Stockholm University

Development of new Fluorination Methods Directed to Fluorine-18 Labelling

Miguel Ángel Cortés González

Doctoral Thesis in Organic Chemistry at Stockholm University, Sweden 2020

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Abstract

This thesis deals with the development of new fluorination reactions and their application to fluorine-18 labelling. Fluorine-18 labelled compounds are employed as tracers in Positron Emission Tomography (PET), which is a powerful non-invasive imaging method in medical diagnostics.

The first part of this thesis focuses on the development of a late-stage halogen exchange-based fluorination method for the synthesis of trifluoromethylated molecules. The first project in this area relies on the application of a copper(I)-based fluorinating reagent to furnish trifluoroacetates, trifluorotoluenes and trifluoroacetamides. The second project involves the translation of this methodology into the fluorine-18 labelling of tertiary and secondary trifluoroacetamides. The targeted substrates were labelled in high radiochemical yield and high molar activity using [^{18}F]Bu_4NF as fluorine source in the presence of an organic activator.

In the second part, the development of electrophilic fluorination reactions using a hypervalent iodine-based reagent is discussed. The first project in this area addresses the development of an electrophilic fluorine-18 fluorination reagent: [^{18}F]fluoro-benziodoxole. The utility of this reagent was demonstrated in the labelling of [^{18}F]fluoro-benzoxazepines. In the second project, the same [^{18}F]fluoro-benziodoxole reagent was used in the rhodium-mediated synthesis of α-[^{18}F]fluoroethers. High molar activities were obtained in these electrophilic labelling processes. In the third project, the fluorine-19 analog fluoro-benziodoxole was used in the palladium-catalyzed iodofluorination of allyl benzenes, styrenes and cycloalkenes. Both iodine and fluorine atoms in the product arise from the same reagent.

Keywords: *fluorine, fluorine-18, late-stage, labelling, nucleophilic, electrophilic, fluorination, positron emision tomography, PET, hypervalent iodine, benziodoxole, metal-free, DBU, copper, palladium, rhodium, carbene.*

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For those who fight

Success is not final;
failure is not fatal.
It is the courage to continue
that counts.
- Winston Churchill

Abstract

This thesis deals with the development of new fluorination reactions and their application to fluorine-18 labelling. Fluorine-18 labelled compounds are employed as tracers in Positron Emission Tomography (PET), which is a powerful non-invasive imaging method in medical diagnostics.

The first part of this thesis focuses on the development of a late-stage halogen exchange-based fluorination method for the synthesis of trifluoromethylated molecules. The first project in this area relies on the application of a copper(I)-based fluorinating reagent to furnish trifluoroacetates, trifluorotoluenes and trifluoroacetamides. The second project involves the translation of this methodology into the fluorine-18 labelling of tertiary and secondary trifluoroacetamides. The targeted substrates were labelled in high radiochemical yield and high molar activity using [^{18}F]Bu_4NF as fluorine source in the presence of an organic activator.

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List of publications

This thesis is based on the following publications, referred to in the text by their roman numerals. The author´s contribution to each publication is reported in the contribution list (Appendix A). Reprints were made with the kind permission of the publishers (Appendix B).

I. Synthesis of Trifluoromethyl Moieties by Late-Stage Copper (I) Mediated Nucleophilic Fluorination
A. Bermejo Gómez, M. A. Cortés González, M. Lübcke, M. J. Johansson, M. Schou, K. J. Szabó.
J. Fluorine Chem. **2017**, *194*, 51-57.

II. Efficient DBU Accelerated Synthesis of ^{18}F-Labelled Trifluoroacetamides
A. Bermejo Gómez, M. A. Cortés González, M. Lübcke, M. J. Johansson, C. Halldin, K. J. Szabó, M. Schou.
Chem. Commun. **2016**, *52*, 13963-13966.

III. [^{18}F]fluoro-benziodoxole: a no-carrier-added electrophilic fluorinating reagent. Rapid, simple radiosynthesis, purification and application for fluorine-18 labelling
M. A. Cortés González, P. Nordeman, A. Bermejo Gómez, D. N. Meyer, G. Antoni, M. Schou, K. J. Szabó.
Chem. Commun. **2018**, *54*, 4286-4289.

