Synthesis and Radiofluorination of Iodophenyl Esters as Tool for the Traceless Staudinger Ligation

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A new synthetic pathway for the preparation of ω-functionalized 2-iodophenyl esters as starting materials for the synthesis of substituted phosphanes is described. A radiolabeling of these esters with fluorine-18 has led to building blocks which were reacted with HPPh2 in a Pd-catalyzed P-C cross coupling to establish new phosphanes. These compounds can be applied as mild and bioorthogonal radiolabeling agents by means of the traceless Staudinger ligation. A route to access this class of compounds has been established.

Key words: Staudinger Ligation, Traceless, Bioorthogonal, Radiofluorination, PET, X-Ray Structure

Introduction

Imaging techniques like PET and SPECT are based on the application and detection of decaying radionuclides which are connected to a biologically active molecule to form the radiotracer. Both techniques have been used extensively for non-invasive diagnosis, staging and therapy control of diseases at the cellular and molecular level [1]. The availability of radiotracers is limited by the speed of synthetic methods. Moreover, the introduction of fluorine-18 (t½ = 109.8 min) remains a special challenge due to harsh reaction conditions [2]. Normally, peptides, proteins, antibodies or oligonucleotides can not be labeled directly. Therefore, bifunctional labeling agents have been developed for the radiolabeling of these compounds under mild conditions [3].

Several bioconjugation techniques, including acylation, imidation or thioether formation, are known [4]. However, every method has its limitations. True bioorthogonal ligations are rarely applied [5]. One of these methods is the Cu-catalyzed Huisgen cycloaddition, which proved to be a valuable tool for an efficient 18F labeling of peptides [6]. Furthermore, the traceless/non-traceless Staudinger ligation was established as a powerful bioconjugation approach for the labeling of small organic and bioactive molecules under mild conditions and in the absence of cytotoxic copper salts [7, 8]. Phosphane derivatives and azides act as bioorthogonal conjugation partners in this ligation. To obtain such phosphanes, building blocks with good leaving groups for the introduction of radiofluorine or for the insertion of other labels and a coupling position for the azide moiety are essential. Thus, we have developed an easy and convenient synthesis route to fluor- and tosyl-functionalized 2-iodophenyl esters, that were used as building blocks for the construction of phosphate-containing bifunctional labeling agents for the traceless Staudinger ligation. In this paper we show the preparation and radiofluorination of these ester derivatives and the synthesis of sample phosphanes.

Results and Discussion

2-Iodophenyl esters with good leaving groups (e. g. tosylate, mesylate, nosylate) were the initial point of our studies. These leaving groups are important for the introduction of radiofluorine. Moreover, other labels can still be introduced into the target molecule. Direct esterifications of 2-(phosphano)phenol with ω-haloalkyl group-containing acid derivatives were not amenable due to the formation of phosphonium salts with the ω-haloalkyl residue. Therefore, several tosylated and mesylated acetic and propionic acids have been synthesized in one step from the corresponding iodo compounds. Acetate and propionate scaffolds with tosyl or mesyl leaving groups are important key intermediates and are used as building blocks e. g.
acetate to yield the sulfonated acid derivatives. After the removal of the solvent, the crude product was washed 3 times with ethyl acetate to yield the sulfonated acid derivatives 2a–d as colorless solids in excellent purity and nearly quantitative yield. Unfortunately, a direct esterification of compounds 2a–d with 2-iodophenol failed. Several attempts were made, and various esterification techniques were applied, but the desired 2-iodophenyl esters 3a–d could not be obtained. Therefore a different reaction path was developed.

In addition, it was possible to obtain single crystals of compound 2c suitable for an X-ray crystal structure determination from a saturated ethyl acetate solution. Crystallographic data are given in Table 1. A view of the molecular structure of compound 2c in the crystal is shown in Fig. 1. The compound crystallizes in the triclinic space group P1 with Z = 2. In the solid state hydrogen-bonded dimers are present, which are arranged around a center of inversion with distances of 2.628 Å between the oxygen atoms O1 and O2 # (symmetry operation for the generation of O2 #: 2 − x, y, 1 − z). These dimers are arranged in the crystalline material such that all the planar tosyl groups are parallel to each other (Fig. 2).

