

**Development of efficient (radio)fluorination reactions  
of hypervalent iodinanes for synthesising electron  
rich  $^{18}\text{F}$ -labelled fluoroarenes for imaging of N-  
methyl-D-aspartate receptors**

*Dissertation for the degree of Philosophiae Doctor*

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## **Preface**

In this dissertation is presented work to fulfil the thesis requirements for the Doctor of Philosophy degree at University of Oslo. The work has been carried out in the group of PET chemistry under main supervision of Patrick Riss and co-supervision of Ragnhild Paulsen in the period September 2014 - August 2018 with funding from the faculty of Mathematics and Natural sciences, UiO (realomics SRI) and the Norwegian research council (NFR ES 231553). I am grateful to realomics for giving me a PhD fellowship.

## **Acknowledgements**

I wish to thank my main supervisor Patrick Riss for hiring me and for all the encouragement, support and fruitful discussions along the route. I also want to thank my co-supervisor Ragnhild Paulsen and fellow PhD student Marthe for many discussions during our collaboration. In addition, I am thankful to have had two fellow PhD candidates Waqas and Santosh who have had to listen to me whine about failed experiments. Furthermore, I am grateful to my former master's student Gaute and bachelor students Beatriz and Karoline who has worked hard alongside me in some of my projects aiding progress. Moreover, I would like to thank Eleni and Shivashankar for contributing to the NMDA project. Frode and Dirk for providing an excellent NMR instrument park with easy and quick access and to Runar for being very helpful ordering and shipping chemicals to and from all over the world. I also like to thank Osamu Sekiguchi for measuring countless MS samples. In addition, I am very thankful to Olaf Prante for helping out and sending us rat brains when in dire need. I also want to say thank you to my lovely fiancé Regene and the rest of my family for all the love and support.

## Abstract

Fluorine-18 is the most important radionuclide in Positron Emission Tomography (PET) due to its excellent decay characteristics and convenient half-life (110 minutes). Metal free radiofluorination reactions for electron deficient arenes are abundant in the literature, but methods incorporating fluorine-18 into electron rich arenes are not. Methods typically utilise various transition metals, which is undesirable in PET. The only radiofluorination method for synthesising electron rich  $^{18}\text{F}$ -labelled fluoroarenes is the use of hypervalent iodinanes, specifically iodonium ylides, although in limited yield and in a high yield variation.

By systematically investigating the radiofluorination reaction of iodonium ylides we expanded the methodology to afford good to high yields for non-activated and deactivated substrates. An oxygen mediated precursor degradation process was found to be the major culprit in the radiofluorination reaction of iodonium ylides. In addition, we also identified residual iodine from precursor preparation causing reduced yields with poor reproducibility. Precursor syntheses and radiofluorination reaction conditions were developed to afford ylides in markedly improved yields and with low yield variability. Furthermore, we identified triphenylphosphane as a catalyst which assisted radiofluorination of iodonium ylides. However, further work is needed in order to elucidate the phosphane-mediated mechanism of action. In addition, formamides are described as methylamine masking groups, well suited for preparing and radiofluorinating iodonium ylides. The masking group protects basic amines from oxidation. It is also shown that the masking group can easily be reduced or hydrolysed to the primary or secondary amine under metal free conditions.

Hypervalent iodinanes are further described as fluorination precursors for transition metal free preparative synthesis of fluoroarenes. We investigated the effect of solvent and fluoride source and identified two parallel reaction pathways. An aryne intermediate was found to be the source of undesired, fluorinated constitutional isomers. An *ipso*-specific fluorination reaction was developed via carefully selecting solvent and fluoride source. By synthesising anhydrous crypt-222/KF, which has superior solubility properties in organic solvents, we avoided the inefficient *in situ* formation of crypt-222/KF in anhydrous DMF thus affording significantly improved yields. The stoichiometric fluorination reaction did not afford improved yields in presence of triphenylphosphane. The formation of oxidised phosphane was observed using  $^{31}\text{P}$ -NMR under stoichiometric conditions.

The developed methodologies are well suited for synthesising *ortho*-fluorinated analogues of electron rich arenes, an abundant motif in NMDA ligands. The methods were applied in order to functionalise the NMDA ligand dextrorphan with an *ortho*-fluorine substituent. In addition, a focused library of fluorinated ligands based on NR2B antagonist Ro 04-5595 was constructed. Several potent, fluorinated NMDA/NR2B ligands were identified. Lead compound Ro 04-5595 was radiolabelled with an  $^{11}\text{C}$ -methyl group and evaluated via PET imaging. *In vivo* PET data from rat show moderate brain uptake and fast pharmacokinetics with an NR2B like distribution. High-resolution autoradiographic images using [ $^3\text{H}$ ]Ro 04-5595 show retention primarily in NR2B rich regions cortex, hippocampus, thalamus and striatum with very low binding in cerebellum, which is devoid of NR2B receptors. In addition, both enantiomers of Ro 04-5595 were synthesised and individually evaluated via competitive autoradiography. The displacement study indicate that only (*R*)-Ro 04-5595 is a potent NR2B ligand. We believe that future investigation using PET in non-human primates has good chances to validate [ $^{11}\text{C}$ ]-(*R*)-Ro 04-5595 as a suitable ligand for studying NR2B receptors *in vivo*.

We believe that our combined findings make the use of hypervalent iodinanes the favoured radiofluorination methodology for sterically hindered and/or electron rich substrates, a substrate scope that well complement the de-nitro-fluorination strategy. The methodologies are well suited for synthesising electron rich  $^{18}\text{F}$ -labelled fluoroarenes, a common motif in NMDA/NR2B ligands.

## List of publications

- I:** **Jakobsson, J. E.**; Grønnevik, G.; Riss, P. J., Organocatalyst-assisted Ar-<sup>18</sup>F bond formation: a universal procedure for direct aromatic radiofluorination. *Chem Commun (Camb)* **2017**, 53 (96), 12906-12909.<sup>1</sup>
- II:** **Jakobsson J. E.**; Riss, P. J., Transition metal free, late-stage, regiospecific, aromatic fluorination on preparative scale using KF/Crypt-222 complex. *RSC Advances* **2018**, 8, 21288-21291.<sup>2</sup>
- III:** **Jakobsson J. E.**; Grønnevik, G.; Rafique, W.; Hartvig K.; Riss, P. J., Formamide as an unconventional amine protecting group for PET radiochemistry. *Eur. J. Org. Chem.* **2018**, 3701-3704.<sup>3</sup>

## Submitted manuscripts

- IV:** **Jakobsson, J. E.**; Gourni, E.; Shivashankar K.; Brito, B. and Riss, P. J., Synthesis and in vivo characterization in rodent brain of the subtype selective NR2B NMDA receptor ligand [<sup>11</sup>C]Ro 04-5595 as a radio-tracer for positron emission tomography. Submitted.





## Contribution to publications

- I:** Participated in designing the project and conducted the majority of the experiments. Synthesised all precursors and reference molecules and conducted the majority of the radiofluorination experiments. Took part in writing the article.
- II:** Designed the project and conducted all of the experimental work. Lead author.
- III:** Participated in designing the project and performed proof of principle experiment. Guided Gaute Grønnevik through the reduction optimisation experiments, precursor synthesis and reference synthesis of **5a-9a** and **4b-9b**. Wrote the majority of the article, synthesised all remaining compounds except reference **2b** and **2c**, performed radioactive work applying the method to compounds **1a-c** and **2a-c**. Designed and developed the synthesis for making *N*-monomethyl derivatives of **2b**. Guided Karoline Hartvig through the synthesis of **2c**.

## Contribution to submitted manuscripts

- IV:** Participated in designing the project. Synthesised all compounds. Interpreted autoradiographic and wiping experiments performed by Eleni Gourni and Beatriz Brito using [<sup>3</sup>H]ifenprodil. Performed and analysed autoradiography and wiping experiments using [<sup>3</sup>H]Ro 04-5595. Participated in writing the article.

## List of important terms, abbreviations and nomenclature

9-BBN = 9-borabicyclo[3.3.1]nonane

Ar = aryl

BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

B<sub>max</sub> = receptor density

Boc = *tert*-butyloxycarbonyl

Carrier added = the prepared radioisotope has been diluted with added non-radioactive isotopes of the same element

Carrier free = the prepared radioisotope has essentially not been diluted with non-radioactive isotopes of the same element

CuAAC = copper alkyne azide cycloaddition

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE = dichloroethane

DCM = dichloromethane

Decay corrected yield = the yield is corrected for decay

DMF = *N,N*-dimethylformamide

DMSO = dimethylsulfoxide

EOS – end of synthesis

eq. = equivalents

EWG = electron withdrawing group

FWHM = full width half maximum; the peak width at half the maximum height of a function.

HPLC = high performance liquid chromatography

HRMS = high resolution mass spectrometry

Hz = hertz

ID = injected dose

Incorporation yield = percent of radionuclide incorporated into radiotracer + side-products

LAH = lithium aluminium hydride

LG = leaving group

mCPBA = *m*-chloroperbenzoic acid

min = minutes

Molar activity = becquerel per mole ( $A_m$ )

mw = microwave

n.d.c. yield = non decay corrected yield, radioactivity at a certain time point divided by radioactivity at a reference point

NHC = N-heterocyclic carbene

NMR = nuclear magnetic resonance

ox = oxidation

No carrier added = no non-radioactive isotopes of the same element has been added to the radiotracer. Note difference between no carrier added and carrier free.

PET = positron emission tomography

PET isotope = an isotope decaying via  $\beta^+$  decay used in PET imaging

p.i. = past injection

r.t. = room temperature, typically 20-25 °C

Radioisotope = radioactive isotope

Radiotracer = chemical compound carrying at least one atom of a radioactive isotope

RCY = radiochemical yield

$R_f$  = retention factor, expressed as migration of sample divided by migration of eluent.

sec = seconds

TBAF = tetra-*n*-butylammonium fluoride

TEAB = tetraethylammonium bicarbonate

TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxy

THF = tetrahydrofuran

TLC = thin layer chromatography

Tracer principle = a radiotracer should only observe and not trigger a biological response in the subject

Tf = trifluoromethanesulfonyl

Ts = *para*-toluenesulfonyl

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## 1 - Aim of Study

- Increase the knowledge of the radiofluorination of iodonium ylides aimed at yield variations and regioselectivity. Use the obtained knowledge to reduce the reaction variability and increase the reaction yield thus ultimately widening the substrate scope specifically aimed at electron rich arenes, a ubiquitous motif in NMDA/NR2B ligands.
- Translate the radiofluorination of iodonium ylides to preparative organic chemistry to allow for stoichiometric fluorination reactions aimed at NMDA/NR2B ligands.
- Synthesise a focused library of fluorinated derivatives based on Ro 04-5595 aimed at investigating NMDA/NR2B receptors via PET imaging. Perform a PET study with the most promising NR2B ligand.





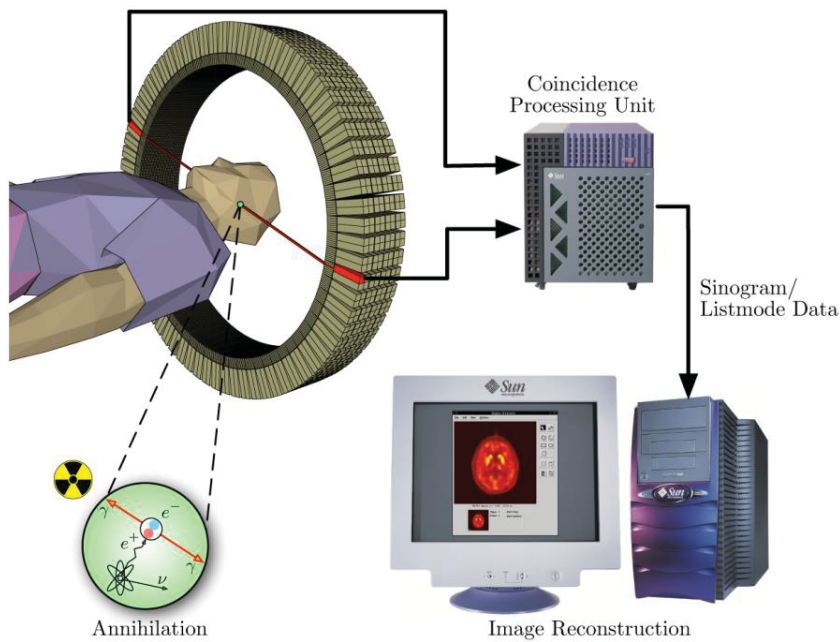
## 2 – Introduction

### 2.1 - Imaging

Molecular imaging is used for visualising molecular pathways inside living organisms. The technique is non-invasive and observes biochemical processes without disturbing them. Molecular imaging is a powerful tool useful for diagnosis of e.g. cancer and Alzheimer's disease and to unravel biological mechanisms. Examples of molecular imaging tools are MRI (magnetic resonance imaging), PET (positron emission tomography) and SPECT (single-photon emission computed tomography). Hybrid techniques combining e.g. PET with MRI (PET-MRI) yield morphological data that combined with functional data ease data interpretation.

#### 2.1.1 - PET imaging

PET imaging relies on radioactive isotopes decaying via  $\beta^+$  decay, for instance fluorine-18 (Scheme 1). The decaying nuclide transforms a proton to a neutron under the emission of a positron and an electron neutrino, the positron travels through the surrounding tissue until it pairs with an electron in an annihilation event thus producing two almost antiparallel high-energy photons due to conservation of momentum from the positron. These photons are detected using scintillation crystals precisely oriented around the radioactive source. By comparing the time of detection using a coincidence processing unit, two photons emitted from the same annihilation event can be linked and a point along the photons propagation axis is calculated. By collecting a large number of coincidences, a PET image constituted by a 3D map over the decaying radioactivity is constructed. The radiotracer often has a selectivity towards a certain kind of receptors or tissue type and will visualise the distribution of for instance bone tissue, blood flow, metabolism or a specific receptor type. The obtained 3D information visualizes the *in vivo* distribution of radioactivity over time and yield valuable information about the subject that is useful for diagnosing various disease states.



**Scheme 1:** Principle behind PET imaging. The scheme describe an annihilation event producing two 511 keV photons detected by scintillation crystals. The coincidence processing unit detect them as photons originating from the same annihilation event. Addition of many coincidences is used to construct the PET image. Scheme is reproduced from Wikipedia.<sup>4</sup>

### 2.1.2 - PET isotopes

Desirable properties for PET radionuclides is a high proportion of  $\beta^+$  decay to allow for efficient imaging (Table 1). In addition, the half-life need to be long enough to allow for both radiotracer synthesis and PET imaging but short enough to limit patient's radioactivity dose. For neuroimaging, spatial resolution is of extra importance. A low  $\beta^+$  energy allows for higher resolution PET images since the travelled distance of the positron is shorter. The two most important PET isotopes are carbon-11 and fluorine-18.