IV. Rhodium-mediated ^{18}F-oxyfluorination of diazoketones using fluorine-18-containing hypervalent iodine reagent
M. A. Cortés González, X. Jiang, P. Nordeman, G. Antoni, K. J. Szabó.
Chem. Commun. **2019**, *55*, 13358-13361.

V. Palladium-Catalyzed Iodofluorination of Alkenes Using Fluoro-Iodoxole Reagent
N. O. Ilchenko, M. A. Cortés, K. J. Szabó.
ACS Catal. **2016**, *6*, 447-450.

Abbreviations

Abbreviations are used in accordance with the standards of the subject.[†] Aditional or unconventional abbreviations are listed below.

α	Alpha particle
18-c-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
Bnep	Neopentyl glycolato boron
Boc	*tert*-Butyloxycarbonyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
Dibenzo-18-c-6	2,3,11,12-Dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene
DiCy-18-c-6	2,3,11,12-Dicyclohexano-1,4,7,10,13,16-hexaoxacyclooctadecane
DMAP	4-Dimethylaminopyridine
DMT	4,4′-Dimethoxytrityl
DOPA	3,4-Dihydroxyphenylalanine
dppe	Bis(diphenylphosphino)ethane
esp	α,α,α′,α′-Tetramethyl-1,3-benzenedipropionic acid
FDG	2-Deoxy-2-[^{18}F]fluoroglucose
F-TEDA	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane
K_{222}	4,7,13,16,21-Pentaoxa-1,10-diazabicyclo[8.8.5]tricosane
LG	Leaving group
MeCN	Acetonitrile
MS	Molecular sieves
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
NFSI	*N*-Fluorobenzenesulfonimide
OPiv	2,2-Dimethylpropionate
OTf	Trifluoromethanesulfonate
RT	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TMG	*N*,*N*,*N*´,*N*´-Tetramethylguanidine
TPA	Triphenylacetate
TREAT·3HF	Triethylamine trihydrofluoride
X	Anionic ligand

[†]*The ACS Style Guide*, American Chemical Society, Oxford University Press, New York 2006.

Radiochemical terms and units

The use of radiochemical units and terms has been inconsistent throughout the literature. The lack of unified and consensual nomenclature rules has prompted the improper use of established terms and the appearance of "self-invented" terms. This has made the comparison of different methodologies a difficult task, as often different terms have been used to describe one single parameter. In 2017, the European Association of Nuclear Medicine published an article in which the terms and units proper of radiochemistry and radiopharmaceutical sciences were harmonized.[‡] The radiochemical units, terms and parameters used in this thesis are used in accordance with these nomenclature rules. These terms are defined as follows:

Activity is the quantitative measure of radioactivity. It is measured in Becquerels (Bq). One Becquerel equals to one disintegration per second.

Radiochemical yield (RCY) is the amount of activity in the product expressed as a percentage of the activity used in one process. It is determined by radio-HPLC or radio-TLC analysis of the crude reaction mixture and it is decay-corrected. In reports prior to the publication of the nomenclature rules, this parameter was often referred to as radiochemical conversion (RCC).

Activity yield (AY) refers to the amount of radioactive product that is obtained from a starting amount of activity. It is expressed as a percentage between the activity in an isolated radioactive compound (measured in Becquerels) and the initial activity used in the process. This value is not corrected for decay and the time-point in which it is measured must be stated. In certain cases, authors have reported activity yields that have been corrected for decay. Those cases are indicated throughout the text.

Molar activity (A_m) refers to a measured amount of activity per mole of compound. It is measured in GBq/μmol and expresses the extent of contamination of a labelled product with the natural isotope.

Radiochemical purity (RCP) refers to the absence of other radioactive compounds in relation to the compound of interest.

Carrier is the non-radioactive analog of a radioactive compound. It is normally added deliberately to ensure that the labelled compound will behave normally.

Post-target refers to the synthesis by alternative means of a radioactive species that is normally obtained from the cyclotron.

