8**, R_t = 11.5 min for **9**]

General procedure for the deprotection to [^{11}C]10 and [^{11}C]11

For deprotecting the activating groups, the addition of 0.1 mL of 6M HCl solution to either [^{11}C]**8** or [^{11}C]**9** and heating to 100 ºC for 2 min was sufficient. A second sample was taken for analysis on chiral radioHPLC to determine the enantiomeric ratio of amino acid with chiral HPLC (Reprosil chiral-aa, methanol/water 70/30, 1 mL·min^{-1}, 214 nm for [^{11}C]**10** L-Glu R_t = 7.1 min and D-Glu 11.1 min; 90/10 for [^{11}C]**11**: L-Gln R_t = 8.2 min and D-Gln 12.3 min).

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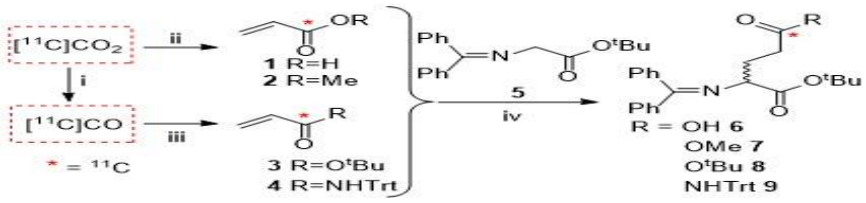
Entry for the Table of Contents



Novel Michael addition to obtain various amino acid derivatives. Online transformations possible in carbon-11 chemistry: i) Reduction with molybdenum at 850 °C; ii) Coupling of $[^{11}C]CO_2$ with Vinyl-MgBr and quenching with water or Fischer esterification; iii) Coupling of [^{11}C]CO with Vinyl-I and Pd-xantphos with *tert*-butanol or tritylamine, iv) Michael addition with base.

^{11}C-Radiochemistry, Michael reaction

Ulrike Filp

Page No. – Page No.

Efficient synthesis of ^{11}C-acrylesters, ^{11}C-acrylamides and their applica[illegible] in Michael addition reactions for tracer development.