**Table 1:** Common isotopes used in PET.<sup>5-7</sup>

<b><u>Isotope</u></b>	<b><u>Half-life</u></b>	<b><u>% <math>\beta^+</math></u></b>	<b><u>average <math>\beta^+</math> energy (MeV)</u></b>	<b><u><math>\beta^+</math> FWHM (mm)</u></b>
<sup>11</sup> C	20.4 min	100	0.386	0.92
<sup>13</sup> N	9.97 min	100	0.492	1.49
<sup>15</sup> O	122 sec	100	0.735	2.48
<sup>18</sup> F	110 min	97	0.250	0.54

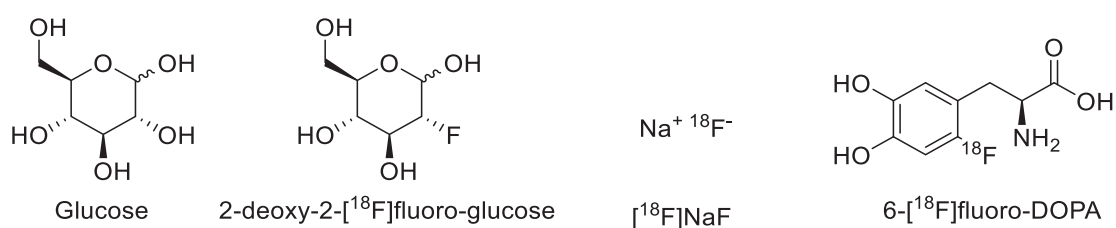
Carbon-11 has a moderate half-life of 20 minutes which both complicates both synthesis and imaging. Carbon-11 carbon dioxide is produced in a cyclotron via bombarding a nitrogen-14 target with protons in the presence of trace oxygen (Table 2, entry 1). Heteroatoms like nitrogen and oxygen are frequently occurring motifs in drug molecules. However, the positron emitting isotopes nitrogen-13 and oxygen-15 have too short half-lives (10 min and 122 sec respectively) to allow for both labelling of small molecules and subsequent imaging. Nitrogen-13 is used as [<sup>13</sup>N]NH<sub>3</sub> and Oxygen-15 as [<sup>15</sup>O]H<sub>2</sub>O, [<sup>15</sup>O]CO or [<sup>15</sup>O]O<sub>2</sub> e.g. for myocardial perfusion imaging. Among the PET radionuclides, fluorine-18 possesses the most favourable decay properties along with the highest spatial resolution for imaging and a very practical half-life of 110 min. Fluorine is present in many drug molecules; nevertheless, means of its incorporation into organic scaffolds need further improvement.<sup>8-10</sup> Bombarding oxygen-18 enriched water with protons in a cyclotron target affords fluorine-18 as [<sup>18</sup>F]F<sup>-</sup> (Table 2, entry 2) along with a small amount of carrier fluorine-19. Conversely, fluorine-18 ([<sup>18</sup>F]F<sub>2</sub>) is produced in a cyclotron via bombardment of a neon-20 target with deuterons in presence of carrier fluorine gas<sup>11</sup> (Table 2, entry 3). [<sup>18</sup>F]F<sub>2</sub> can also be produced via proton bombardment of oxygen-18 gas, followed by isotopic exchange with fluorine gas in presence of a noble gas carrier.<sup>12</sup>

**Table 2:** Production route for the most important radioisotopes.<sup>6</sup>

<u>Entry</u>	<u>Isotope</u>	<u>Production route</u>
1	<sup>11</sup> CO <sub>2</sub>	<sup>14</sup> N(p, α) <sup>11</sup> C
2	<sup>18</sup> F <sup>-</sup>	0.1-0.5% O <sub>2</sub> <sup>18</sup> O(p, n) <sup>18</sup> F
3	<sup>18</sup> F- <sup>19</sup> F	0.1% F <sub>2</sub> <sup>20</sup> Ne(d, α) <sup>18</sup> F

### 2.1.3 - PET radiotracers

Examples of PET radiotracers are bone cancer tracer [<sup>18</sup>F]NaF,<sup>13</sup> dopamine synthesis imaging agent 6-[<sup>18</sup>F]fluoro-DOPA<sup>14</sup> and the most frequently used PET radiotracer 2-deoxy-2-[<sup>18</sup>F]fluoro-glucose ([<sup>18</sup>F]FDG). [<sup>18</sup>F]FDG is used as a diagnostic tool for detecting early stage cancer (Figure 1).<sup>15</sup> FDG is a fluorinated analogue of glucose where a hydroxyl group in 2-position is replaced with fluorine. Glucose serves as a supply of energy and cancer cells typically have a higher energy consumption rate. Consequently, cancer cells have an increased uptake of [<sup>18</sup>F]FDG compared to normal healthy cells. However, the absence of the 2-hydroxyl group in FDG prevents glucose from completing the metabolic cycle which lead to partially metabolised [<sup>18</sup>F]FDG trapped inside the cell. The outcome is an accumulation of fluorine-18 labelled radiotracer in cancer cells, which can be imaged using a PET scanner.



**Figure 1:** Glucose and glucose metabolism imaging agent 2-deoxy-2-[<sup>18</sup>F]fluoro-glucose,<sup>15</sup> [<sup>18</sup>F]NaF binds to calcium in bone and is used for detecting and diagnosing bone diseases.<sup>13</sup> 6-[<sup>18</sup>F]fluoro-DOPA is a fluorinated form of dopamine and used for investigating dopaminergic pathways and diagnose neurodegenerative diseases.<sup>14</sup>

### 2.1.4 - Molar activity

Molar activity is a measure of radioactive decay events per mole of compound (Bq/mol). The maximum theoretical molar activity varies among the radionuclides and increases with decreasing half-life. During radiotracer synthesis, the maximum theoretical molar activity is not approached;

typical molar activities are significantly lower (Table 3). Isotopic dilution wherein another isotope of the same element is added either intentionally or unintentionally reduces the molar activity. Some sources of isotopic dilution are deliberate addition of carrier such as in concentration dependent autoradiography experiments, production of [ $^{18}\text{F}$ ]F<sub>2</sub> or contamination from equipment and/or reagents (F<sup>-</sup> from for instance a Teflon stirrer bar).<sup>16</sup> Examples of typical molar activities compared to theoretical molar activities achieved are for building blocks [ $^{11}\text{C}$ ]CO<sub>2</sub>, 500-10 000 times lower,<sup>6</sup> for [ $^{18}\text{F}$ ]F<sup>-</sup> 100-1000 times lower<sup>6</sup> and for [ $^{18}\text{F}$ ]F<sub>2</sub> 100 000 – 600 000 times lower.<sup>17</sup> A high molar activity is very important when imaging low concentration targets. The amount of radiotracer that can be injected is limited since the imaged system should only be observed not affected.<sup>18</sup>

**Table 3:** Theoretical molar activity for carbon-11 and fluorine-18.

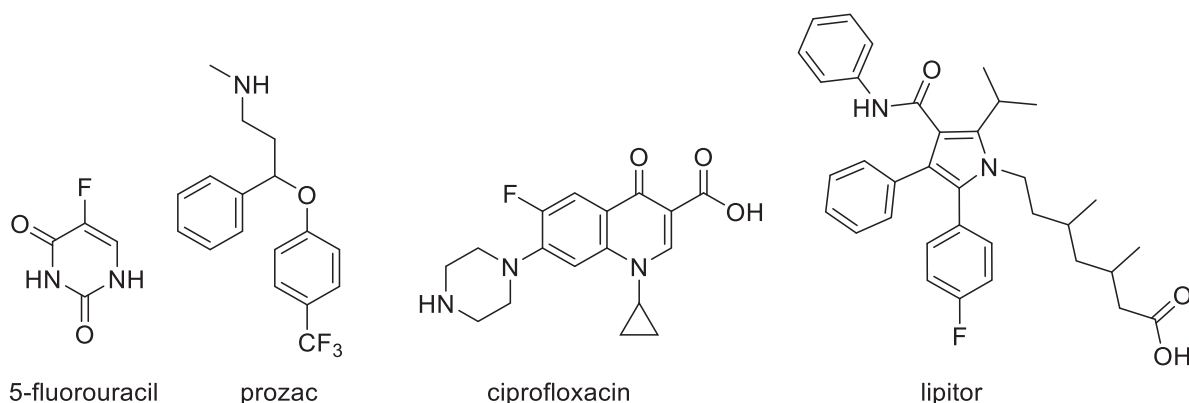
<u>Entry</u>	<u>Isotope</u>	<u>Theoretical A<sub>m</sub> (GBq/nmol)</u>
1	$^{11}\text{C}$	340
2	$^{18}\text{F}$	63

## 2.2 - Fluorine

Fluorine, F, atomic number 9, is the most electronegative element and the lightest element among the halogens. The only stable isotope of fluorine is  $^{19}\text{F}$ , which is also an NMR active nucleus. Furthermore, fluorine is the 13<sup>th</sup> most abundant element on earth that in its elemental form is a highly reactive diatomic gas ( $\text{F}_2$ ). Therefore, fluorine in nature is found as the anion fluoride,  $\text{F}^-$ . Fluorine can make hydrogen bonds, but they are weaker compared to oxygen and nitrogen.<sup>19</sup>

### 2.2.1 - Fluorine in pharmaceuticals

Fluorine is usually present in organic molecules as either alkyl fluoride or aryl fluoride. The prevalence of fluorine in pharmaceuticals is increasing,<sup>20</sup> possibly due to an increased number of available fluorination reactions and commercially available fluorinated building blocks.<sup>9</sup> Prevalence of fluorine in drug molecules was 20% in 2013 of which around half is fluoroarenes.<sup>i</sup> Selected examples of common pharmaceuticals containing fluoride is shown in Figure 2.

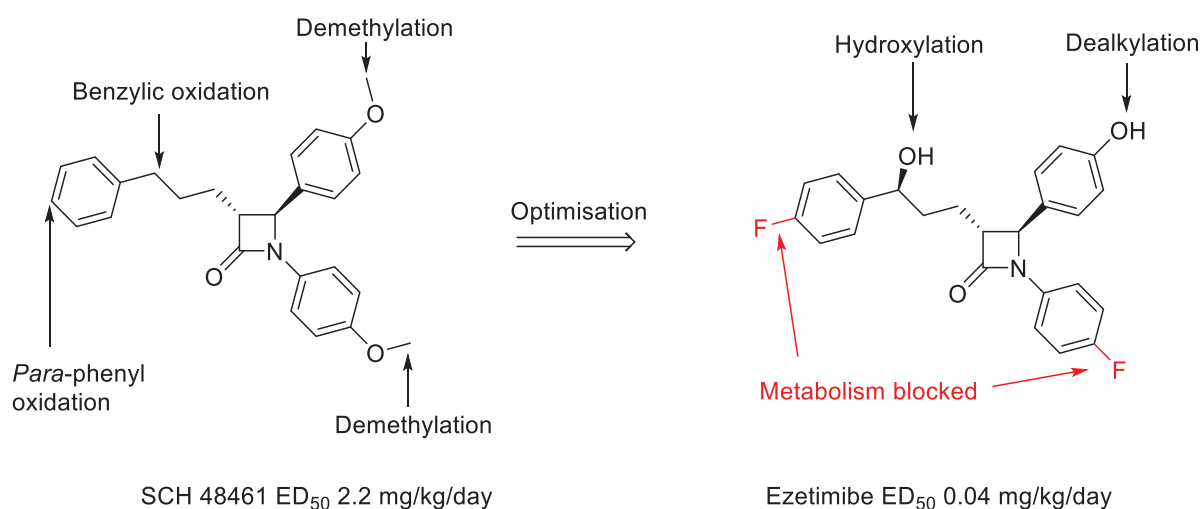


**Figure 2:** Common pharmaceuticals containing fluorine. 5-fluorouracil is an anti-cancer medication, prozac is an antidepressant, ciprofloxacin is an antibiotic and lipitor is a lipid lowering agent.

Incorporating fluorine into aromatic rings change the electronic distribution and can dramatically alter physicochemical properties. Introduction of fluorine in late stage drug development is used as a tool for fine-tuning drug candidate's properties, such as biological half-life, bio absorption and binding profile.<sup>21-23</sup> The stability of the ArF bond make it a useful tool for preventing oxidation

<sup>i</sup> Veronique Gouverneur lecture slide from BOSS XV 2016; <http://www.oxfordsynthesiscdt.ox.ac.uk/resources/SBM-CDT-Fluorine.pdf> (accessed 20180724).

of oxidation-prone ArH positions, such as *para*-phenyl oxidations, exemplified in Scheme 2.<sup>22</sup> Fluorine is commonly treated as a bioisostere for H<sup>18, 24</sup> but is more similar in size to OH.<sup>8, 25</sup> Furthermore, fluorine can be introduced to construct mechanism based inhibitors e.g. 5-fluorouracil (Figure 2).<sup>20</sup> Fluorinated drug molecules are becoming increasingly more common and despite the plethora of available fluorination reactions, there is a need for good robust, reliable routes introducing fluorine making especially fluoroarenes.<sup>9-10</sup> Exemplified in Scheme 2 is an optimisation process: Via introducing fluorine into the cholesterol lowering drug SCH 48461 the pharmacodynamic properties are enhanced and the effective dose is reduced by 50 times thus creating ezetimibe.<sup>26</sup>



**Scheme 2:** Example of a pharmaceutical development process, redrawn scheme from Rosenblum *et. al.*<sup>26</sup>

### 2.2.2 - Fluorination reactions (fluoroarenes)

This thesis is concerned with transition metal free fluorination strategies using fluoride ion. For broader reviews over fluorination reactions see Campbell *et. al.*,<sup>9</sup> Liang *et. al.*,<sup>24</sup> Hollingworth *et. al.*,<sup>27</sup> Lee *et al.*<sup>28</sup> and Riss *et. al.*<sup>29</sup>

Fluoride has a strong solvation in water that, via hydrogen bonding, diminishes nucleophilicity. Fluorination reactions are therefore typically performed under anhydrous conditions to enhance nucleophilicity. Different fluorination methodologies are often used for constructing substrates with either radioactive fluorine-18 or non-radioactive fluorine-19. Introduction of the two isotopes have different synthetic requirements such as time constraints, yield requirements, method of

purification, building block availability etc. A methodology that is useful for both radioactive and non-radioactive preparations of fluoroarenes would limit synthetic work and could streamline PET radiotracer development.

A classical fluorination reaction is the Balz-Schiemann reaction (Scheme 3, a) that utilise anilines and tetrafluoroboric acid in combination with sodium nitrite, affording useful yields of fluoroarenes on preparative scale.<sup>30</sup>

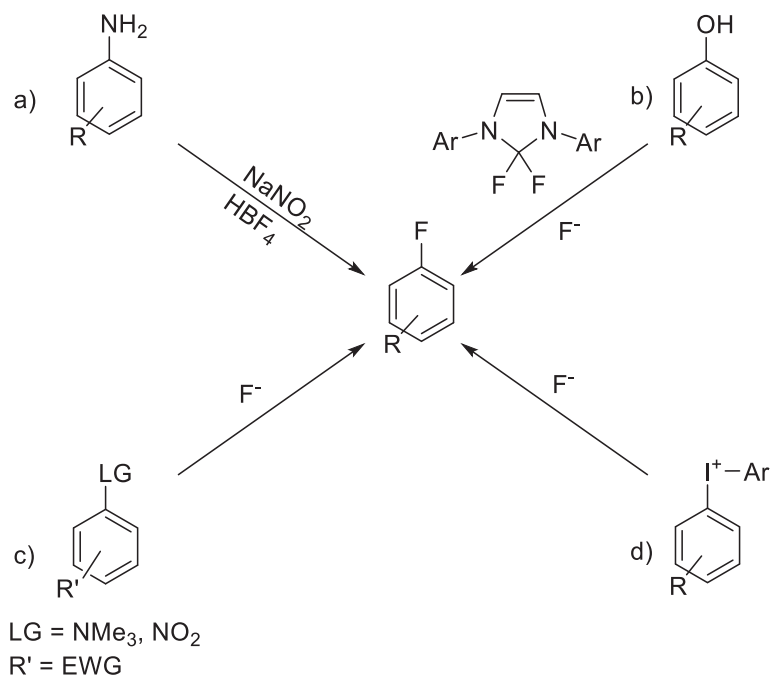
Another fluorination strategy developed by Ritter and co-workers fluorinate phenols via a deoxyfluorination reaction, using excess caesium fluoride and a fluorinated NHC that afford high yields for a broad range of substrates (Scheme 3, b).

A third route are dehalo- and de-nitro-fluorination reactions (Scheme 3, c) which utilise widely synthetically available halogen or nitro leaving groups. The use is however limited to activated substrates (i.e. aromatic systems holding electron withdrawing *ortho* or *para* substituents (-C(=O)R, -(C=O)OR, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>)).

A fourth type of fluorination precursors are diaryliodonium salts (Scheme 3, d). However, the methodology produces a mixture of products with fluorine on either of the two arenes with a



reaction selectivity that can be challenging to predict. The regioselectivity is modified by addition of copper(I) salts.<sup>31</sup>



**Scheme 3:** Four different fluorination strategies. a) Balz-Schiemann reaction<sup>30</sup> b) deoxyfluorination of phenols<sup>32</sup> c) nucleophilic fluorination of activated arenes (S<sub>N</sub>Ar) d) Fluorination of diaryliodonium salts.<sup>31</sup>

## 2.3 - Fluorine in PET

### 2.3.1 - Practical aspects working with [ $^{18}\text{F}$ ] $\text{F}^-$

Although a radioactive isotope and a non-radioactive isotope of the same element behave chemically the same, e.g. fluorine-18 and fluorine-19, there are practical differences between radiochemistry and conventional chemistry. A major difference is reaction stoichiometry. The quantity of [ $^{18}\text{F}$ ] $\text{F}^-$  and [ $^{19}\text{F}$ ] $\text{F}^-$  combined is generally in the nanomol to picomol range<sup>16</sup> whereas the precursor and reagent concentrations are often in the low micromol range. Therefore a reagent excess of >1000 times is used.<sup>18</sup> For reagents stable under the radiofluorination conditions their concentration is approximately constant during the course of the reaction. For bimolecular reactions, reaction rates are proportional to the concentration of fluoride. The practical consequence is reduced reaction times often with high RCY within minutes. However, the minute quantities of [ $^{18}\text{F}$ ] $\text{F}^-$  can render undesired side reactions with trace impurities coming from solvents, reagents, pipette tips or other equipment problematic.

Another major difference compared to conventional chemistry is the available synthesis time, which is limited by the half-life of fluorine-18. Therefore, reactions and purification steps need to be fast and efficient. For instance after three half-lives (5 h 30 min ( $^{18}\text{F}$ ), (61 min ( $^{11}\text{C}$ )) only 1/8 of the starting radioactivity remains.