Two different starting materials for the preparation of 2-iodophenylesters were found (Scheme 2). In the first path, a–d bromoalkylcarboxylic esters 6a and 6d could be obtained in high yields (77 and 99%) from the reaction of respective acid chlorides 5a,b with 2-iodophenol in the presence of Et3N as a
base in anhydrous dichloromethane. The crude products were distilled in high vacuum for purification. In the second path, ω-chloroalkylcarboxylic esters 6b and 6c were obtained by conversion of lactones 4a, b into the appropriate ω-chloroalkyl acid chlorides with dichloromethyl methyl ether [14] followed by the treatment with 2-iodophenol in dry dichloromethane in a one-pot synthesis procedure as shown in Scheme 2. Purification was done via distillation in high vacuum.

Compounds 6b–d were converted into the respective ω-iodoalkyl derivatives 7b–d using NaI in acetonitrile at ambient temperature under Finkelstein conditions overnight. A preparation of the respective propyl derivative 7a from bromo compound 6a was not successful due to an elimination reaction yielding 2-iodophenyl acrylate [15]. To introduce fluorine-18, good leaving groups are required in the precursor. The syntheses of the appropriate tosylate-containing compounds 8a, b were accomplished by the reaction of ω-iodoalkyl esters 7b, c with silver tosylate in acetonitrile at ambient temperature for 16 h in the dark with excellent yields (94 % for 8a and 95 % for 8b). In the same manner, the respective ω-fluoroalkyl compounds 9a, b as non-radioactive analogs were prepared using silver fluoride under the reaction conditions used for the tosylate compounds with yields of 89 % (9a) and 90 % (9b). Finally, the fluorinated iodophenyl ester 9a was reacted with HPPPh2 in a Pd-catalyzed P-C coupling to the desired phosphane 10 which can be used in traceless Staudinger ligation reactions as a (radio)labeling agent for azide-functionalized small organic and bioactive molecules. The cross-coupling of diphenylphos-

<table>
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<th>t (min)</th>
<th>mprecursor (mg)</th>
<th>RCY (%)</th>
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<td>100</td>
<td>10</td>
<td>17.5</td>
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Table 2. Conditions and radiochemical yield (RCY) for the preparation of [18F]9a.

* Conversion determined via radio-TLC.

Scheme 2. Synthetic route to fluorinated and tosylated iodophenyl esters 8a, b and 9a, b.

Scheme 3. Pd-catalyzed P-C coupling to phosphane 10.

The tosylated butyric ester 8a represents an ideal sample for radiolabeling purposes. Optimal labeling conditions with [18F]fluoride were achieved by the variation of the solvent, the temperature and the base. Results are shown in Table 2. The temperature and the reaction time seem to have only little influence on the radiochemical yield (RCY). No radiofluorination product was obtained using DMF or DMSO as solvents. Only low-yield conversion to [18F]9a was observed when acetonitrile was used as solvent (entries 1 and 2). The use of n-Bu4NOH instead of K2CO3 as base is important. Best results were obtained using a mixture of acetonitrile and t-BuOH (v : v = 1 : 4) at 100 °C and a reaction time of 10 min [16]. The radio-TLC (Fig. 3) showed 58 % conversion into the desired 2-iodophenyl ester [18F]9a (see entry 6 in Table 2 and Scheme 4).
Finally, it was tried to convert the radiolabeled analog [\(^{18}\text{F}\)9a] with HPPb2 in a Pd-catalyzed P-C cross-coupling reaction. In contrast to compound 9a, the reaction of HPPb2 with the radiolabeled [\(^{18}\text{F}\)9a] failed (Scheme 4). Unfortunately, no fluorine-18-labeled phosphane [\(^{18}\text{F}\)10] was found.

**Conclusion**

In this paper we demonstrated an easy and convenient route to 2-iodophenyl carboxylic esters \(\omega\)-functionalized with good leaving groups, which were successfully labeled with fluorine-18. The respective non-radioactive analog was obtained in high yields. Furthermore, the fluorinated iodophenyl esters were applied as starting materials for the preparation of fluoro-containing phosphanes in a Pd-catalyzed P-C cross-coupling reaction. An approach to the respective radiolabeled phosphane with fluorine-18 was not yet successful.