[‡] H. H. Coenen, A. D. Gee, M. Adam, G. Antoni, C. S. Cutler, Y. Fujibayashi, J. M. Jeong, R. H. Mach, T. L. Mindt, V. W. Pike and A. D. Windhorst, *Nucl. Med. Biol.* **2017**, *55*, v-xi.

Contents

1 Introduction

Fluorine is the 13th most abundant element in Earth´s crust, while carbon is only the 15th most abundant element. However, naturally occurring fluorinated organic molecules are scarce (Figure 1): only five natural products containing fluorine have been unambiguously identified and isolated (taking into account that 8 different ω-fluorinated fatty acids were isolated from the same plant).[1] One significant reason for this scarcity is that the fluoride anion, the predominant form in which fluorine exists in nature, has very low abundance in oceans (1.3 ppm) whereas chloride (20 000 ppm) and bromide (70 ppm) are much more abundant. In addition, the high solvation energy of fluoride (-117 kcal/mol) decreases its nucleophilicity in aqueous media, which dominates the chemistry of life. Interestingly, iodide has a much lower abundance (0.02 ppm) than fluoride, and yet, more than 120 natural organic compounds contain iodine. The reason for this is that, unlike fluoride, iodide can be oxidized by haloperoxidases (as well as chloride and bromide).[1b, 2] Thus, in biological systems the nucleophilic fluorination is encumbered by the high solvation energy of fluoride, while the electrophilic fluorination is prevented by its high oxidation potential.

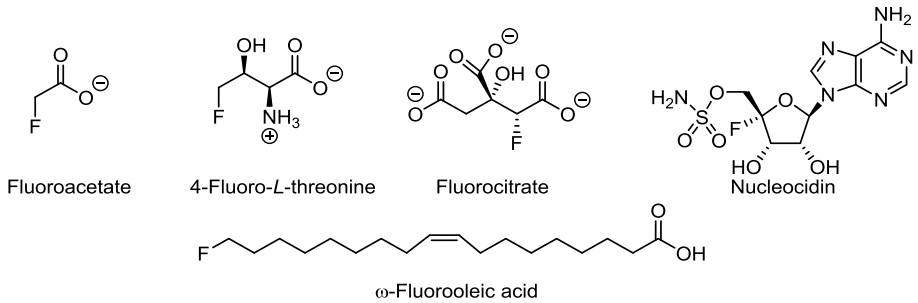


Figure 1. Fluorinated naturally occurring organic compounds.

Despite these difficulties, fluorine has found its way into biologically active compounds through organic synthesis. The small size of fluorine and its high electronegativity make the fluorine substituent a perfect tool for the modulation of the physicochemical (pKa, conformation) and pharmacological (metabolic stability, lipophilicity) properties of bioactive compounds.[3] As a result, more than 20% of marketed drugs (50% of the blockbusters)[4] and

agrochemicals contain at least one fluorine atom in their structure and it is often a key component to ensure their desired properties and activity.[4-5]

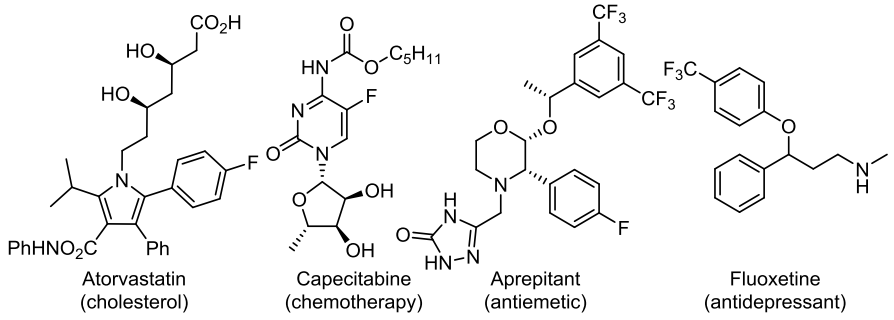


Figure 2. Examples of fluorine-containing drugs. Common commercial names from left to right: Lipitor®, Xeloda®, Emend® and Prozac®.