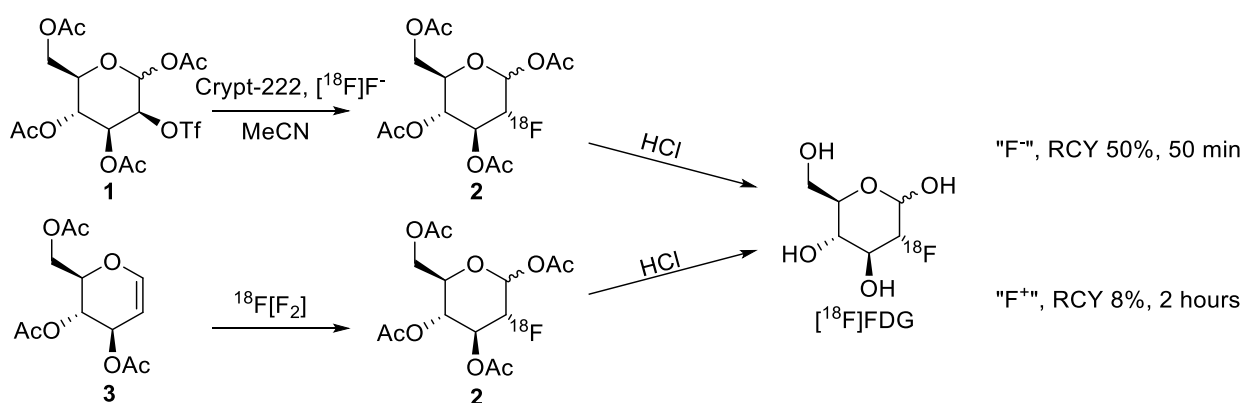
The ultimate goal for most method and radiotracer development research is clinical application. Radiotracer productions should therefore avoid toxic reagents to ease potential future translation. High reproducibility with small batch quality deviations is also important in radiotracer productions. A successful radiotracer synthesis route is generally adapted to a synthesis module. Automation allow routine radiotracer production using larger amounts of radioactivity but also limits the scope over accepted chemical manipulations.

The radiofluorination reaction progress is typically monitored via radioTLC and/or radioHPLC. The reaction progress is expressed as radiochemical yield (RCY), which is the ratio of incorporated  $^{18}\text{F}^-$  to unreacted  $^{18}\text{F}^-$  in solution. Consequently, side products with moderate to high volatility are undetected on radioTLC e.g. [ $^{18}\text{F}$ ]fluorobenzene produced from radiofluorination of e.g. diaryliodonium salts.<sup>33</sup> Identification of volatile species is made by keeping a balance sheet over the radioactivity. The overall yield is either expressed as decay corrected yield where starting- and

product- radioactivity are decay corrected to a common time point, or non-decay corrected yield (n.d.c.) which is time dependent and the actual yield obtained.

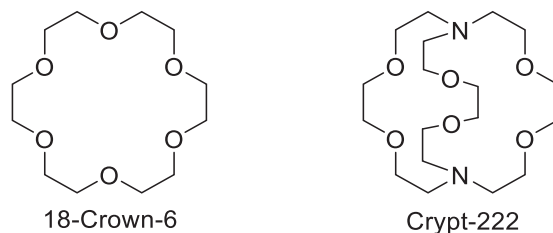
## 2.4 - Radiofluorination reactions

Analogous to conventional chemistry, there are two main types of radiofluorination reactions, electrophilic and nucleophilic. Electrophilic fluorination reactions utilise fluorine gas ( $[^{18}\text{F}]\text{F}_2$ ) or analogues thereof,<sup>17</sup> whereas nucleophilic fluorination reactions utilise fluoride ( $[^{18}\text{F}]\text{F}^-$ ). Moreover, the differences to traditional stoichiometric chemistry render the use of  $[^{18}\text{F}]\text{F}_2$  very limited, due to the inherent low molar activity. Low molar activity  $[^{18}\text{F}]\text{F}_2$  makes synthesis of radiotracers in high molar activity and consequently imaging of low density targets impossible (see molar activity above). A successful example using  $[^{18}\text{F}]\text{F}_2$  is an early synthesis of  $[^{18}\text{F}]\text{FDG}$  (Scheme 4).



**Scheme 4:** Synthesis of  $[^{18}\text{F}]\text{FDG}$ . Above is shown a nucleophilic fluorination reaction with  $^{18}\text{F}$  starting with a substitution of triflate for  $[^{18}\text{F}]\text{F}^-$  followed by a hydrolysis step.<sup>34</sup> Below is shown an electrophilic  $^{18}\text{F}$ -fluorination of an alkene using fluorine gas  $[^{18}\text{F}]\text{F}_2$  followed by a hydrolysis step. Unwanted formation of other regioisomers as side products is not shown.<sup>15</sup>

Nucleophilic radiofluorination reactions utilise  $[^{18}\text{F}]\text{F}^-$  as fluorine source and afford significantly higher molar activities than electrophilic fluorine gas ( $[^{18}\text{F}]\text{F}_2$ ). However since  $[^{18}\text{F}]\text{F}^-$  is produced in an aqueous solution (Table 2, entry 2), water need to be carefully removed (*see above*). A typical process start with immobilising aqueous  $[^{18}\text{F}]\text{F}^-$  on a quaternary ammonium phase-transfer cartridge.  $[^{18}\text{F}]\text{F}^-$  is eluted using a solution containing a base and a phase transfer catalyst (Figure 3). The solvents are evaporated at elevated temperatures under a flow of dry inert gas. MeCN is added portion wise to azeotropically distil off residual water. The phase transfer catalyst complex the counterion ( $\text{K}^+$ ) thus making fluoride more exposed and therefore enhance nucleophilicity. After evaporation, the radiofluorination reaction is commonly performed in polar aprotic solvents such as DMSO, MeCN or DMF to avoid hydrogen bonding.



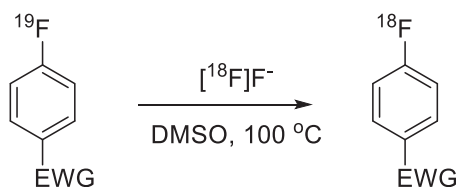
**Figure 3:** Two potassium complexation phase transfer catalysts, 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) and crypt-222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane).

### 2.4.1 - Aliphatic radiofluorination reactions

There are two main types of nucleophilic radiofluorination reactions, aliphatic and aromatic. Aliphatic radiofluorination reactions are typically  $S_N2$  type reactions and frequently utilise tosyl, mesyl or triflyl leaving groups, exemplified in the nucleophilic synthesis of FDG (Scheme 4).<sup>35</sup> This thesis is concerned with aromatic radiofluorination reactions (for a selected review covering aliphatic radiofluorination reactions see Miller *et. al.*<sup>16</sup>).

### 2.4.2 - Aromatic radiofluorination reactions

The Balz-Schiemann reaction using anilines and the deoxyfluorination reaction of phenols (Scheme 3, a and b) are not practical in radiofluorination reactions. Carrier added fluorine-19 ( $NHC-F_2$  and  $HBf_4$ ) greatly reduces the molar activity. Although, work by Riss *et. al.*<sup>36</sup> show that diazonium salts with a polymer bound tosylate counterion can be radiofluorinated in absence of  $HBf_4$ . The reaction provide low yields but no carrier added radiotracers. Another reaction that has less use is the isotopic-exchange reaction with fluoride as leaving group (Scheme 5, isotopic exchange), which provide radiotracers in limited molar activities due to added carrier.<sup>37</sup>



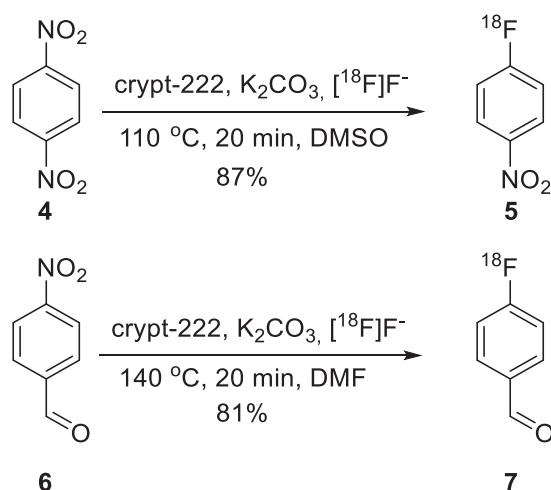
**Scheme 5:** Schematic illustration of isotopic exchange of fluorine-19 with fluorine-18 via an  $S_NAr$  reaction.

## 2.5 - Radiofluorination reactions

There are both transition metal free and transition metal mediated methodologies for synthesising radiofluorinated arenes starting from high molar activity  $^{18}\text{F}^-$ . This thesis is mainly concerned with transition metal free radiofluorination reactions. Along with an overview of the transition metal free radiofluorination strategies is also presented the perhaps two most versatile transition metal mediated methodologies (copper mediated radiofluorination of boronates,<sup>38-39</sup> and diaryliodonium salts<sup>40</sup>). Other transition metals used for the construction of  $^{18}\text{F}$ -fluoro fluoroarenes are Ni,<sup>41</sup> Pd,<sup>42-43</sup> and Ru.<sup>44</sup>

### 2.5.1 - De-nitro-fluorination reactions

A classical aromatic radiofluorination reaction is the de-nitro-fluorination reaction. However the substrate scope is limited to activated arenes such as **4** or **6** (Scheme 6).<sup>45</sup>

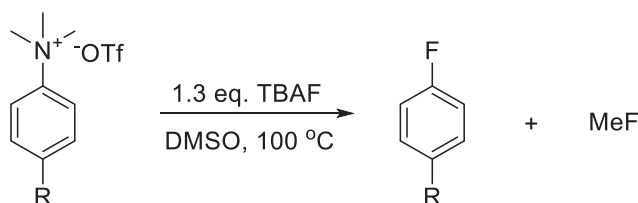


**Scheme 6:** Examples of de-nitro-fluorination reactions.<sup>46</sup>

### 2.5.2 - Aryl trimethylammonium salts

Trimethylamine is a very good leaving group and aryl trimethylanilinium salts provide excellent radiofluorination yields for activated arenes **5** and **7**. However, for non-activated arenes **8-11**, fluorination takes place on one of the methyl groups yielding [<sup>18</sup>F]fluoromethane as main product, demonstrated by Sun *et. al.*<sup>47</sup> using stoichiometric fluoride (Table 4).

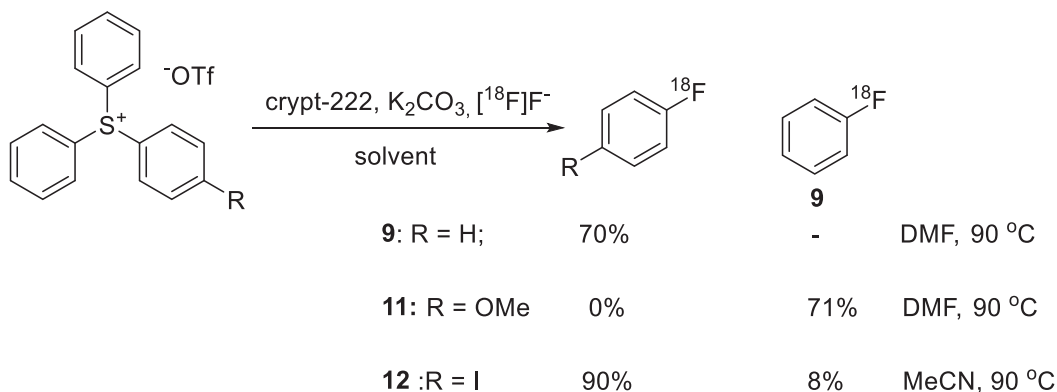
**Table 4:** Product distribution for fluorination of trimethylanilinium salts.<sup>47</sup>



<u>Entry</u>	<u>Compound</u>	<u>R</u>	<u>ArF : MeF</u>
1	<b>5</b>	NO <sub>2</sub>	>99:1
2	<b>7</b>	CHO	>99:1
3	<b>8</b>	Br	2:98
4	<b>9</b>	H	<1:99
5	<b>10</b>	Me	<1:99
6	<b>11</b>	OMe	<1:99

### 2.5.3 - Triarylsulfonium salts

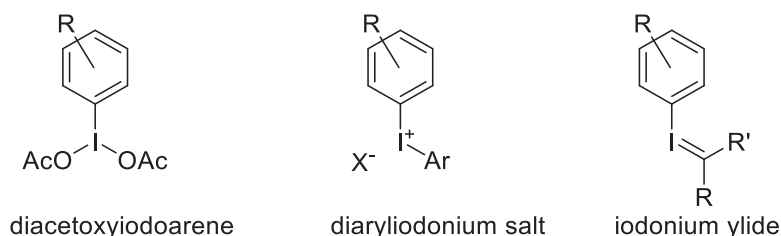
Triarylsulfonium salts (Scheme 7) are used as precursors for radiofluorination reactions and are similar to aryl trimethylammonium salts (*see above*).<sup>48</sup> However, radiofluorination of electron rich arenes does not afford the desired product (**11**) but instead produces [<sup>18</sup>F]fluorobenzene (**9**) from radiofluorinating one of the phenyl ligands. This regioselectivity problem is analogous to the [<sup>18</sup>F]fluoromethane side-product during radiofluorination of trimethylanilinium salts (*see above*) and radiofluorination of the undesired ligand in diaryliodonium salts (*see below*). Notable, however, is the high RCY of 4-[<sup>18</sup>F]fluoro-1-iodobenzene (**12**) in 71%.



**Scheme 7:** Substrate scope for radiolabelling of triarylsulfonium salts.<sup>48</sup>

### 2.5.4 - Iodines

Organic compounds containing iodine in higher oxidation states are known as hypervalent iodine compounds or iodanes. A benefit of iodanes is their environmental benignness, making them well suited for PET radiotracer production.<sup>49</sup> Hypervalent iodanes are divided into several subclasses, of which diaryliodonium salts, iodonium ylides and diacetoxyiodoarenes are important for production of <sup>18</sup>F-labelled fluoroarenes (Figure 4).<sup>50</sup>

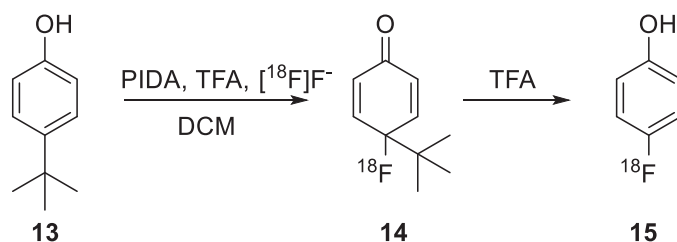


**Figure 4:** Three types of hypervalent iodanes used in PET radiochemistry.

Diacetoxyiodoarenes were used by Haskali *et. al.*<sup>51</sup> as radiofluorination precursors. These provide access to primarily activated <sup>18</sup>F-labelled fluoroarenes, albeit in significantly reduced yields to the corresponding diaryliodonium salt or iodonium ylides.

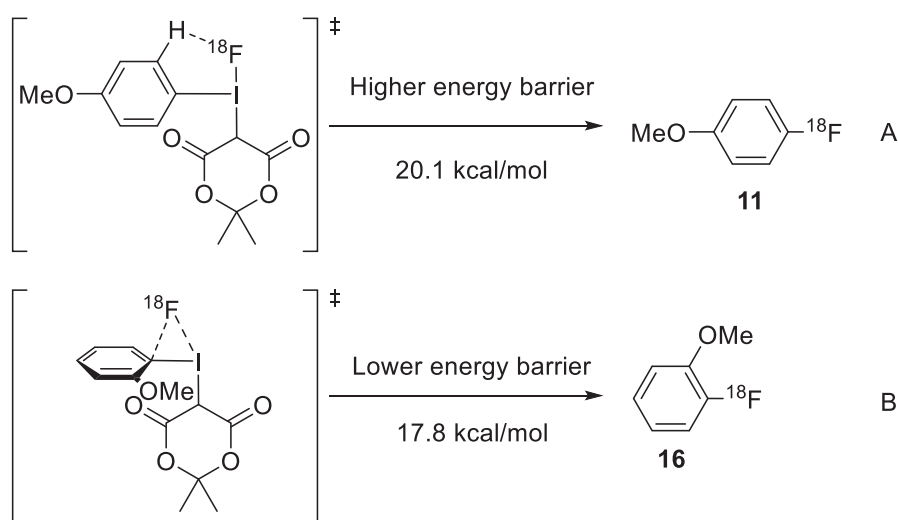
Diacetoxyiodobenzene has further been used as oxidant in *para*-radiofluorination of phenols (**15**) described by Gao *et. al.*<sup>52</sup> (Scheme 8).





**Scheme 8:** Nucleophilic radiofluorination of a phenol via a hypervalent iodine mediated redox reaction.<sup>52</sup>

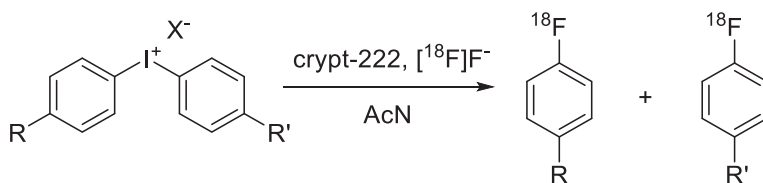
Hypervalent iodinanes typically provide enhanced RCY for substrates holding substituents *ortho* to iodine. The *ortho*-effect is observed for diacetoxyiodoarenes,<sup>51</sup> diaryliodonium salts<sup>50, 53</sup> and iodonium ylides.<sup>1, 50, 53-56</sup> Rotstein *et. al.*<sup>57</sup> explain the *ortho* effect for fluorination of iodonium ylides as a lower energy barrier for the reductive elimination of <sup>18</sup>F-labelled fluoroarenes for substrates having *ortho* substituents (**16**). The *ortho*-substituent prevent a stabilising H-F interaction due to steric reasons (Scheme 9) compared to the non *ortho*-substituted arene (**11**).<sup>57</sup>



**Scheme 9:** Reproduced mechanistic suggestion and calculated energy barriers for the radiofluorination of iodonium ylides by Rotstein *et. al.*<sup>57</sup> An *ortho* substituent prevent H-F bonding thus reducing the stabilisation of the transition state and thereby reduce the energy barrier for a reductive elimination (pathway B) yielding **16** compared to pathway A yielding **11**.