**Experimental Section**

**Reagents and techniques**

NMR spectra were recorded on a Varian Inova-400 spectrometer; chemical shifts of the \(^1\text{H}, ^{13}\text{C}, ^{19}\text{F}, \) and \(^{31}\text{P}\) spectra are reported in parts per million (ppm) using the solvent shifts for \(^1\text{H} \) and \(^{13}\text{C}, \) CFCl\(_3\) for \(^{19}\text{F}, \) and H\(_2\)PO\(_4\) for \(^{31}\text{P}\) spectra as internal standard. Mass spectra (MS) were obtained on a Quattro/LC mass spectrometer (MICROMASS) by electron spray ionization or on a Bruker autolFlex II TOF/TOF mass spectrometer (Matrix: DHB, reflector mode). The melting points were determined on a Galen III (Cambridge Instruments) apparatus (Leica, Vienna, Austria) and are uncorrected. Microanalyses were carried out with a Hekatech CHNS elemental analyzer EuroEA 3000. Dry solvents (\(N,N\)-dimethyl acetamide, acetonitrile, CH\(_2\)Cl\(_2\)) were purchased from Fluka (anhydrous, over molecular sieves, 99.7 %). Other chemicals were purchased from Sigma-Aldrich, Fluka or Acros and were used as received. Chromatographic separations and TLC detections were carried out with Merck silica gel 60 (63 – 200 \(\mu\)m) and Merck silica gel 60 F254 sheets, respectively. TLCs were developed by visualization under UV light (\(\lambda = 254 \text{~nm}\)). All reactions concerning the Pd-catalyzed coupling of HPPb2 and the borane-phosphane adduct formation were carried out under an argon atmosphere using Schlenk techniques.

The radioactive compound was identified with analytical radio-TLC by comparison of the retention factor of the reference compound. Decay-corrected radiochemical yields (RCYs) were quantified by integration of radioactive peaks on a radio-TLC, which was developed in a solution of petroleum ether and EtOAc (\(v:v = 8:1\), using a radio-TLC scanner (Fuji, BAS2000). \([^{18}\text{F}]\)Fluoride was produced utilizing the PET cyclotron Cyclone 18/9 (IBA, Belgium). \([^{18}\text{O}]\)H\(_2\)O was irradiated with protons (18 MeV, 30 \(\mu\)A) exploiting the \(^{18}\text{O}(p,n)^{19}\text{F}\) nuclear reaction.

**Crystal structure determination of 2c**

Diffraction data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer using graphite-monochromatized MoK\(_\alpha\) radiation (\(\lambda = 0.71073 \text{~Å}\)), and the diffraction measurement was done at \(-100 \text{~°C}\). The unit cell dimensions were recorded and refined by using the angular settings of 8783 reflections, and the structure was solved by Direct Methods using SHELXS-97 and refined against \(\text{F}^2\) on all data.
by full-matrix least-squares with SHELXL-97 [17]. All non-
hydrogen atoms were refined anisotropically; all hydrogen
atoms bonded to C atoms were placed on geometrically cal-
culated positions and refined using a riding model. Table 1
summarizes the crystallographic data.

CCDC 748404 contains the supplementary crystallo-
graphic data for this paper. These data can be obtained free
of charge from The Cambridge Crystallographic Data Centre
via www.ccdc.cam.ac.uk/data_request/cif.

General synthesis procedure for compounds 2a–d

1 eq. of o-o-iodocarboxylic acid 1a, b was dissolved in dry
acetonitrile, and 1.38 eq. of the respective silver salt was
added. The reaction mixture was stirred at r.t. overnight
in the dark. Afterwards, the solution was filtered, the solvent
was removed in vacuo, and the residue was washed three
times with ethyl acetate. Finally, the ethyl acetate was re-
moved in vacuo, and the final product was obtained without
further purification.

(Tosyloxy)acetic acid (2a)

Iodoacetic acid (1.0 g, 5.38 mmol) and silver tosylate
(1.93 g, 6.9 mmol) in acetonitrile (25 mL) were reacted
according to the general procedure. Yield: 1.2 g (95 %) of
2a. M. p. 134 °C. 1H NMR (400 MHz, CD 3CN): δ = 2.45
(s, 3 H, CH 3), 4.57 (s, 2 H, CH 2), 7.44 (d, J = 8.0 Hz,
2 H, H meta), 7.80 (d, J = 8.0 Hz, 2 H, H ortho). – 13C
NMR (101 MHz, CD 3CN): δ = 21.7 (CH 3), 65.8 (CH 2),
128.9 (C meta), 131.0 (C meta), 133.5 (C para), 146.5 (C para), 178.6 (C =O). – MS ((+)-ESI): m/z = 342.2 (M+Na)+.
– C 9H 10O 5S (244.26): calcd. C 49.17, H 4.95, S 13.13; found C 49.17,