1.1 Positron Emission Tomography

The interest in fluorinated compounds has dramatically increased in recent years as a result of the development of positron emission tomography (PET).[6] PET is a non-invasive imaging technique that enables the visualization of physiological processes *in vivo*. This technique has been recognized as a leading diagnostic tool in different areas of medicine such as oncology, cardiology and neurology, playing an important role in the early detection of numerous diseases.[6j] PET relies on the use of radiotracers: bioactive molecules containing an unstable positron-emitting nuclide in their chemical structure. Based on the tracer principle, these radiotracers are administered to a subject in a very small amount so they do not have any pharmacological effect on the biological system, serving only as indicators of the behavior and evolution of the radiotracer.[6]

Once the radiotracer has been administered to a subject, the unstable isotope decays, generating (among other particles) a positron (β^+), which is the antiparticle of the electron. This positron travels a certain distance until it has lost part of its kinetic energy and it collides with an electron (e^-) in the surrounding tissue. The collision of these two particles results in an annihilation event, which generates two gamma photons directed in opposite directions. The simultaneous detection of these photons allows for the spatial location of the positron emission site and, after data treatment, allows for the construction of the PET image (Figure 3).[6c, 6j, 7]

Figure 3. PET imaging chain. From left to right: bombardment, labelling, quality control, scanning, processed PET image.

There are several positron-emitting nuclides that can be generated in a low-energy cyclotron and used for PET. These nuclides are characterized by their half-life and their positron energy.[6c] Furthermore, depending on the nuclear reaction, target and carrier used to generate them they can be accessed in different forms (Table 1).

Table 1. Common short-lived radionuclides used in PET.

Nuclide	Half-life [min]	Positron energy [MeV]	Nuclear reaction	Target + additive (carrier)	Product
^{15}O	2.04	1.74	$^{15}N(d,n)^{15}O$	N_2 (O_2)	$[^{15}O]O_2$
^{13}N	9.97	1.20	$^{16}O(p,\alpha)^{13}N$	H_2O	$[^{13}N]NO_x$
				H_2O + EtOH	$[^{13}N]NH_3$
^{11}C	20.4	0.97	$^{14}N(p,\alpha)^{11}C$	$N_2 + O_2$	$[^{11}C]CO_2$
				$N_2 + H_2$	$[^{11}C]CH_4$
^{18}F	109.7	0.64	$^{20}Ne(d,\alpha)^{18}F$	Ne (F_2)	$[^{18}F]F_2$
			$^{18}O(p,n)^{18}F$	$[^{18}O]H_2O$	$[^{18}F]F^-$

Fluorine-18 (^{18}F) holds a privileged position among the positron-emitting nuclides for two reasons: i) its long half-life (109.7 min) allows for the development of complex chemistry and ii) its low positron energy allows for the obtention of high-resolution images. Furthermore, this nuclide can be generated in two different forms. However, due to the technical and inherent difficulties of using $[^{18}F]F_2$,[6a, 6c, 6g, 6j] it is more common to generate this nuclide as $[^{18}F]$fluoride ($[^{18}F]F^-$). This is achieved by bombarding oxygen-18 enriched water with a beam of accelerated protons according to the following nuclear reaction:

$$^{18}O + p \rightarrow {}^{18}F + n$$

As a result of these advantageous properties, numerous tracers based on fluorine-18 have been developed, each of them designed to image and diagnose specific processes and diseases (Figure 4).