### 2.5.5 - Diaryliodonium salts

Radiofluorination of diaryliodonium salts were described by Pike and Aigbirhio in 1995.<sup>33</sup> By using symmetrical iodonium salts electron rich substrate 4-[<sup>18</sup>F]fluoroanisole (**11**) was afforded in up to 88% RCY (Scheme 10, entry 1). However unsymmetrical iodonium salts with one electron rich and one electron neutral ligand (R=OMe and R'=H; (**18**)) afforded exclusively fluorination of the electron neutral moiety **9**. Electronic effects direct the radiofluorination to the *ipso*-carbon of the least electron rich arene.<sup>58</sup> Unfortunately, starting from symmetrical iodonium salts is synthetically challenging and impractical when synthesising more complex radiotracers. In addition alcoholic solutions of diaryliodonium salt can be used to elute fluoride from QMA cartridges, thus avoiding both base and phase transfer catalysts.<sup>59</sup> An effort to reduce the relatively large yield variability (*see above*) was made by Carroll *et. al.*<sup>60</sup> who provide a protocol for increasing the reproducibility and yield of fluorination reactions of diaryliodonium salts by adding various radical scavengers. However, diaryliodonium salts are light sensitive and experiments conducted in darkness showed no yield improvement in presence of proposed radical scavenger TEMPO.<sup>61</sup>



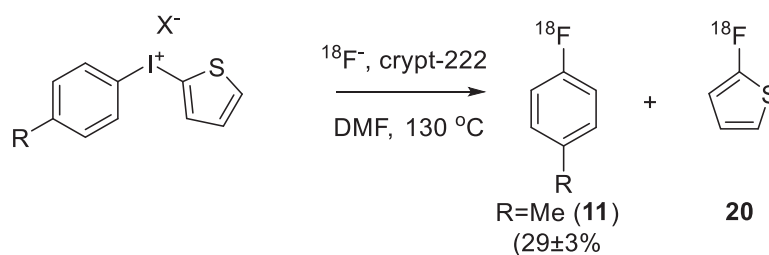
**17:** X = Cl, R = R' = H, 31-78% RCY (**9**, R=H)

**18:** X = Br, R = OMe, R' = H, 88% (**9**, R=H)

**19:** X = OTf, R = R' = OMe, 73%<sup>a</sup> (**11**, R=OMe)

**Scheme 10:** 30 mg precursor, 110 °C, 35 min. [a] = 85 °C, 40 min.<sup>33</sup>

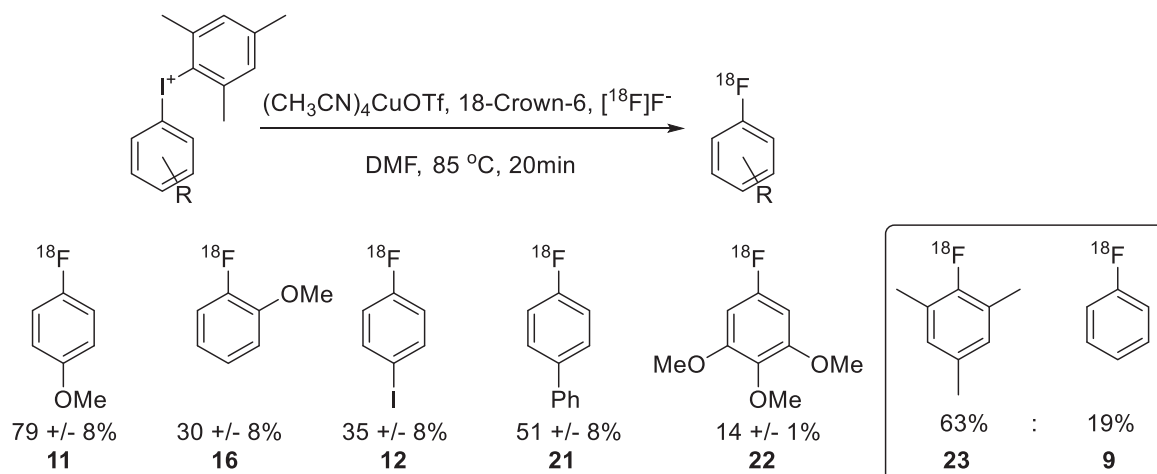
A variation of Pikes diaryliodonium salts utilise a thienyl ligand (Scheme 11). 2-Thienyliodonium salts allow radiofluorination of unsymmetrical precursors making 4-[<sup>18</sup>F]fluoroanisole (**11**) in 29±3%.<sup>62</sup> However, 2-thienyliodonium precursors have been reported notoriously challenging to synthesise, store and radiofluorinate due to instability.<sup>40, 63</sup>



**Scheme 11:** General radiofluorination of a 2-thienyl iodonium salt (RCY for **11** is from X=Br).<sup>62</sup>

### 2.5.6 - Copper mediated radiofluorination of diaryliodonium salts

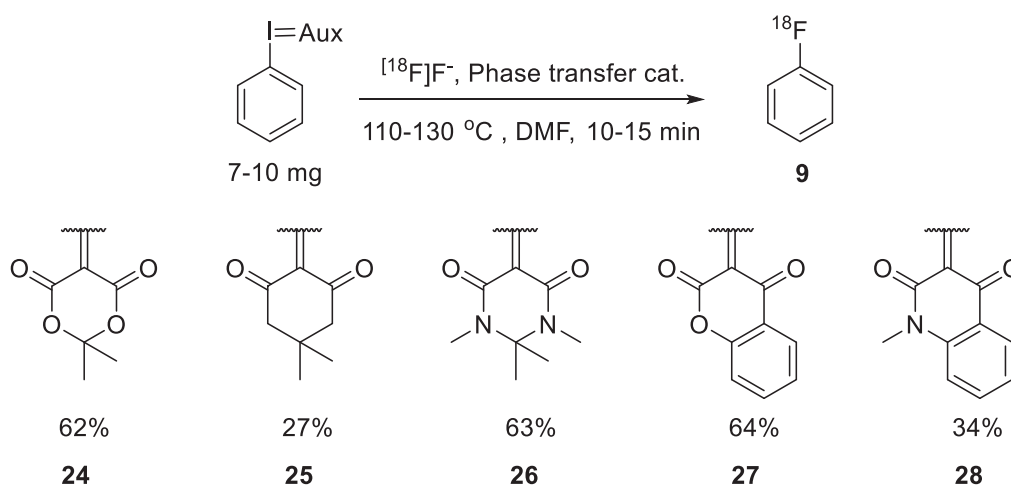
Radiofluorination of diaryliodonium salts in presence of copper(I) bearing a mesitylene ligand is described by Sanford and co-workers<sup>40, 64</sup> (Scheme 12). The reaction is typically regioselective towards the less substituted ring but vary with electronic effects.<sup>31, 40</sup> The selectivity is the opposite of what is expected from the transition metal free methodology described by Pike and co-workers. In addition, substrates do not benefit from *ortho*-substitution.<sup>61, 65</sup> The transition metal mediated strategy produce electron rich arenes under mediation by copper(I) in modest to good yields under both sub-stoichiometric and stoichiometric conditions.<sup>31, 40</sup> Noticeable is that 4-[<sup>18</sup>F]fluoroanisole (**11**) was produced in a high RCY (70±8%) although *ortho*-substituted 2-[<sup>18</sup>F]fluoroanisole (**16**) afforded less than half the yield (30±8%). Surprisingly more activated substrates 4-[<sup>18</sup>F]fluoro-1-iodobenzene (**12**) and 4-phenyl-1-[<sup>18</sup>F]fluorobenzene (**21**) afforded lower RCY (35±8% and 51±8% respectively). Electron rich 5-[<sup>18</sup>F]fluoro-1,2,3-trimethoxybenzene (**22**) was produced in 36±11%.<sup>40</sup> No fluorination on the mesitylene moiety (**23**) is described, which for the transition metal free work by Pike and co-workers is the predominating radiofluorinated species.<sup>61</sup>



**Scheme 12:** Examples of RCY for some selected substrates from Ichiishi *et. al.*<sup>40</sup> Boxed = product distribution from a copper free reaction at 150 °C using the corresponding chloride salt in a microreactor by Pike and co-workers.<sup>65</sup>

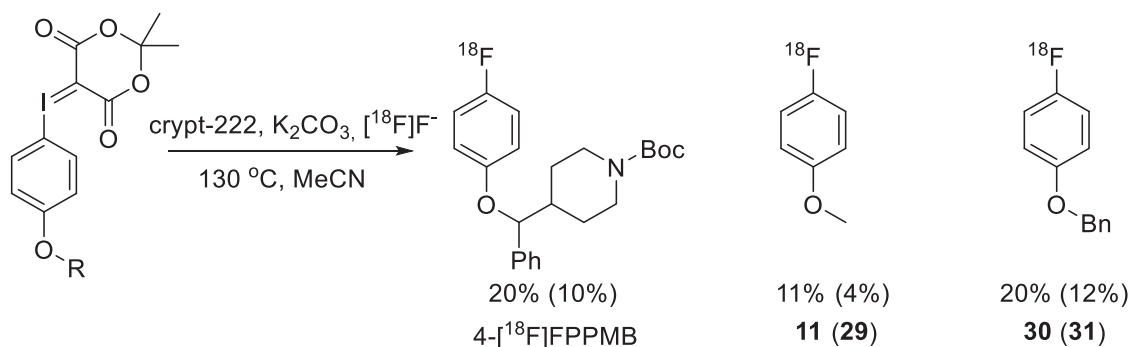
### 2.5.7 - Iodonium ylides

Iodonium ylides were first described as radiofluorination precursors by Satyamurthy and Barrio in a patent from 2010.<sup>66</sup> A selected overview over described auxiliaries is shown in Scheme 13. Meldrums acid (**24**), barbituric acid (**26**) and benzopyrandonone (**27**) derived auxiliaries afford comparable radiofluorination yields. Dimedone (**25**) and tetrahydroquinolinedione (**28**) provided a lower RCY of **9**.



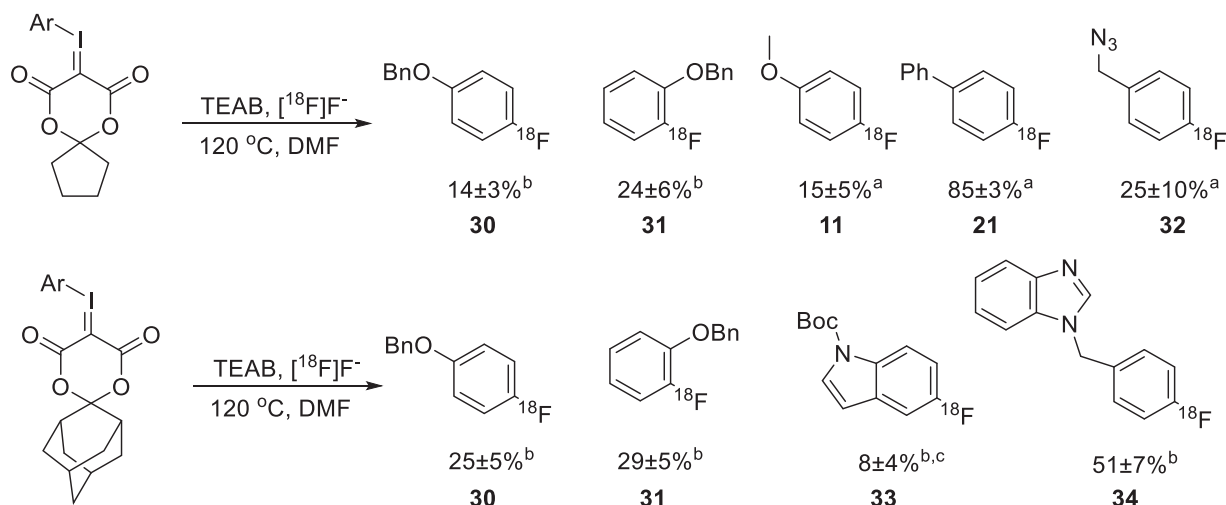
**Scheme 13:** First generation of iodonane- $\lambda^3$ -ligands for radiofluorination making  $[\text{}^{18}\text{F}]\text{fluorobenzene}$ .<sup>66</sup>

Iodonium ylides were utilised by Cardinale *et. al.* to radiofluorinate electron rich 4- $^{18}\text{F}$ FPPMP in 20% yield<sup>67</sup> (Scheme 14). However, an unexpected radiofluorinated 3-regioisomer is formed under the reaction conditions. This unexpected regioisomer distribution is also presented for the radiofluorination of 4- $^{18}\text{F}$ fluoroanisole (**11**, 11% and **29**, 4%) and 1-benzyloxy-4- $^{18}\text{F}$ fluorobenzene (**30**, 20% and **31**, 12%).



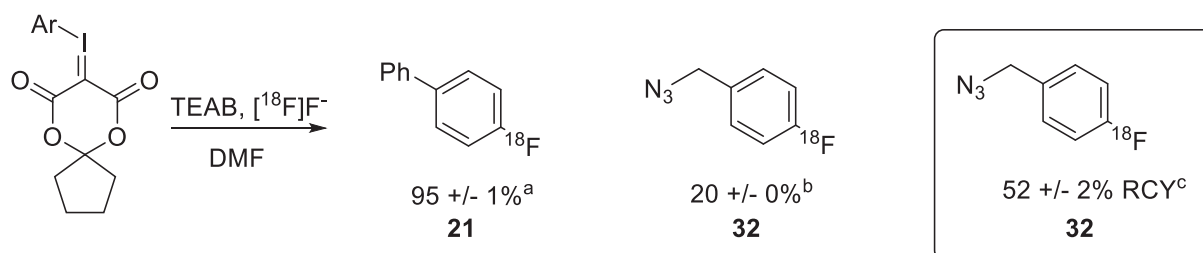
**Scheme 14:** Radiofluorination isomer distribution reported by Cardinale *et. al.*<sup>67</sup> RCY refer to *ipso*-product and *ortho*-product within parenthesis.

A further derivatisation of the auxiliary was made by Rotstein *et. al.* who synthesised a spirocyclic ligand<sup>55</sup> (Scheme 15). Radiofluorination afforded comparable RCY as reported by Cardinale *et. al.* with 4- $^{18}\text{F}$ fluoroanisole (**11**, 15±5%) and 1-benzyloxy-4- $^{18}\text{F}$ fluorobenzene (**30**, 14±3%). However, no radiofluorinated constitutional isomers were reported. Activated substrate 4-phenyl-1- $^{18}\text{F}$ fluorobenzene (**21**) was produced in 85±3%. Electron neutral **32** and *ortho*-substituted **31** was produced in comparable yield (25±10% and 24±6% respectively). Rotstein *et. al.* also synthesised an adamantyl analogue (Scheme 14), described to possess additional storage stability and to survive flash column chromatography over silica.<sup>57</sup> Benzyl ethers **30** and **31** were produced in comparable RCY for both auxiliaries in 25±5% and 29±5% respectively. Indole **33** was produced in a meager 8±4% and was quantitatively hydrolysed under the radiofluorination conditions whereas astemizole fragment (**34**) was radiofluorinated in a higher RCY (51±7%). Attempts by Rotstein *et. al.* to improve the radiofluorination yield by adding radical scavengers TEMPO and BHT were unsuccessful.<sup>55</sup>



**Scheme 15:** Notable radiolabelling examples using spirocyclic iodonium ylides [a] = Rotstein *et. al.*<sup>55</sup> [b] = Rotstein *et. al.*<sup>57</sup> [c] quantitative Boc-hydrolysis under labelling conditions.

The radiofluorination reactions of iodonium ylides were further investigated using microfluidics and optimised reaction conditions afforded activated substrate 4-phenyl-1-<sup>18</sup>F-fluorobenzene (**21**) in 95% yield in 32 sec.<sup>68</sup> (Scheme 16). Building block (1-azidomethyl-4-<sup>18</sup>F-fluorobenzene (**32**) was afforded in 20% yield using microfluidics, whereas optimised conventional radiochemistry afforded a RCY of 52±2%.<sup>56</sup> The azide **32** and derivatives thereof has been used as a building block for bioconjugations using a CuAAC reaction with sensitive bio-compounds aimed at PET imaging.