(Methanesulfonyloxy)acetic acid (2b)

Iodoacetic acid (1.0 g, 5.38 mmol) and silver methanesul-
fonate (1.51 g, 7.42 mmol) in acetonitrile (25 mL) were reac-
ted according to the general procedure. Yield: 807 mg (97 %) of
2b. M. p. 113 °C. 1H NMR (400 MHz, CD 3CN): δ = 3.12
(s, 3 H, CH 3), 4.73 (s, 2 H, CH 2), 7.44 (br. s, 1 H, OH). – 13C
NMR (101 MHz, CD 3CN): δ = 38.5 (CH 3), 65.8 (CH 2),
168.3 (C =O). – MS ((+)-ESI): m/z (%) = 253 (48) [M+Na]+.
– C 9H 10O 5S (230.24): calcd. C 46.95, H 4.38, S 13.93; found C 46.88,

3-(Tosyloxy)propionic acid (2c)

3-Iodopropionic acid (1.5 g, 7.5 mmol) and silver methanesul-
fonate (2.1 g, 10.35 mmol) in acetonitrile (25 mL) were reac-
ted according to the general procedure. Yield: 1.23 g (99 %) of
2c. M. p. 63 °C. 1H NMR (400 MHz, CD 3CN): δ = 2.73
(t, J = 8.0 Hz, 2 H, H ortho), 3.03 (s, 3 H, CH 3), 4.38 (t, J =
8.0 Hz, 2 H, CH 2CH 2CO), 7.41 (br. s, 1 H, OH). – 13C
NMR (101 MHz, CD 3CN): δ = 34.2 (CH 2CH 2CO), 37.3 (CH 3), 67.1 (CH 2CH 2CO), 171.9 (C =O). – MS ((+)-ESI): m/z (%) = 191 (81) [M+Na]+.
H 4.75, S 19.06.

2-Iodophenyl 3-bromopropanoate (6a)

2-Iodophenol (300 mg, 1.36 mmol) was dissolved in dry
dichloromethane (5 mL), and 3-bromopropanoyl chloride 5a
(0.2 mL, 1.50 mmol) was added dropwise at 0 °C. The mixture
was stirred at r.t. for 2 h, the solvent was removed, and
the residue was purified via bulb tube distillation to yield 6a
as a pale-yellow liquid (548 mg, 82 %). B. p. 130 °C.

2-Iodophenyl 4-chlorobutanoate (6b)

Zinc chloride (47 mg, 0.35 mmol) was added to a solution
of γ-butyrolactone 4a (0.3 mL, 3.48 mmol) in dichloromethyl
methyl ether (0.5 mL, 4.53 mmol), and the resulting mixture
was stirred at 60 °C for 2 h. Then a solution of 2-iodophenol
(766 mg, 3.48 mmol) and Et 3N (1 mL, 6.97 mmol) in
dichloromethane (5 mL) was added dropwise at 0 °C, and
the mixture was stirred at r. t. overnight. The mixture was washed
with 3 × 15 mL of a 1 M KOH solution, and the organic
layer was dried over Na 2SO 4. After the removal of the sol-
vent the residue was purified via bulb tube distillation to yield 6b as pale-yellow liquid (405 mg, 36%). B. p. 120 °C/5 × 10⁻³ mbar. Rf = 0.69 (petroleum ether/EtOAc 8:1). - ¹H NMR (400 MHz, CDCl₃): δ = 1.75 – 1.82 (m, 2 H, H-β), 2.41 (t, 3J = 7.2 Hz, 2 H, H-γ), 3.14 (t, 3J = 6.3 Hz, 2 H, H-γ), 6.38 – 6.42 (m, 1 H, 4-H), 6.82 – 6.83 (m, 2 H, 5-H, 6-H), 7.49 (d, 3J₃,δ = 7.8 Hz, 1 H, 5-H). - ¹³C NMR (101 MHz, CDCl₃): δ = 24.2 (C-β), 26.5 (C-γ), 32.4 (C-δ), 34.1 (C-ε), 34.2 (C-γ), 91.5 (C-2), 123.4 (C-6), 127.5 (C-4), 129.4 (C-5), 137.9 (C-3), 151.9 (C-1), 170.5 (C=O). - MS (+)-ESI: m/z (%) = 419 (10) [M+Na]⁺, 421 (10) [M+Na, ¹⁸⁷Br]⁺. - C₁₂H₁₄BrO₂ (397.05): calcul. C 36.30, H 3.55; found C 36.74, H 3.38.