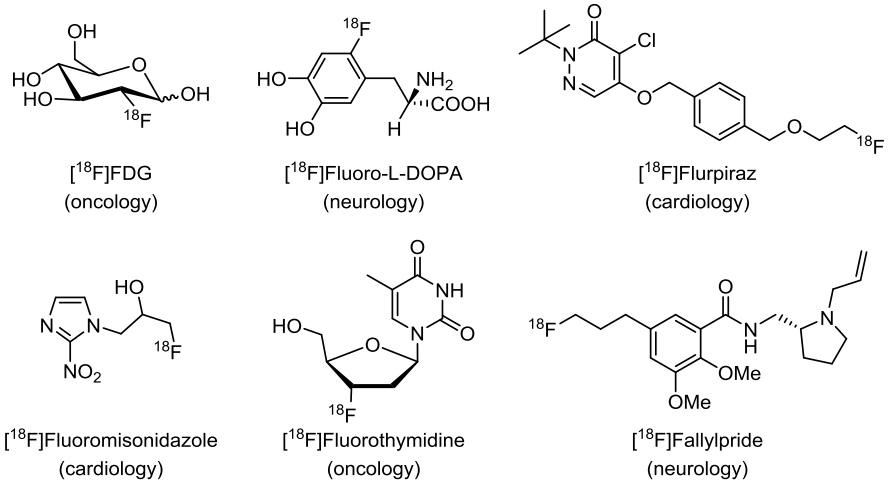


Figure 4. ^{18}F-containing radiotracers and their field of imaging.

1.2 Methods for the synthesis of fluorine-containing organic molecules.

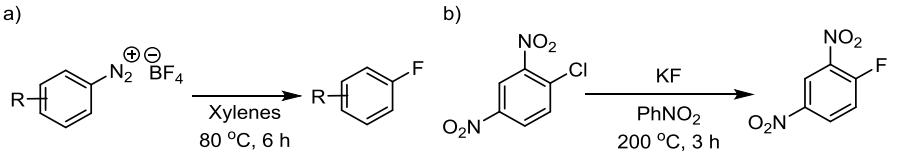
Traditionally, fluorination of organic substrates was performed using highly reactive electrophilic fluorinating reagents (*e.g.* F_2, HF, XeF_2) that suffer from low selectivity, or using nucleophilic alkali-metal fluorides (such as KF) that require harsh reaction conditions or reactive intermediates to overcome their low reactivity. The increasing demand for complex fluorinated drugs and materials has motivated an enormous development in mild, selective and functional group-tolerant fluorination chemistry. Over the past decade, new nucleophilic and electrophilic reagents have been designed to overcome the particular difficulties of each field, aiming especially to late-stage fluorination processes.[8]

1.2.1 Nucleophilic fluorination

The main challenge in the formation of C–F bonds using nucleophilic fluorine sources arises from the high solvation energy of fluoride and its tendency to be stabilized by hydrogen bonding. This stabilization renders the fluoride anion weakly nucleophilic and therefore unreactive. Such limitation can be circumvented by careful removal of hydrogen bond donors, increasing the nucleophilicity of fluoride. However, this simultaneously increases its basicity, which can lead to undesired side-reactions.[9]

1.2.1.1 Nucleophilic fluorine-19 fluorination

The earliest report on the synthesis of aryl fluorides is the Balz-Schiemann reaction. This reaction is based on the thermal decomposition of aryldiazonium tetrafluoroborate salts (Scheme 1a).[10] This process has been the object of numerous applications, studies and modifications[11] but the explosive nature of diazonium salts has hindered its transfer to industrial scale. A second method is a halogen-exchange reaction (Halex).[12] Here, a halogen substituent is exchanged for fluorine in electron-poor arenes at high temperatures (Scheme 1b). The instability of the diazonium salts in the Balz-Schiemann reaction and the high temperatures required in the Halex process make these reactions unsuitable for the requirements of modern chemistry.



Scheme 1. a) Balz-Schiemann reaction. b) Halex reaction.

In this context, transition-metal catalysis is a powerful tool in organic synthesis that has contributed enormously to the development of fluorine chemistry, resulting in milder reaction conditions and wide substrate scope.[8a, 8f, 9, 13] However, this approach is not exempt of difficulties, caused again by the inherent properties of fluorine. The strength of the metal-fluorine bonds and the difficult reductive elimination (caused by insufficient orbital interaction between fluorine and the organic ligand) are the main challenges in the otherwise thermodynamically favorable formation of C–F bonds (Figure 5).[9]