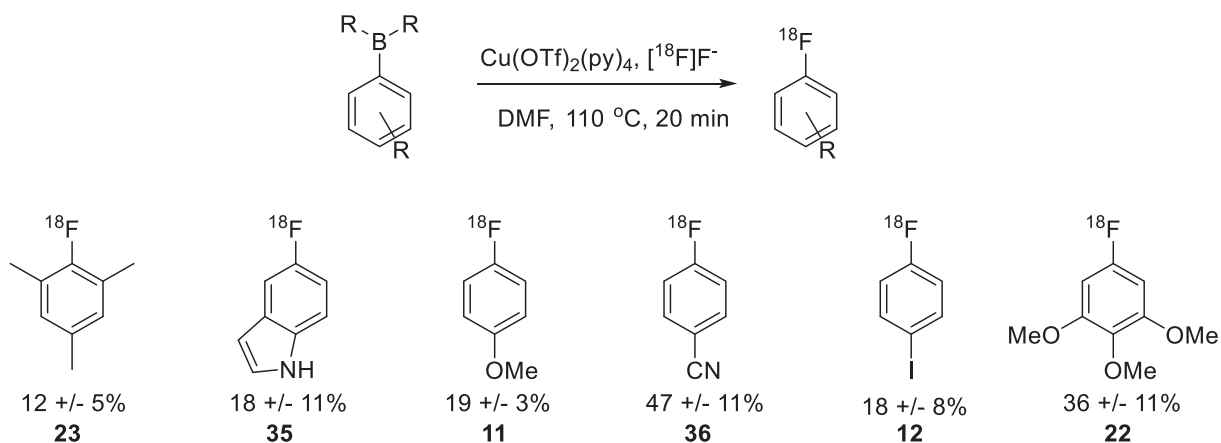


**Scheme 16:** [a] 200 °C [b] 210 °C [c] 120 °C.

Iodonium ylides have been used for synthesising several radiotracers for PET imaging.<sup>56, 63, 67, 69-72</sup> An interesting head-to-head comparison of spirocyclic iodonium ylides to boronic esters proved the ylides as superior precursors in terms of both reproducibility and yield.<sup>63</sup> Proposed radical scavenger TEMPO was added to the radiofluorination reactions, although its effect is not investigated.

## 2.5.8 - Copper mediated radiofluorination of boronic acids/esters

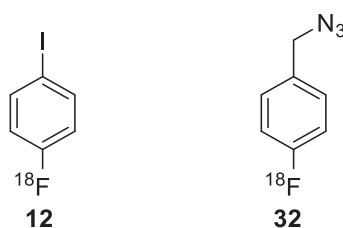
A radiofluorination method developed independently by the Sanford/Scott research groups<sup>38</sup> and the Gouverneur research group,<sup>39</sup> demonstrate a copper(II) mediated radiofluorination of boronic acids and esters.<sup>73</sup> Selected examples in Scheme 17 show a high RCY for electron rich substrate 5-<sup>18</sup>F]fluro-1,2,3-trimethoxybenzene (**22**, 36±11%). However, radiofluorination of sterically hindered 2,4,6-trimethyl-<sup>18</sup>F]fluorobenzene (**23**, 12±5%) produce a lower incorporation of fluoride. Activated substrate 4-<sup>18</sup>F]fluorobenzonitrile) (**36**) afford 47±11% RCY and more challenging substrate unprotected 5-<sup>18</sup>F]fluoroindole (**35**, 18±11%) is radiofluorinated in comparable yields to 4-<sup>18</sup>F]fluoroanisole (**11**, 19±3%) and 4-<sup>18</sup>F]fluoro-1-iodobenzene (**12**, 18±8%).



**Scheme 17:** Selected radiofluorination examples from Mossine *et. al.*<sup>38</sup>

## 2.6 - Multistep radiofluorination and functional group tolerance

Some radiotracers are very challenging or impossible to access directly using existing methodologies, e.g. introduction of fluorine-18 into sensitive biomolecules due to instability under direct radiofluorination conditions. For instance, azide **32** can be coupled to alkynes via a CuAAC reaction.<sup>68</sup> Aryl iodides such as 4-[<sup>18</sup>F]fluoro-1-iodobenzene (**12**) has proven valuable building blocks for transition metal catalysed cross coupling reactions constructing larger complex radiotracers. For instance, **12** has been used in Stille, Sonogashira and Buchwald-Hartwig cross coupling reactions constructing nucleosides,<sup>74</sup> for the labelling of peptides<sup>75</sup> and for accessing 4-[<sup>18</sup>F]fluorophenylpiperazine eventually constructing a D4 receptor ligand.

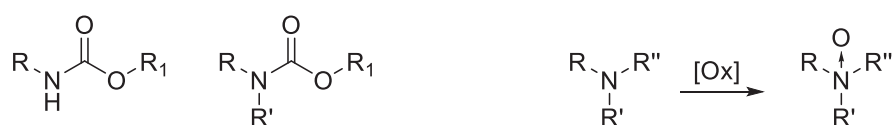


**Figure 5:** Two important <sup>18</sup>F-labelled fluoroarene building blocks.<sup>76-78</sup>

Not only biomolecules are challenging to radiofluorinate, small molecular compounds can also be difficult to access. For instance, small molecular drugs bearing protic functionalities or competing nucleophiles can diminish fluorides nucleophilicity, outcompete fluoride or in other ways disturb the radiofluorination reaction. For instance, both secondary amines and tertiary amines has been reported to quench the radiochemical yield in the radiofluorination of pinacolboranes.<sup>79</sup> A solution is to mask amine functionalities via use of protecting groups. Primary and secondary amines are routinely masked as their respective carbamates (Scheme 18), however tertiary amines are not. A protecting group need to be stable and not interfere with the reaction conditions used in precursor synthesis and in the radiofluorination step. In addition, a protecting group need to be both easily introduced and removed in high yield preferably under mild reaction conditions free from toxic reagents. Protecting groups developed for use in organic synthesis, where there are no time constraints, are not always compatible to short lived radiotracers such as <sup>18</sup>F (110 minutes). Further work developing protecting groups compatible with radiochemistry could broaden the substrate scope over available radiotracers.



Different kinds of radiofluorination precursors have different functional group compatibility with regard to both preparation and radiofluorination. The precursor class of hypervalent iodinanes has for instance an oxidation step during their synthesis in which free amines often are oxidised (Scheme 18). The typical strategy for avoiding oxidation is to add a strong acid that protonate the amines. However this strategy only works intermittently and is incompatible with acid-sensitive functional groups. Hypervalent iodinanes are the only transition metal free radiofluorination methodology that consistently afford high RCY yields for sterically hindered substrates regardless of activation.<sup>1, 66</sup>



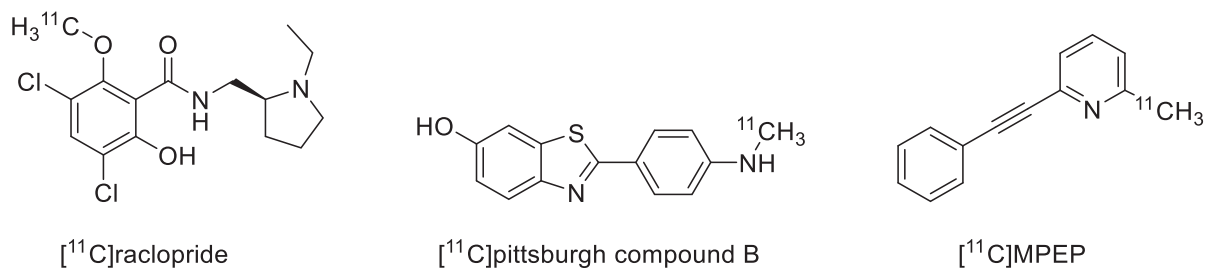
**Scheme 18:** To the left: general primary and secondary amine protected as a carbamate. To the right, oxidation of a tertiary amine.

## 2.7 - Carbon

Carbon, C, atomic number 6 is the 15<sup>th</sup> most abundant element on earth. All life is carbon based and all organic molecules have carbon atoms incorporated. Carbon-carbon and carbon-heteroatom bond forming reactions are abundant in literature. Carbon in nature is found primarily as non-radioactive carbon-12 (99%) and carbon-13 (1%) but also traces of the  $\beta^-$  emitter carbon-14 ( $1.5 \times 10^{-6}$  ppm).<sup>80</sup>

## 2.8 - Carbon in PET

Among the carbon isotopes, carbon-11 is a positron emitting nuclide with use in PET imaging. Carbon-11 is produced via the  $^{14}\text{N}(p, \alpha)^{11}\text{C}$  reaction (Table 2) in presence of  $\text{O}_2$  or  $\text{H}_2$  affording  $[^{11}\text{C}]\text{CO}_2$  and  $[^{11}\text{C}]\text{CH}_4$  respectively. Although fluorine-18 is often the preferred radionuclide in PET studies due to its longer half-life and more practicable logistics, not all PET radiotracer candidates are fluorinated compounds, and available radiofluorination reactions are limited.<sup>16, 18, 25, 81</sup> Carbon-11 offers an attractive and practical alternative for PET radiotracer synthesis and imaging. The shorter half-life of carbon-11 compared to fluorine-18 also allows for *in vivo* PET studies with repeated injections in the same subject. A selection of carbon-11 PET radiotracers is shown in Figure 6.



**Figure 6:** Dopamine D2 antagonist [ $^{11}\text{C}$ ]raclopride,<sup>82</sup> beta-amyloid plaque imaging agent [ $^{11}\text{C}$ ]pittsburgh compound B<sup>83</sup> and metabotropic glutamate receptor antagonist [ $^{11}\text{C}$ ]MPEP.<sup>84</sup>

### 2.8.1 - Carbon-11 building blocks

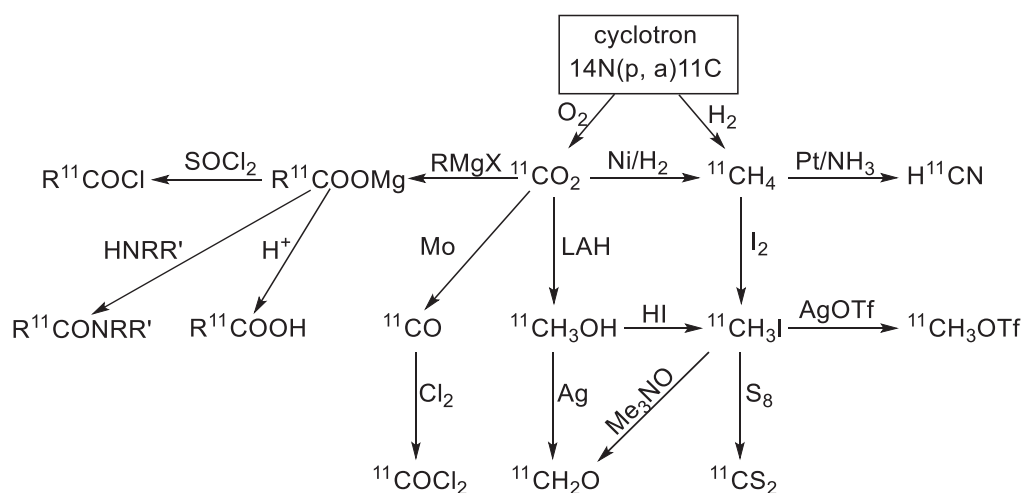
Cyclotron produced [ $^{11}\text{C}$ ]CO<sub>2</sub> can be used directly for radiolabelling<sup>85</sup> but is typically converted into more reactive species.<sup>16, 86-87</sup> There are many possibilities for synthetic manipulations with the diverse toolbox of available  $^{11}\text{C}$ -building blocks. However, the considerably shorter half-life of carbon-11 compared to fluorine-18 (Table 1) necessitate both efficient and fast radiolabelling reactions, analysis and logistics. A compromise is often made between RCY and radiochemical decay since RCY is quickly counteracted by radioactive decay. Although the potential possibilities for constructing complex organic molecules via multistep synthesis is unlimited, the short half-life of carbon-11 permits time consuming reactions and purification steps.<sup>16</sup>

There exist two different routes for synthesising [ $^{11}\text{C}$ ]CH<sub>3</sub>I (Scheme 19), the wet method and the dry method. In the wet method, [ $^{11}\text{C}$ ]CO<sub>2</sub> is reduced with LAH in THF creating [ $^{11}\text{C}$ ]MeOH.<sup>87</sup> The

intermediate  $[^{11}\text{C}]\text{MeOH}$  is further treated with hydroiodic acid<sup>87</sup> or  $\text{PPh}_3\text{I}_2$ <sup>88</sup> and converted into  $[^{11}\text{C}]\text{CH}_3\text{I}$ . The wet method has the drawback that atmospheric  $^{12/13}\text{CO}_2$  sequestered by LAH is a source of radiochemical dilution which can limit the molar activity.

The dry method start with  $[^{11}\text{C}]\text{CH}_4$ <sup>89</sup> either produced in target or via a nickel mediated hydrogenation of  $[^{11}\text{C}]\text{CO}_2$  (Scheme 19) at elevated temperatures (360-400 °C).<sup>89-91</sup> The intermediate  $[^{11}\text{C}]\text{CH}_4$  is iodinated via a radical iodination at 700-750 °C using elemental iodine to afford  $[^{11}\text{C}]\text{CH}_3\text{I}$ .<sup>91</sup>

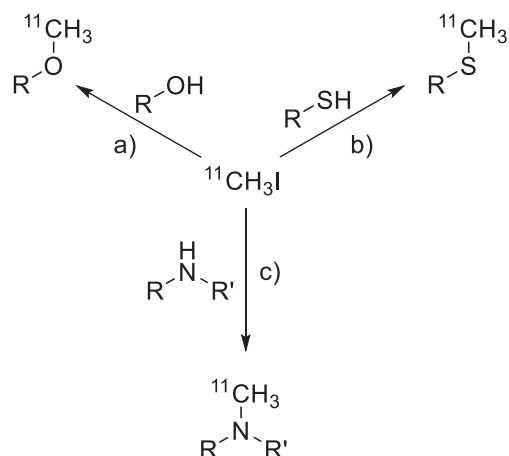
Another key building block,  $[^{11}\text{C}]\text{HCN}$  (Scheme 19) can be prepared via the Andrussov reaction by treating  $[^{11}\text{C}]\text{CH}_4$  with ammonia over platinum at 750-1000 °C.<sup>92</sup>



**Scheme 19:** A selection of chemical manipulations for constructing a broad range of carbon-11 building blocks used for PET radiotracer synthesis. Reproduced from Dahl *et. al.*<sup>86</sup> in combination with Miller *et. al.*<sup>16</sup>

### 2.8.2 - Heteroatom methylation reactions

The most important route for synthesis of carbon-11 radiotracers for clinical use is heteroatom radiomethylation reactions<sup>86</sup> (Scheme 20) using either  $[^{11}\text{C}]\text{MeI}$ <sup>86</sup> or  $[^{11}\text{C}]\text{MeOTf}$ .<sup>93</sup> Overalkylation of amines is non-problematic in radiochemistry since only trace quantities of the alkylating reagent is present, unlike in stoichiometric methylation reactions (section 2.3.1). The reaction is often performed via either captive-solvent<sup>94</sup> or on-cartridge<sup>95</sup> methods.

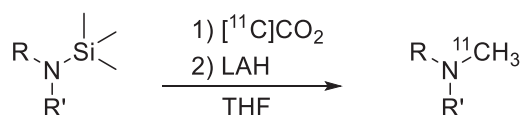


**Scheme 20:** General heteroatom [ $^{11}\text{C}$ ]methylation reactions starting from [ $^{11}\text{C}$ ]MeI. a) Alcohol, b) thiol c) amine.

Radioalkylation via the captive-solvent<sup>94</sup> method proceeds by injecting the precursor dissolved in a polar aprotic solvent into an HPLC injection loop followed by passage of [ $^{11}\text{C}$ ]MeI through the line. The reagent is allowed to react with the precursor and the reaction mixture is subsequently injected into an HPLC column for purification.

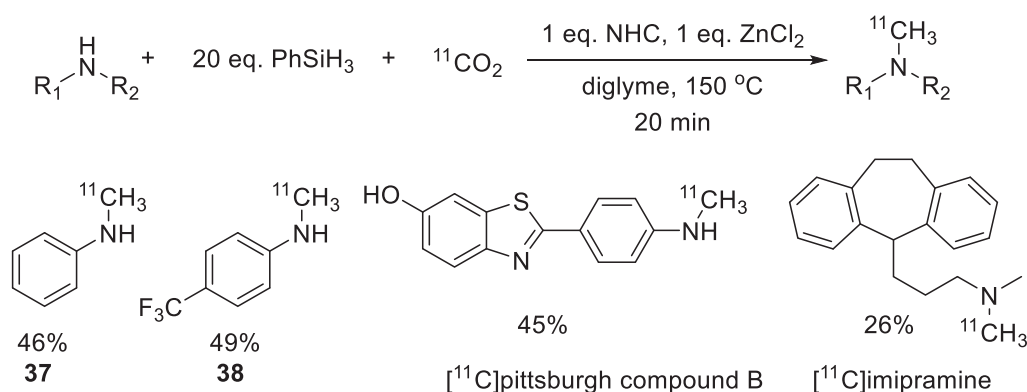
For the on-cartridge<sup>95</sup> method, a small amount of precursor is trapped on a reverse phase cartridge. The radiomethylating reagent [ $^{11}\text{C}$ ]MeI is passed through the cartridge where it reacts with the precursor. The product is subsequently eluted and purified via, for instance, additional cartridges or HPLC.

Amines can also be directly radiomethylated using cyclotron produced [ $^{11}\text{C}$ ]CO<sub>2</sub>, thus eliminating the need for producing [ $^{11}\text{C}$ ]MeI. An early approach by Ram *et. al.*<sup>96</sup> (Scheme 21) treat the corresponding silyl amine with [ $^{11}\text{C}$ ]CO<sub>2</sub> followed by an LAH reduction reaction that furnish N- $^{11}\text{C}$  methyl amines.