2-Iodophenyl 4-isobutylcinnamate (7b)

Nal (1.74 g, 11.59 mmol) was added to a solution of 6b (0.94 g, 2.89 mmol) in acetic acid (10 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified via bulb tube distillation to yield 7b as a pale-yellow liquid (1.08 g, 90%). B. p. 160 °C/3 × 10⁻³ mbar. Rf = 0.67 (petroleum ether/EtOAc 8:1). - ¹H NMR (400 MHz, CDCl₃): δ = 1.77 – 1.84 (m, 2 H, H-β), 2.32 (t, 3J = 7.0 Hz, 2 H, H-γ), 2.74 (t, 3J = 6.8 Hz, 2 H, H-δ), 6.38 – 6.39 (m, 1 H, 4-H), 6.80 – 6.83 (m, 2 H, 5-H, 6-H), 7.48 (d, 3J₃,δ = 7.0 Hz, 1 H, 3-H). - ¹³C NMR (101 MHz, CDCl₃): δ = 51.1 (C-γ), 28.5 (C-β), 34.9 (C-α), 91.0 (C-2), 123.3 (C-6), 127.6 (C-4), 129.4 (C-5), 139.6 (C-3), 150.2 (C-1), 169.9 (C=O). - MS (+)-ESI: m/z (%) = 439 (20) [M+Na]⁺. - C₁₀H₁₀I₂O₂ (415.99): calcul. C 28.87, H 2.42; found C 29.13, H 2.57.

2-Iodophenyl 5-isopentylcinnamate (7c)

Nal (1.91 g, 12.75 mmol) was added to a solution of 6c (1.08 g, 3.19 mmol) in acetic acid (10 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified via bulb tube distillation to yield 7c as a yellow liquid (1.21 g, 88%). B. p. 140 °C/3 × 10⁻³ mbar. Rf = 0.72 (petroleum ether/EtOAc 8:1). - ¹H NMR (400 MHz, CDCl₃): δ = 1.43 – 1.52 (m, 4 H, H-β, γ), 2.17 (t, 3J = 7.0 Hz, 2 H, H-γ), 2.62 (t, 3J = 6.6 Hz, 2 H, H-δ), 6.41 (dt, 3J = 6.3 Hz, 3J = 2.34 Hz, 4 H, 1-H, 4-H), 6.82 – 6.88 (m, 2 H, 5-H, 6-H), 7.50 (d, 3J₃,δ = 7.8 Hz, 1 H, 3-H). - ¹³C NMR (101 MHz, CDCl₃): δ = 5.4 (C-δ), 25.8 (C-β), 32.8 (C-γ), 33.2 (C-α), 91.0 (C-2), 123.4 (C-6), 127.6 (C-4), 129.4 (C-5), 139.6 (C-3), 151.8 (C-1), 170.2 (C=O). - MS (+)-ESI: m/z (%) = 453 (100) [M+Na]⁺. - C₁₂H₁₃BrO₂ (430.02): calcul. C 30.72, H 2.81; found C 31.34, H 2.92.

2-Iodophenyl 6-bromohexanoate (7d)

Nal (1.13 g, 7.56 mmol) was added to a solution of 6d (1.00 g, 2.52 mmol) in acetic acid (5 mL), and the mixture was stirred at 50 °C overnight. After the removal of the solvent the residue was purified via bulb tube distillation to yield 7d as a yellow liquid (0.82 g, 74%). B. p. 120 °C/3 × 10⁻³ mbar. Rf = 0.82 (petroleum ether/EtOAc 8:1). - ¹H NMR (400 MHz, CDCl₃): δ = 1.07 – 1.13 (m, 2 H, H-γ),...
1.33 – 1.38 (m, 2 H, H-β), 1.41 – 1.48 (m, 2 H, H-δ), 2.24 (t, J = 7.5 Hz, 2 H, H-α), 2.64 (t, J = 7.0 Hz, 2 H, H-ε), 6.41 (dt, 3C4H4 = 7.5 Hz, 3C4H6 = 1.6 Hz, 1 H, 4-H), 6.85 (t, 3C4H5 = 7.8 Hz, 1 H, 5-H), 6.92 (d, 3C1H4 = 7.8 Hz, 1 H, 6-H), 7.50 (d, 3C1H3 = 7.8 Hz, 1 H, 3-H). – 13C NMR (101 MHz, C6D6): δ = 60.0 (C-ε), 23.6 (C-β), 21.2 (CH3), 28.3 (C-γ), 33.5 (C-α), 69.6 (C-δ), 91.0 (C-2), 123.4 (C-6), 127.5 (C-4), 128.2 (C-ortho), 129.4 (C-3), 134.5 (Cipso), 139.6 (C-3), 144.2 (Cpara), 151.8 (C-1), 169.8 (C=O). – MS (+)-ESI: m/z (%) = 298 (20) [M–TsO]+, 483 (100) [M+Na]+, − C17H17O5S (460.28): calcd. C 39.94, H 3.83; found C 39.72, H 3.82; found C 44.19, H 3.79.

2-Iodophenyl 4-(tosyloxy)butanoate (8a)

AgOTs (1.02 g, 3.64 mmol) was added to a solution of 7b (1.08 g, 2.60 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified via column chromatography (petroleum ether/EtOAc 8:1) to yield 8a as a pale-yellow liquid (603 mg, 0.81 mmol) in dry acetonitrile (2 mL) under an argon atmosphere. The mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified via bulb tube distillation to yield 8a as a pale-yellow liquid (603 mg, 0.81 mmol) in dry acetonitrile (2 mL) under an argon atmosphere. The mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified via bulb tube distillation to yield 8a as a pale-yellow liquid (603 mg, 0.81 mmol) in dry acetonitrile (2 mL) under an argon atmosphere.

M. Pretze et al. · Synthesis and Radiofluorination of Iodophenyl Esters

2-Iodophenyl 4-fluorobutanoate (9a)

AgF (112 mg, 0.88 mmol) was added to a solution of 7b (91 mg, 0.22 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified via bulb tube distillation to yield 9a as a pale-yellow liquid (40 mg, 89%). B.p. 100 °C C5 × 10−3 mbar. Rf = 0.63 (petroleum ether/EtOAc 8:1). – 1H NMR (400 MHz, C6D6): δ = 1.69 – 1.78 (m, 2 H, H-β), 2.29 (t, J = 7.3 Hz, 2 H, H-α), 4.08 (dt, 3JHF = 46.9 Hz, 3JHF = 3.7 Hz, 2 H, H-γ), 6.40 (dt, 3J1H4 = 7.5 Hz, 3J1H6 = 2.3 Hz, 1 H, 4-H), 6.82 – 6.84 (m, 2 H, 5-H, 6-H), 7.49 (d, 3J1H4 = 7.8 Hz, 1 H, 3-H). – 13C NMR (101 MHz, C6D6): δ = 30.1 (d, 3JC2F = 19.6 Hz, C-β), 34.2 (d, 3JC1F = 4.7 Hz, CH3), 82.3 (d, 3JC1F = 165.3 Hz, C-γ), 93.6 (C-2), 123.4 (C-6), 126.7 (C-4), 130.0 (C-5), 139.6 (C-3), 152.2 (C-1), 170.9 (C=O). – 19F NMR (376 MHz, C6D6): δ = −220.7. – MS (+)-ESI: m/z (%) = 332 (10) [M+Na+]+, − C17H17O5S (460.28): calcd. C 39.8, H 3.27; found C 38.66, H 3.09.

2-Iodophenyl 6-fluorohexanoate (9b)