**Scheme 21:**  $^{11}\text{C}$ -Methylation of silylamines from [ $^{11}\text{C}$ ]CO<sub>2</sub> by Ram *et. al.*<sup>96</sup>

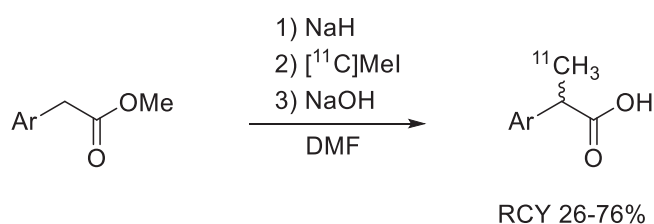
A more recent approach described by Liger *et. al.*<sup>97</sup> use PhSiH<sub>3</sub> as reductant with ZnCl<sub>2</sub> and NHC as mediators for radioalkylation of amines. The reaction is performed in a one pot system and avoid the use of LAH and synthesis of silylamines. Anilines are less nucleophilic than the corresponding aliphatic amines and are more challenging to radioalkylate using [<sup>11</sup>C]MeI or [<sup>11</sup>C]MeOTf.<sup>86</sup> Primary anilines **37**, **38** and Pittsburgh compound B (Scheme 22) are prepared in moderate yields of 46%, 49% and 45% respectively. Aliphatic amine [<sup>11</sup>C]imipramine is also radioalkylated in acceptable yield (26%).



**Scheme 22:** [<sup>11</sup>C]Methylation of amines using [<sup>11</sup>C]CO<sub>2</sub>.<sup>97</sup> Yields are decay corrected and based on trapped [<sup>11</sup>C]CO<sub>2</sub>.

### 2.8.3 - Carbon methylation reactions

Formation of carbon-carbon bonds can be achieved via radioalkylation of enolates (Scheme 23).<sup>98</sup> The ester is pre-treated with a strong base to synthesise the enolate. The enolate is alkylated with [<sup>11</sup>C]MeI and produce racemic products. Further work by Filp *et. al.*<sup>99</sup> use a chiral phase transfer catalyst mediated alkylation of enolates. The enantioselective radioalkylation reaction provide a route to 3-[<sup>11</sup>C]-L-alanine.



**Scheme 23:** [<sup>11</sup>C]Methylation of enolates using [<sup>11</sup>C]MeI, yields are decay corrected.

Carbon-carbon bond forming reactions can also be performed via palladium mediated cross coupling reactions as exemplified in Scheme 24.<sup>87, 100-101</sup>

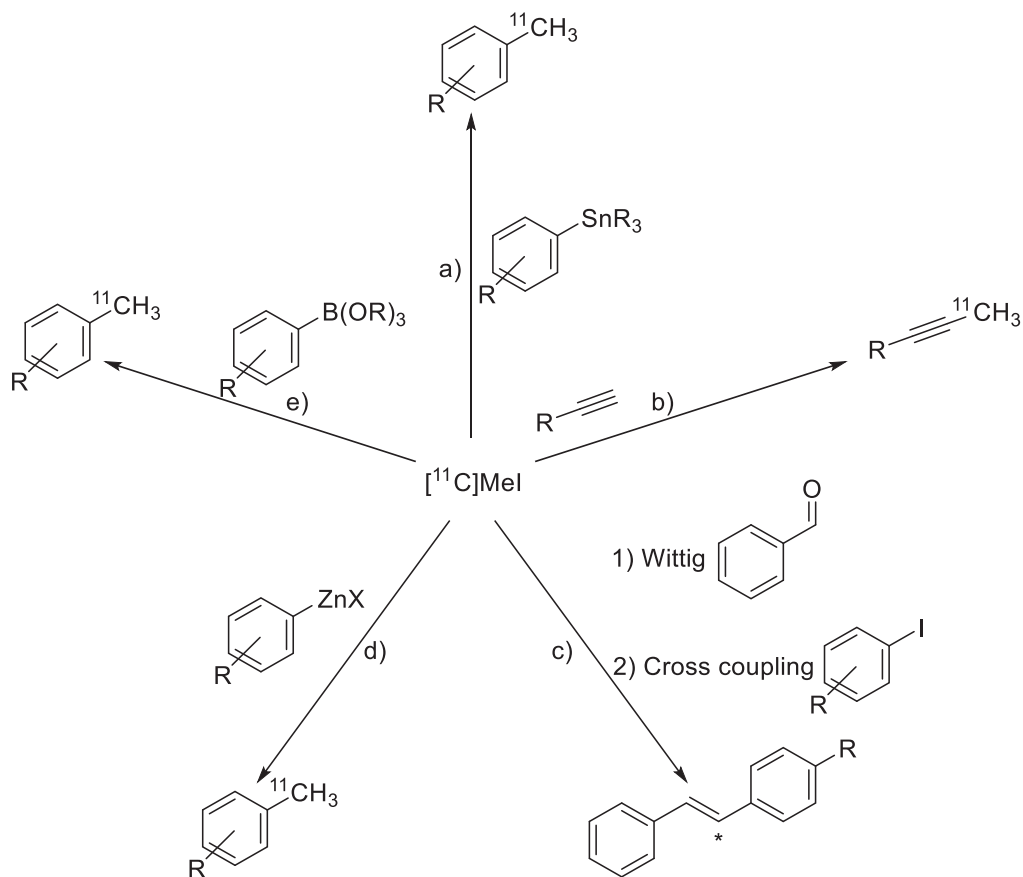
The Stille cross coupling (Scheme 24a) utilise organotin reagents which toxicity complicates its use.<sup>84, 86</sup>

The Sonogashira coupling (Scheme 24b) provide access to [<sup>11</sup>C]methyl alkynes. The cross coupling reaction proceed via transition metal (Cu(I)) mediation.<sup>87</sup>

Björkman *et. al.*<sup>102</sup> showed that a Wittig olefination using [<sup>11</sup>C]MeI, a tertiary phosphane and benzaldehyde produce <sup>11</sup>C-labelled styrene (Scheme 24c). The styrene can further be coupled with aryl halides via a Heck coupling to access <sup>11</sup>C-labelled stilbenes.

The Negishi cross coupling reaction (Scheme 24d) utilise organozinc compounds which are moisture sensitive and challenging to prepare. The Negishi coupling reaction was recently used for synthesising a range of [<sup>11</sup>C]methyl arenes including [<sup>11</sup>C]MPEP.<sup>103</sup>

The Suzuki cross coupling reaction is possibly the most diverse and is based on nontoxic boronic acids and esters (Scheme 24e). Both alkyl and aryl boronates can be coupled with  $[^{11}\text{C}]\text{MeI}$ .<sup>104</sup>

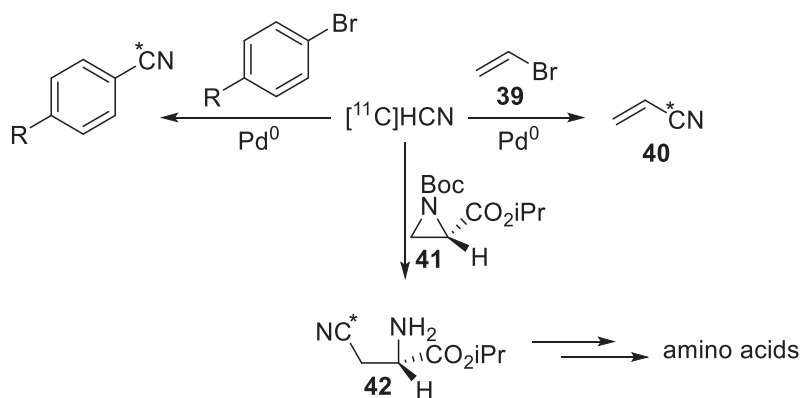


**Scheme 24:** Use of  $[^{11}\text{C}]\text{MeI}$  for constructing unsaturated  $^{11}\text{C}$ -labelled radiotracers via palladium mediated cross coupling reactions.<sup>87, 101</sup> a) Stille cross coupling b) Sonogashira cross coupling c) Wittig olefination followed by a Heck coupling d) Negishi coupling e) Suzuki cross coupling. Asterisk denotes carbon-11 inclusion.



### 2.8.4 - Cyanation reactions

Another important building block for PET radiotracer synthesis is  $\text{H}[^{11}\text{C}]\text{CN}$ , which can be prepared via the Andrussow oxidation reaction where ammonia and methane react over a platinum catalyst at  $1000\text{ }^\circ\text{C}$ .<sup>105</sup> Both acrylonitrile (**40**) and aryl nitriles are readily available via Pd mediated chemistry (Scheme 25). Ring opening of Boc protected aziridine (**41**) provide a starting point for synthesis of amino acids  $[^{11}\text{C}]\text{asparagine}$  and  $[^{11}\text{C}]\text{aspartic acid}$ .<sup>90</sup>



**Scheme 25:** Use of  $[^{11}\text{C}]\text{HCN}$  for constructing aryl nitriles<sup>89</sup> and acrylonitrile<sup>105</sup> under mediation by  $\text{Pd}(0)$  and ring opening of aziridines using  $\text{NBu}_4\text{CN}$ .<sup>90</sup> Asterisks denote carbon-11 inclusion.

### 2.8.5 - Carbonylation reactions

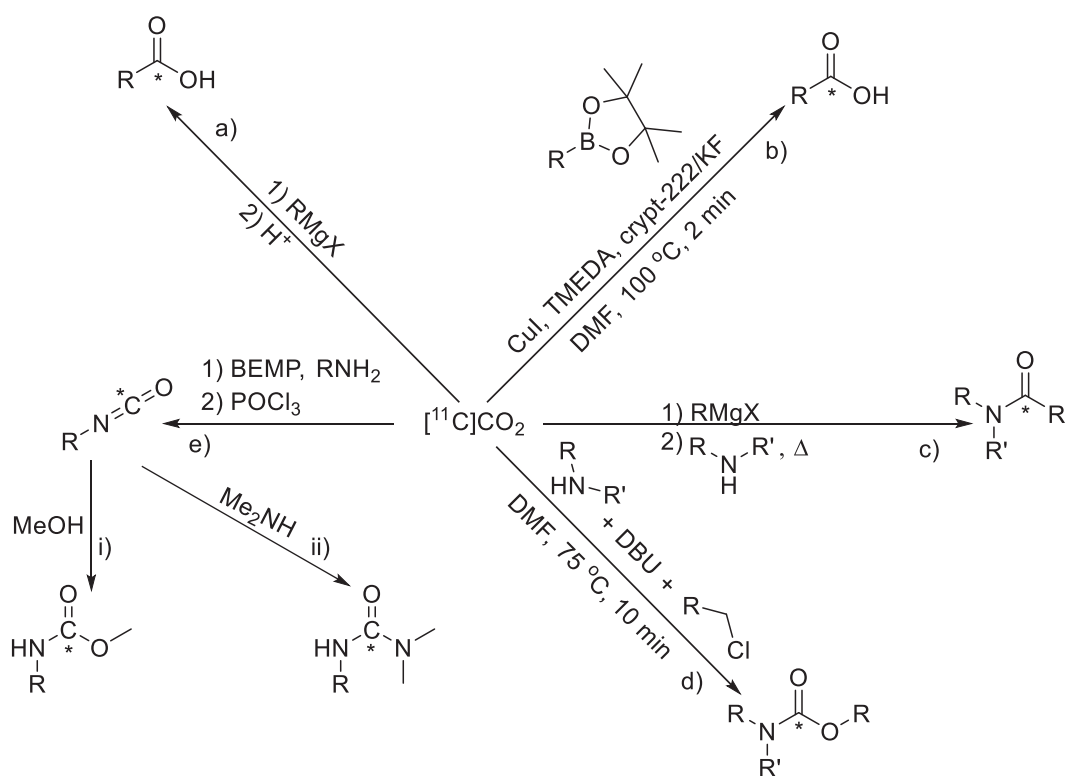
Treating Grignard reagents with  $[^{11}\text{C}]\text{CO}_2$  followed by acidic workup produce the corresponding carboxylic acids (Scheme 26a). However, organometallic reagents sequester atmospheric  $\text{CO}_2$  upon storage which diminishes the molar activity as with LAH (see above).<sup>16</sup> The substrate scope is limited to molecules devoid of electrophilic functional groups that would react with Grignard reagents.

An alternative route was developed by Riss *et. al.*<sup>106</sup> who utilise a  $\text{CuI}$  mediated  $^{11}\text{C}$ -carboxylation of boronic acid esters (Scheme 26b) that efficiently produce carboxylic acids. The method expands the substrate scope considerably.

The intermediate magnesium carboxylate can also be directly reacted with an amine and converted into the corresponding amide (Scheme 26c).<sup>107</sup>

Hooker *et. al.*<sup>108</sup> developed a direct route (Scheme 26d) for providing access to carbamates via a DBU mediated trapping and activation of [<sup>11</sup>C]CO<sub>2</sub>.

Later work by Wilson *et. al.*<sup>109</sup> instead utilise the phosphazene base BEMP for trapping and activating [<sup>11</sup>C]CO<sub>2</sub> for addition to a primary amine. The intermediate is dehydrated using POCl<sub>3</sub> forming isocyanates. Further treatment of the isocyanates with alcohol or amines provide carbamates and ureas respectively (Scheme 26e).



**Scheme 26:** Use of cyclotron produced [<sup>11</sup>C]CO<sub>2</sub> for constructing various [<sup>11</sup>C]carbonyls. a) carboxylic acids<sup>107</sup> b) carboxylic acids<sup>106</sup> c) amides<sup>107</sup> d) carbamates<sup>108</sup> e) carbamates and ureas.<sup>109</sup> Asterisks denote carbon-11 inclusion.

## 2.9 - NMDA/NR2B

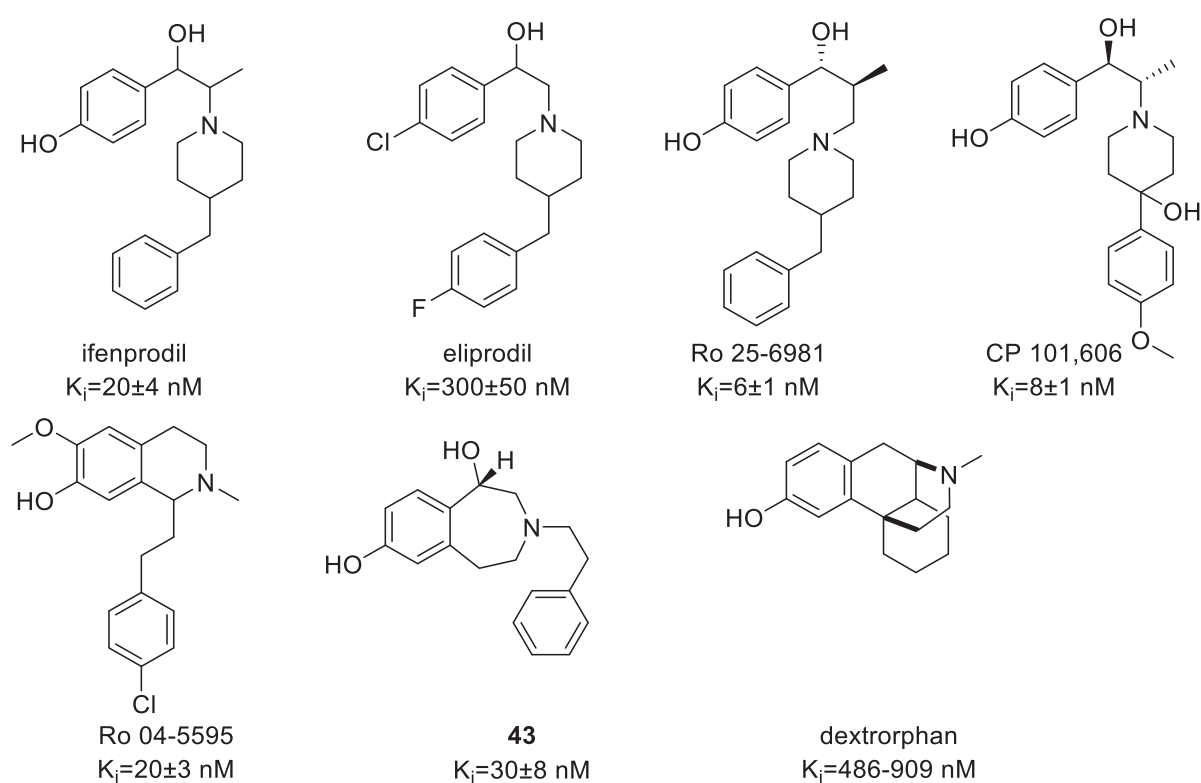
NMDA (*N*-methyl-D-aspartate) receptors are glutamate gated ion channels and essential neurotransmitter receptors in the central nervous system.<sup>110</sup> The channel is activated by binding of the two agonists glutamate and glycine. Binding results in an influx of cations, primarily Ca<sup>2+</sup>.<sup>110</sup> NMDA receptors are built up from eight different NR1 subunits and four different NR2 subunits (A-D). NMDA receptors are tetrameric receptors constituted of two NR1 and two NR2 subunits.<sup>111</sup>