AgF (205 mg, 1.62 mmol) was added to a solution of 7b (362 mg, 0.81 mmol) in dry acetonitrile (2 mL) under an argon atmosphere, and the mixture was stirred at r. t. overnight in the dark. After the removal of the solvent the residue was purified via bulb tube distillation to yield 9b as a colorless liquid (137 mg, 90%). B.p. 95 °C 1/10 mmbar. Rf = 0.52 (petroleum ether/EtOAc 8:1). – 1H NMR (400 MHz, C6D6): δ = 1.17 – 1.22 (m, 2 H, H-γ), 1.31 – 1.36 (m, 2 H, H-β), 1.49 – 1.55 (m, 2 H, H-δ), 2.29 (t, J = 7.6 Hz, 2 H, H-ε), 4.04 (dt, 3JHF = 47.7 Hz, 3JHF = 5.9 Hz, 2 H, H-ε), 6.41 (dt, 3J1H4 = 7.5 Hz, 3J1H6 = 1.6 Hz, 1 H, 4-H), 6.83 – 6.92 (m, 2 H, 5-H, 6-H), 7.51 (d, 3J1H4 = 7.1 Hz, 1 H, 3-H). – 13C NMR (101 MHz, C6D6): δ = 24.5 (C-β), 25.0 (d, 3JC2F = 5.2 Hz, C-γ), 30.3 (d, 3JC1F = 19.6 Hz, C-β), 34.2 (d, 3JC1F = 165.9 Hz, C-ε), 91.0 (C-2), 123.4 (C-6), 127.5 (C-4), 129.4 (C-5), 139.6 (C-3), 151.9 (C-1), 170.5 (C=O). – 19F NMR (376 MHz, C6D6): δ = −218.4. – MS (+)-ESI: m/z (%) = 359 (80) [M+Na+]+, − C17H17O5S (460.28): calcd. C 42.88, H 4.20; found C 43.04, H 4.29.

2-(Diphenylphosphano)phenyl 4-fluorobutanoate (10a)

KOAc (38 mg, 0.39 mmol), HPhP2 (60 μL, 0.32 mmol) and Pd(OAc)2 in catalytical amount were added to a solution of 2-iodophenyl benzoate (9a) (100 mg, 0.32 mmol) in dry DMA (2 mL) under an argon atmosphere. The mixture was stirred at 90 °C for 3 h. Afterwards water (15 mL) and CH2Cl2 (15 mL) were added, the organic layer was separated, and the aqueous layer was extracted with 3× 10 mL CH2Cl2. The combined organic layers were dried over Na2SO4, and the solvent was removed under reduced
pressure. The crude product was purified by column chromatography (petroleum ether/EtOAc 20: 1 → 10: 1) to yield 10 as a colorless syrup (60 mg, 51%). Rf = 0.37 (petroleum ether/EtOAc 8: 1). – H NMR (400 MHz, CDCl3): δ = 1.47 – 1.61 (m, 2 H, H-β), 2.10 (t, J = 7.3 Hz, 2 H, H-γ), 3.92 (dt, JHF = 47.5 Hz, JF = 6.0 Hz, 2 H, H-γ), 6.74 (t, J3J4 = 7.4 Hz, 1 H, 4-H), 6.94 – 6.98 (m, 7 H, 3-H, 5-H, 6-H, Hmeta-Hpara), 7.26 – 7.33 (m, 4 H, Hortho). – 13C NMR (101 MHz, CDCl3): δ = 30.1 (d, JCE = 19.7 Hz, C-β), 34.2 (d, JCE = 4.7 Hz, C-α), 82.4 (d, JCE = 165.0 Hz, C-γ), 123.2 (C-6), 126.3 (C-4), 128.5 (d, JCE = 12.4 Hz, C-2), 129.0 (d, JCE = 24.9 Hz, Cmeta), 130.0 (Cpara). – 13F NMR (376 MHz, CDCl3): δ = −220.2. – 31P NMR (162 MHz, CDCl3): δ = −15.0. – MS (ESI): m/z (%) = 406 (8) [M+K]+. – C22H32FO5P2 (366.37): calcd. C 72.12, H 5.50; found C 72.18, H 5.24.

2-Iodophenyl 4-[18F]fluorobutanoate ([18F]9a)

An anion-exchanger cartridge (Waters, Sep-Pak® Light Accell™ Plus QMA) was activated by rinsing with 5 mL of a 1 M NaHCO3 solution and 10 mL of deionized water. It was charged with [18F]fluoride (500 – 800 MBq) and eluted with 1 mL of a 4.5% TBAOH solution. The solvents were evaporated azeotropically by subsequent addition of three portions of 1 mL each of dry acetonitrile under a stream of nitrogen at 100 °C. 17.5 mg of 6b was dissolved in 0.5 mL dry acetonitrile, and the mixture was added to the [18F]fluoride-containing sealed vial. The resulting solution was heated to 100 °C for 10 min. Samples for analytical radio-TLC were taken after 10 min. Analytical radio-TLC: Rf = 0.62 (petroleum ether/EtOAc 8: 1).

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