NMDA receptors as imaging target have received considerable attention for PET radiotracer development. However there is no selective radiotracer suitable for *in vivo* investigation using PET imaging. NMDA receptors are of interest as imaging targets due to their involvement in neuroplasticity, learning and memory formation.<sup>112</sup> Dysfunction of NMDA receptors are associated with severe neurological disorders such as Parkinson's disease,<sup>110</sup> Alzheimer's disease,<sup>113</sup> neuropathic pain,<sup>114</sup> Huntington's disease<sup>115</sup> and schizophrenia. The involvement of NR2B in disease states and its regional distribution, make NMDA subtype NR2B receptors a highly attractive imaging target for radiotracer development. An NR2B selective radiotracer could facilitate drug discovery by serving as a tool compound or be used in diagnostic imaging. In addition, among NMDA receptors, NR2B selective antagonists have the advantage of being significantly less prone to impair locomotion in subjects compared to other NMDA subunit selective ligands.<sup>116</sup> The brain regions rich in NR2B subunits are the cerebral cortex, hippocampus, striatum and thalamus bulb.<sup>117-118</sup>

### 2.9.1 - NR2B ligands and PET imaging

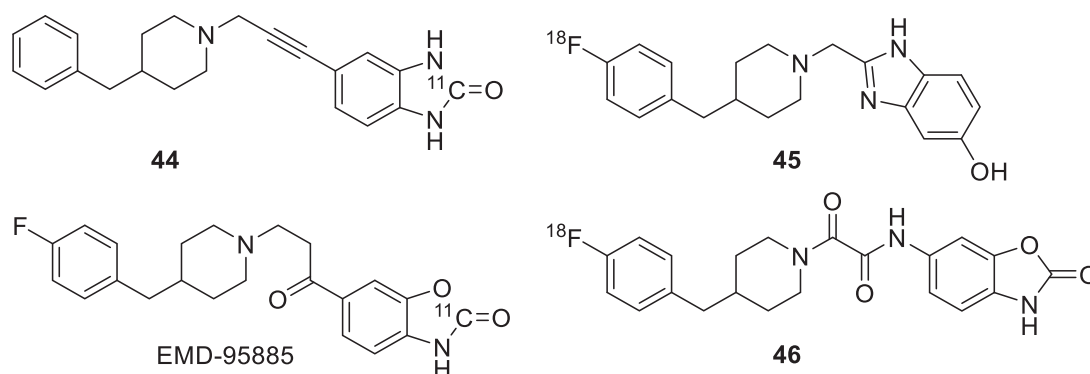
There are several ligands described as NMDA subtype NR2B selective ligands (Figure 6). However, ifenprodil and its derivatives (eliprodil, Ro 25-6981, CP 101,606) have been demonstrated nonselective with cross affinity to  $\sigma$ -receptors.<sup>119-120</sup> Ro 04-5595 and **43** have not been evaluated via PET imaging and do not have known cross affinities. However, aryl methyl ether derivative of **43** (Figure 8, NB1) has shown cross selectivity to  $\sigma$ -receptors in PET imaging.<sup>121</sup> Common cough suppressant dextromethorphan metabolite dextrorphan binds to NMDA receptors with a moderate affinity and has potential for development into a PET radioligand. Common structural features for the NMDA ligands in Figure 6 are electron rich arenes (phenols), a tertiary aliphatic amine and a lipophilic phenethyl chain. Only eliprodil has an

incorporated fluorine but is unsuitable as PET radiotracer due to low NR2B affinity and off target binding to  $\sigma$ -receptors. Therefore, developing a [ $^{18}\text{F}$ ]radiotracer for PET imaging require synthesis of fluorine containing ligands, possibly based on known NR2B ligands. Incorporation of [ $^{18}\text{F}$ ]F $^-$  into electron rich arenes often present in NMDA/NR2B ligands require special radiofluorination techniques. These techniques either rely on transition metals or necessitate further method development.

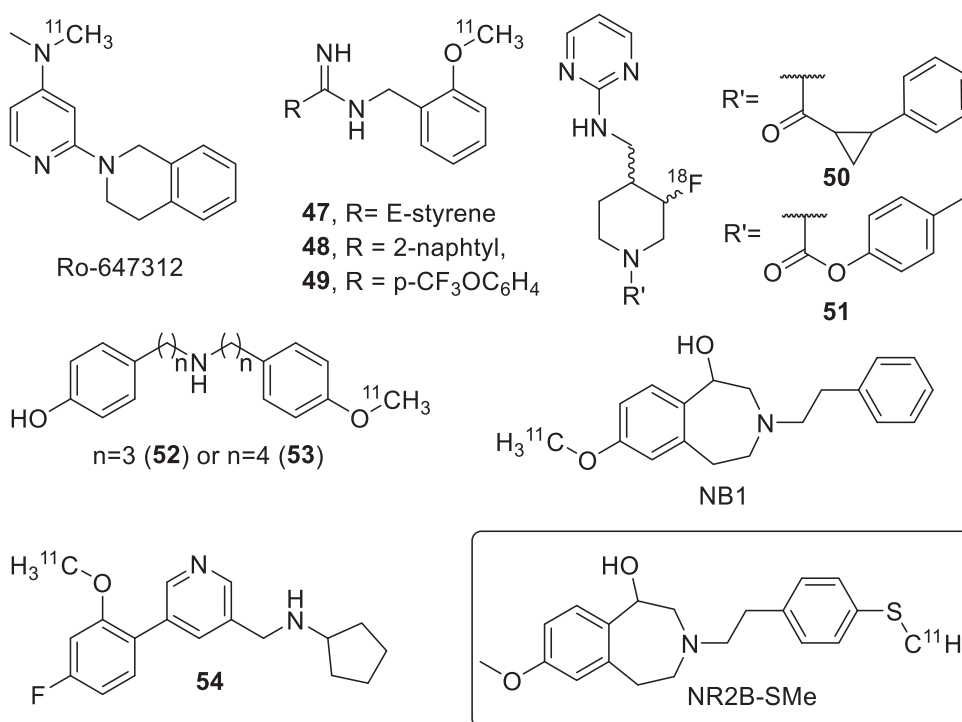


**Figure 6:** A selection of NR2B ligands and their binding affinity. Ifenprodil,<sup>122</sup> eliprodil,<sup>122</sup> CP 101,606,<sup>122</sup> Ro 04-5595,<sup>122</sup> benzodiazepine **43**<sup>123</sup> and dextrorphan<sup>124</sup> (MK-801 displacement).

Several attempts have been made to develop PET tracers for studying NR2B receptors but so far none has been entirely successful. Attempts have been made, both, using  $^{18}\text{F}$  (Figure 7) and  $^{11}\text{C}$  (Figure 8). The candidates have had various concerns, for instance EMD-95885, Ro-647312, NB1, **46** and **52-54** were not selective. Radiotracers **44**, **50**, **51** had no or very low brain uptake whereas **45-49** were metabolised too rapidly. Many of the investigated radiotracers that have shown selectivity issues had a cross affinity to  $\sigma$ -receptors. NR2B-SMe is currently being evaluated by Cai *et. al.*<sup>125</sup>



**Figure 7:** Fluorine-18 radiotracers evaluated using PET imaging. EMD-95885<sup>126</sup> was nonselective, 44<sup>127</sup> had both poor brain uptake and was nonselective, both 45 and 46 were metabolised via a defluorination pathway.<sup>128</sup>



**Figure 8:** Carbon-11 radiotracers evaluated using PET imaging. Ro-647312,<sup>129</sup> 52, 53<sup>130</sup> and NB1<sup>121</sup> were nonselective. The guanidines (47-49)<sup>131</sup> were metabolised too rapidly. Fluoropiperidines (50-51)<sup>132</sup> did not enter the brain. Pyridine cyclopentanamine (54)<sup>133</sup> was unselective with a  $\sigma$ -cross affinity. NR2B-SMe is currently being evaluated by Cai *et al.*<sup>125</sup>

### 3 - Conclusion and Outlook

We have improved the radiofluorination of iodonium ylides, especially for non-activated and deactivated substrates. The methodology was adapted to preparative synthesis (paper I-II). The improvement is important since iodonium ylides are of extra importance in radiotracer productions, due to their unique reactivity providing excellent yields for sterically hindered substrates. In addition, radiofluorination of iodonium ylides is currently the only available transition metal free route for accessing electron rich  $^{18}\text{F}$ -labelled fluoroarenes. The radiofluorination substrate scope of iodonium ylides complements other transition metal free radiofluorination methods well, such as de-nitro-fluorination reactions and use of diaryliodonium salt precursors.

An oxidative degradation pathway was found as the cause for both inconsistent and low RCY (paper I). By purging the reaction mixtures with inert gas, the yield variation was reduced and the RCY was significantly improved. Residual iodine from precursor preparation was found to be the underlying cause for varying yields in between precursor batches. Iodine was removed by washing a solution of the precursor with  $\text{Na}_2\text{S}_2\text{O}_3$ , leading to better batch reproducibility.

Fluoride source and solvent effects was investigated for the stoichiometric fluorination of iodonium ylides (paper II). A TBAF mediated degradation pathway was found as the source of constitutional isomers. The stoichiometric fluorination reaction was optimised to be *ipso*-selective by using a crypt-222/KF complex. The slow *in situ* formation of crypt-222/KF in DMF was recognised as the culprit. Preforming the complex greatly enhanced the fluorination yield. I believe that preformed crypt-222/KF has further use in preparative fluorination reactions of other substrates. Crypt-222/KF has excellent solubility properties in combination with low hygroscopicity, which is problematic for other fluorination reagents (KF, CsF and TBAF). No reduced performance of the crypt-222/KF complex was found after one month in a closed vial at room temperature under air.

These findings also imply that the corresponding radiofluorination reaction using trace quantities of fluoride is *ipso*-selective. However, there are other frequently used phase transfer catalyst for the radiofluorination of iodonium ylides such as TEAB in DMF. In these radiofluorination reactions, TEAB is used in super-stoichiometric amounts and could be the source of constitutional isomers. I believe that the fluorination of iodonium ylides using TEAB should be further

investigated using for instance  $^{19}\text{F}$ -NMR analogous to in paper II. Constitutional radiofluorinated isomers can have different binding profiles and confound the results from PET scans.

It was found that triphenylphosphane enhances the radiofluorination rate of iodonium ylides (paper I). Addition of triphenylphosphane is well suited for automation of PET radiotracer production, has great precedence in organic synthesis and is detectable on the UV trace in HPLC. The role of triphenylphosphane in the fluorination reaction is not known. There are several reasonable mechanistic suggestion for the triphenylphosphane assisted radiofluorination of iodonium ylides. For instance, a reversibly formed  $[\text{PPh}_3\text{F}]^-$  specie could coordinate to the iodine and facilitate the fluorination reaction. Another plausible reaction mechanism involve auxiliary exchange from Meldrum's acid to the phosphane ( $\text{ArI}=\text{Aux}$  to  $\text{ArI}=\text{PPh}_3$ ). The formation of this intermediate could facilitate fluorination but also consume the precursor. Addition of triphenylphosphane to stoichiometric fluorination reactions were unsuccessful. As described in paper II, triphenylphosphane oxide was observed via  $^{31}\text{P}$ -NMR as an oxidation side product in the fluorination of iodonanes, likely in the presence of residual water. The reaction stoichiometry discrepancy is a good example for differences between conventional stoichiometric chemistry and radiochemistry. Consequently, minor precursor consumption is not problematic in radiofluorination reactions but is in preparative synthesis.

We also developed a complimentary masking group strategy for secondary and tertiary amines. The strategy expand the substrate scope over radiotracers that can be radiofluorinated using hypervalent iodonanes (paper III). The masking group strategy avoid N-oxidation and interference of basic amines during the radiofluorination step. Amines protected as formamides ease both precursor synthesis and provide improved radiofluorination yields. Hydrolysis or reduction of the masking group provide access to both the tertiary methylamine and the secondary desmethyl amine. In addition, the activating group strategy serve to activate anilines as *N*-formyl anilines that provide excellent radiofluorination yields of  $^{18}\text{F}$ fluoroanilines. The reduction of amides is chemo selective towards formamides over other amides, which greatly enhance the substrate scope.

The usefulness of the methodologies was demonstrated by synthesising several radiotracers for a range of different targets. To the best of my knowledge, the developed radiofluorination methodology prove today to be the most reliable and highest yielding transition metal free route

for synthesis of non-activated  $^{18}\text{F}$ -labelled fluoroarenes. A notable result is the quantitative radiofluorination of building block 4- $^{18}\text{F}$ fluoro-1-iodobenzene (paper I).

With the developed radiofluorination strategies in mind, we synthesised a small library of fluorinated ligands based on Ro 04-5595. We identified NMDA/NR2B binding ligands (Paper IV), however less promising than the lead compound. We therefore radiolabelled the lead compound with carbon-11. Preliminary *in vivo* studies from PET in combination with high-resolution *in vitro* data from autoradiography in rodents, show radioligand retention in NR2B rich regions. Both PET and autoradiography show low binding in cerebellum. The absence of radioligand binding in cerebellum indicate that there are no problematic  $\sigma$ -receptor cross affinity, which is further supported by binding data recorded by PDSP.<sup>134</sup> The PET scan show fast pharmacokinetics with a rapid washout over the 90-minutes duration. Injection of low molar activity [ $^{11}\text{C}$ ]Ro 04-5595 increased the brain uptake slightly but also lead to faster washout. The faster washout indicate tissue saturability and the higher uptake is likely due to saturation of competing peripheral binding sites outside of the brain.

We did not detect any radioactive metabolites in the metabolite study and found that samples had a very low countrate. The low countrate is likely due to a combination of the short half-life of carbon-11 and to an *in vivo* N- $^{11}\text{C}$ demethylation pathway. The metabolite in this case would be non-problematic gaseous [ $^{11}\text{C}$ ]CO<sub>2</sub>. Further PET studies in larger animals is needed to more accurately investigate the *in vivo* distribution of [ $^{11}\text{C}$ ]Ro 04-5595. In addition, we synthesised enantiomerically enriched ligands and evaluated them individually. Autoradiography results suggest that only the R-enantiomer of Ro 04-5595 is a potent NR2B ligand. I believe that [ $^{11}\text{C}$ ]-(*R*)-Ro 04-5595 has good potential to be useful for studying NR2B receptors *in vivo*. Furthermore, using a single enantiomer in PET imaging would likely reduce non-specific binding and result in better images.



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## **Appendix:**





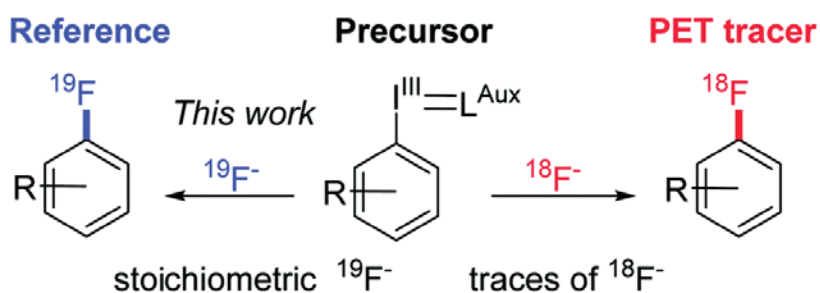


## Paper II

**Jakobsson, J. E.;** Riss, P. J. Transition metal free, late-stage, regioselective, aromatic fluorination on preparative scale using KF/Crypt-222 complex. *RSC Advances* **2018**, 8, 21288-21291

### Abstract

We herein report the development of a convenient, regioselective, aromatic fluorination method of hypervalent iodonium ylides for synthesising fluoro-arenes on a preparative scale. This transition metal free, nucleophilic methodology provides good yields for sterically hindered substrates, irrespective of activation. The methodology simplifies reference synthesis for PET imaging.



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## Transition metal free, late-stage, regiospecific, aromatic fluorination on a preparative scale using a KF/crypt-222 complex†

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We herein report the development of a convenient, regioselective, aromatic fluorination method of hypervalent iodonium ylides for synthesising fluoro-arenes on a preparative scale. This transition metal free, nucleophilic methodology provides good yields for sterically hindered substrates, irrespective of activation. The methodology simplifies reference synthesis for PET imaging.

Fluorinated organic molecules are of importance in crop protection and materials science and as pharmaceuticals due to their unique properties. Aryl fluorides are of particular interest in medicinal chemistry<sup>1</sup> due to their exceptional metabolic stability. For instance, fluorine is often used as a tool in medicinal chemistry for fine tuning the physicochemical properties of drug candidates in late stage development.<sup>2</sup> The presence of fluorine in drug molecules also allows for further investigation by positron emission tomography (PET) *via* incorporation of radioactive fluorine-18 (<sup>18</sup>F, *t*<sub>1/2</sub> = 110 min). The radionuclide <sup>18</sup>F is ideal for PET imaging, due to its very advantageous half-life and decay characteristics.<sup>3</sup>

Current late stage fluorination methodologies of arenes and heteroarenes are often based on expensive, potentially toxic transition-metals (Ag/Cu,<sup>4</sup> Cu,<sup>5</sup> Ni,<sup>6</sup> Pd<sup>7</sup>) or involve electrophilic fluorination reagents and may necessitate the use of additional, advanced equipment such as gloveboxes to achieve more anhydrous conditions. Therefore a mild, versatile and selective fluorination methodology that utilises cheap nucleophilic fluoride for late stage formation of fluoroarenes is highly sought after.<sup>8</sup> In addition, we aim to progress into greener, more environmentally friendly alternatives with easy to handle chemicals by moving away from toxic transition metals. In order to be independent from classical substrates of the S<sub>N</sub>Ar reaction, we chose hypervalent iodine species as fluorination precursors. The hypervalent iodine chemistry utilises the plethora of well-investigated and described iodination protocols and iodonium ylide forming reactions as a basis for constructing aryl fluorides. Such a method would also bridge the gap

between preparative organic chemistry and radiochemistry thus applying the same precursor for synthesising both radiotracer and reference compound in the last step (Scheme 1). Radio-fluorination of iodonium ylides is well described,<sup>9</sup> however in radiochemistry reagent stoichiometry is vastly different with the precursor used in >1000 fold excess over no carrier added fluorine-18, the limiting reagent.‡ For the methodology to be useful on preparative scale the precursor should ideally be the limiting reagent and a cheap fluorination reagent such as KF, CsF or TBAF used in excess. We therefore employed a reverse translational approach developing a preparative organic protocol for the fluorination reaction under stoichiometric conditions. Through this new protocol, PET chemistry is merged with preparative organic chemistry enabling use of iodonium ylides as versatile fluorination precursors.

Electron deficient substrates can undergo a classical S<sub>N</sub>Ar reaction<sup>10</sup> therefore for this investigation we decided to use 2-fluoroanisole as model compound since it is both sterically hindered and electron rich and therefore challenging to produce. All reactions were performed without access to glove box using standard equipment and precautions to allow for good reproducibility in between labs. We began by screening the most common nucleophilic fluorination reagents in organic, dipolar aprotic solvents (Table 1).

Caesium fluoride produced mere trace amounts of product (2), possibly owing to its high hygroscopicity and difficulty of excluding moisture (Table 1, entry 1). Tetrabutylammonium fluoride trihydrate yielded a higher conversion (2, 9%) but also 3-fluoroanisole (3) as side product (0.6%) (Table 1, entry 2). We have previously observed that the reaction is moderately sensitive to moisture<sup>9b</sup> on radiochemical scale so we

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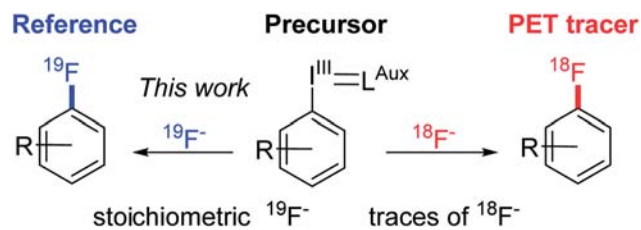
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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra03757d

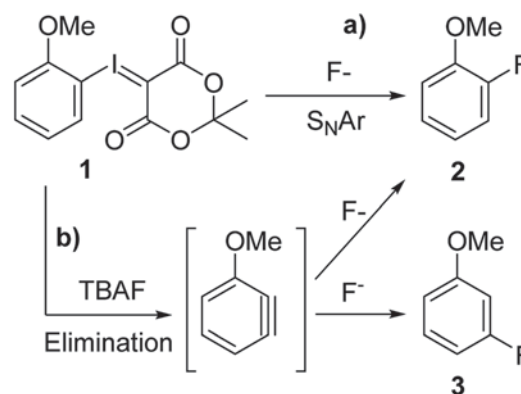
‡ We found no benefit of adding triphenylphosphane as previously reported,<sup>9b</sup> we argue that the reason is that the iodonium ylide is slowly reduced by the phosphane, and consumed reagent is a problem in preparative chemistry that is not encountered in radiochemistry where substrate is used in >1000 fold excess. <sup>31</sup>P NMR show PPh<sub>3</sub>O as minor side product, ESI.†





Scheme 1 Illustrate a back-translational approach, developing an organic chemistry protocol for synthesising reference compound on preparative scale.

synthesised the anhydrous  $\text{TBAF}(t\text{-BuOH})_4$  complex,<sup>11</sup> which although it increased the yield fourfold (Table 1, entry 2) also produced more of the undesired constitutional isomer that would render purification considerably more difficult (Table 1 entry 3). Heating the reaction mixture for a longer time made no difference (Table 1, entry 4) meaning that the constitutional isomer formation is unrelated to product degradation, varying the temperature did not resolve the selectivity problem either (ESI<sup>†</sup>). Earlier literature reports suggest that fluorination of aryl bromides goes through an aryne intermediate when using the very basic tetraalkylammonium fluorides<sup>12</sup> in DMSO as well as radiofluorination of iodonium ylides using  $\text{KF}/\text{crypt-222}$  in MeCN.<sup>9a</sup> We assumed that since reagent basicity is solvent dependent choosing another solvent could circumvent the problem. However, we found that use of either propylene carbonate or DMSO (Table 1, entries 5 and 6) yielded a comparable ratio of 2-fluoroanisole (2) to 3-fluoroanisole (3) (11 + 1% and 5 + 1% respectively) and that the reaction in both chlorobenzene and MeCN (Table 1, entries 7 and 8) proceeded primarily through an aryne intermediate (12% + 25% and 5 +



Scheme 2 Shows two competing reaction pathways for fluorination of 1 using  $\text{TBAF}(t\text{-BuOH})_4$ . (a) Nucleophilic substitution, (b) TBAF mediated aryne formation and subsequent fluorination yielding both 2 and 3.

9% respectively). We concluded that we have two competing reaction pathways and that the aryne intermediate formation is facilitated by TBAF (Scheme 2). By reducing the equivalents of  $\text{TBAF}(t\text{-BuOH})_4$  from 2 to 1 the yield was marginally decreased to 30% but the formation of 3-fluoroanisole (3) reduced by three quarters to  $0.3 \pm 0.1\%$  (Table 1, entry 9). This finding suggest that use of tetraalkylammonium fluorides in radiofluorination reactions does not suffer from formation of constitutional isomers since only trace quantities of fluoride is used, which is in agreement with Rotstein *et al.*<sup>9c</sup> By increasing the equivalents of  $\text{TBAF}(t\text{-BuOH})_4$  complex to 4 equivalents, 5% desired 2-fluoroanisole (2) and 6% undesired 3-fluoroanisole (3) (Table 1 entry 10) were obtained, further supporting our hypothesis.

With this finding, we decided to move away from tetraalkylammonium fluorides and investigate metal fluorides in combination with phase transfer catalysts (Table 2) to enhance both solubility and nucleophilicity.

Addition of conventional phase transfer catalyst potassium complexing crown ether 18-crown-6 to  $\text{KF}$  produced only traces of product (Table 2, entry 1). Surprisingly neither  $\text{CsF}$  nor  $\text{KF}$  in combination with cryptand crypt-222 produced satisfactory results,  $1 \pm 1\%$  and  $8 \pm 2\%$  of 2-fluoroanisole (2) respectively (Table 2, entries 2 and 3) but with a  $^{19}\text{F}$  NMR spectrum devoid of the 3-fluoroanisole signal (3). We hypothesised that the limited solubility of potassium fluoride<sup>13</sup> in DMF made formation of  $\text{KF}/\text{crypt-222}$  complex too slow to allow for an efficient fluorination reaction since the iodonium ylide substrate slowly degrade under the fluorination conditions.<sup>9b</sup>  $^{13}\text{C}$ -NMR shows only partial formation of  $\text{crypt-222}/\text{K}^+$  complex after 2 hours of heating  $\text{KF}$  and crypt-222 in DMF at  $130^\circ\text{C}$  (ESI<sup>†</sup>) strengthening our hypothesis. Adding water to the reaction mixture to facilitate  $\text{KF}/\text{crypt-222}$  complex formation would destroy the substrate and strongly diminish the nucleophilicity of fluoride. Therefore, we anticipated that the fluorination complex need to be formed in advance. We made the  $\text{KF}/\text{crypt-222}$  complex from a solution of MeCN/ $\text{H}_2\text{O}$  adding 33 mol%  $\text{K}_2\text{CO}_3$  to hinder evaporation of  $\text{HF}$ . The complex was thoroughly dried for several days under high vacuum. In line with our hypothesis, the pre-formed  $\text{KF}/\text{crypt-222}$  complex produced a significantly

Table 1 Shows the constitutional isomer distribution as result of varying fluoride source and solvent



Entry	Reagent	Solvent	Yield <sup>a</sup> % (2)	Yield <sup>a</sup> % (3)
1	$\text{CsF}$	DMF	Traces	0
2	$\text{TBAF} \cdot 3\text{H}_2\text{O}$	DMF	9%	0.6%
3	$\text{TBAF}(t\text{-BuOH})_4$	DMF	$31 \pm 4\%$	$1.4 \pm 0.0\%$
4	$\text{TBAF}(t\text{-BuOH})_4$	DMF <sup>b</sup>	$32\%^a$	1.4%
5	$\text{TBAF}(t\text{-BuOH})_4$	PC	11%	1%
6	$\text{TBAF}(t\text{-BuOH})_4$	DMSO	5%	1%
7	$\text{TBAF}(t\text{-BuOH})_4$	PhCl	12%	25%
8	$\text{TBAF}(t\text{-BuOH})_4$	MeCN	5%	9%
9	1.5 eq. $\text{TBAF}(t\text{-BuOH})_4$	DMF	$30 \pm 0\%$	$0.3 \pm 0.1\%$
10	4 eq. $\text{TBAF}(t\text{-BuOH})_4$	DMF	$5 \pm 0.2\%$	$6 \pm 0.2\%$

<sup>a</sup>  $^{19}\text{F}$  NMR yield using 4-fluorobiphenyl as internal standard. Standard deviation is given for reactions performed in duplicate. Product identities were confirmed from spiking with reference compound.

<sup>b</sup> 1 h reaction time. PC = propylene carbonate.



Table 2 Shows the constitutional isomer distribution as result of varying fluoride source and solvent. Reaction performed on **1** (1.9 mg, 5  $\mu$ mol) and fluorination reagent (10  $\mu$ mol) in DMF (0.5 ml) at 130 °C for 20 min

Entry	Reagent	Yield <sup>a</sup> % (2)	Yield <sup>a</sup> % (3)
1	KF/18C6	1 $\pm$ 0%	0
2	CsF/crypt-222	1 $\pm$ 1%	0
3	KF/crypt-222	8 $\pm$ 2%	0
4	KF/crypt-222	46 $\pm$ 2% <sup>b</sup>	0
5	1.5 eq. KF/crypt-222	36% <sup>b</sup>	0
6	4 eq. KF/crypt-222	43% <sup>b</sup>	0

<sup>a</sup> <sup>19</sup>F NMR yield using 4-fluorobiphenyl as internal standard. Where standard deviation is given, the reaction was performed in duplicate. Product identities were confirmed from spiking with reference compound. <sup>b</sup> Preformed KF/crypt-222 complex containing 33 mol% K<sub>2</sub>CO<sub>3</sub> to avoid formation of HF during drying of KF/crypt-222 complex. Crypt-222 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane.

higher yield (46  $\pm$  2%) gratefully without formation of any constitutional isomers (Table 2, entry 4). The pre-made KF/crypt-222 complex is not visibly hygroscopic and is an easy to weigh free flowing powder (ESI<sup>+</sup>) that can be stored for at least several weeks in a closed vial at room temperature without any impairment of the fluorination yield. Increasing or reducing the equivalents of KF/crypt-222 complex did not improve the yield further (Table 2, entries 5 and 6). The complex readily dissolves in DMF and <sup>13</sup>C-NMR gives three new signals upfield of the host crypt-222.

With the optimised fluorination conditions in hand, we set out to screen a range of substrates to examine the reaction scope (Fig. 1). 4-Fluoroanisole (**4**) was produced in a significantly lower yield (10  $\pm$  1%) than 2-fluoroanisole (**2**, 46  $\pm$  2%), the large difference is likely due to the substrate being both deactivated and lacking an *ortho*-substituent thus not benefitting from the *ortho*-effect.<sup>14</sup> Fluorination of non-activated substrates produced fluorobenzene (**5**) and 4-chloro-1-fluorobenzene (**6**) in modest yields (33  $\pm$  2% and 26  $\pm$  4%) but good enough to be useful for synthesising sufficient material of reference compounds where milligram quantities is sufficient. Fluorination constructing 5-fluoro-*m*-xylene (**7**) proceeded in an acceptable yield (36  $\pm$  1%) whereas sterically hindered constitutional isomer 2-fluoro-*m*-xylene (**8**) was produced in a high yield (78  $\pm$  7%) demonstrating the benefit of *ortho*-substitution. Activated substrates 4-fluorodimethylbenzamide (**9**) and 4-fluorobenzonitrile (**10**) were as expected obtained in high to excellent yields (70  $\pm$  3% and 52  $\pm$  18%) albeit under milder conditions then used for S<sub>N</sub>Ar-fluorinations. Activated drug compound tropane (**11**) was produced in near quantitative yield (88  $\pm$  7%) (90% isolated yield) and the challenging to access morphinane (**12**) fluorinated well in 30  $\pm$  1% (20% isolated yield), sufficient for testing its potential use as an NMDA-PET radioligand. The radiotracer [<sup>18</sup>F] **12** was synthesised in 38% isolated yield (150 MBq > 95% RCP after cartridge purification). Activated tropane was readily fluorinated in room temperature yielding 33% of **11**. Encouraged by the positive results we decided to investigate how well the pre-dried KF/crypt-222

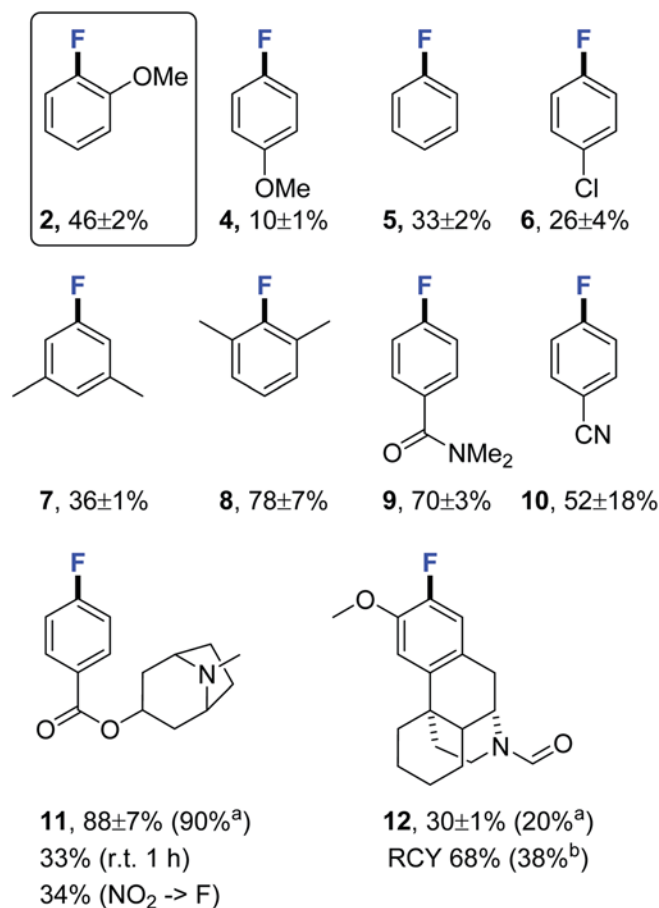


Fig. 1 Fluorination substrate scope under the developed conditions. <sup>19</sup>F NMR yields using 4-fluorobiphenyl as internal standard. Where standard deviation is given, the reaction was performed in duplicate. Product identities were confirmed from spiking with reference compound. Reaction performed on ylide (5  $\mu$ mol) and crypt-222/KF/K<sub>2</sub>CO<sub>3</sub> (4 : 3 : 1) (6.6 mg, 10  $\mu$ mol of KF) in DMF (0.5 ml) at 130 °C for 20 min. Radiofluorination performed using ylide (3.7  $\mu$ mol), crypt-222 (5 mg, 13  $\mu$ mol) K<sub>2</sub>CO<sub>3</sub> (0.92 mg, 5.5  $\mu$ mol) and <sup>18</sup>F<sup>-</sup> (400 MBq) in DMF (0.5 ml) at 130 °C for 20 min. <sup>a</sup>Isolated yield using tracer principle after cartridge purification (C<sub>18</sub> and Si). <sup>b</sup>Non-decay corrected isolated yield after cartridge purification (C<sub>18</sub> and Si) in >95% RCP. RCY = radiochemical yield. Crypt-222 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane. Entry for **2** is identical to Table 2 entry 4.

complex fluorinated activated nitro arenes. We synthesised the NO<sub>2</sub>-precursor of (**11**) for a direct comparison and attempted fluorination under standard conditions obtaining **11** in 34% yield compared to 88  $\pm$  7% when using the iodonium ylide precursor. Fluorination at room temperature produced only traces of product after 1 hour (ESI<sup>+</sup>).

A transition metal free fluorination method based on an anhydrous fluorine complex and iodonium ylides useful for preparative aromatic fluorination reactions is successfully demonstrated. Merging radiochemistry and conventional organic chemistry by employing the same precursor eliminates the need of additional synthetic work. An additional advantage of using a transition metal free methodology is to avoid possible interference during biological characterisation and during



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translation into clinical radiochemistry. We successfully demonstrate the use of the methodology by synthesising complex derivatives *via* a late stage fluorination reaction and the radioactive counterparts from the same precursor. The method is a good compliment to existing methodologies and with high yield reproducibility expands the accessible chemical space of fluorinated drug molecules.

## Conflicts of interest

There are no conflicts of interest to declare.

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