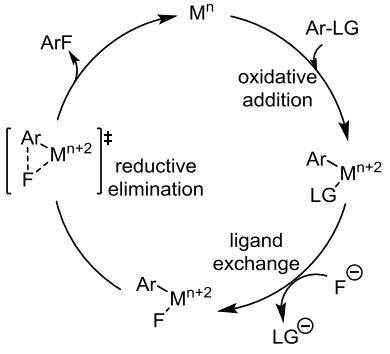
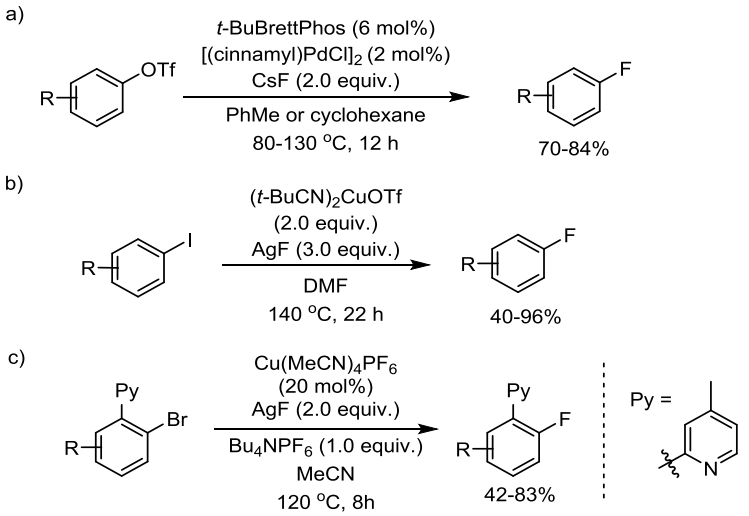


Figure 5. Mechanism for metal-catalyzed fluorination of arenes.

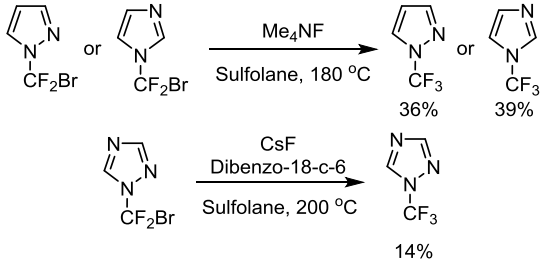
Significant efforts[14] have been made to realize the elusive C_{sp^2}–F metal-catalyzed bond formation using Rh[14b] and Pd[14c-f] metal complexes. These efforts were however mainly unsuccessful, due to the favored competing P–F bond formation (arising from the phosphine ligands). A major

breakthrough took place when Buchwald and co-workers[15] reported the reductive elimination from a Pd–F complex bearing a monodentate phosphine ligand. In this reaction, aryl triflates were efficiently transformed into the corresponding fluorides using CsF (Scheme 2a). Shortly after, the copper-mediated fluorination of arenes was reported by Hartwig and co-workers,[16] using AgF as fluoride source. Unfortunately, this process requires a large excess of copper and is limited to aryl iodides (Scheme 2b). Recently, the copper-catalyzed fluorination of bromoarenes has been reported by Liu and co-workers.[17] This reaction relies on the presence of a pyridyl directing group in order to stabilize the Cu(I) species (Scheme 2c). A key feature of these reactions is the formation of a metal fluoride species that facilitates the reductive elimination to form the C–F bond.



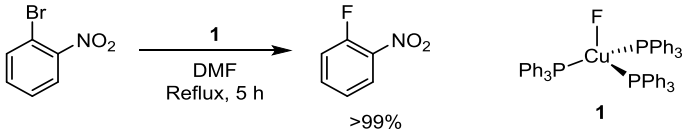
Scheme 2. a) Pd-catalyzed fluorination of arenes. b) Cu-mediated fluorination of arenes. c) Cu-catalyzed fluorination of arenes.

The nucleophilic fluorination of sp^3-type carbons is well established, with a myriad of appropriate reaction conditions, leaving groups and fluorine sources.[8a, 8f-h, 13c] A challenging and relatively unexplored area of research is the introduction of fluorine into carbon centers that already contain fluorine atoms.[18] Despite the existence of numerous protocols for the direct nucleophilic and electrophilic introduction of trifluoromethyl groups,[8f, 9] the formation of these motifs by nucleophilic substitution at a difluorinated center is an attractive procedure to access trifluoromethyl moieties in a late-stage fashion. In an early report on this approach, Sokolenko and Yagupolskii[19] synthesized *N*-trifluoromethylated imidazole, pyrazole and 1,2,4-triazole under harsh reaction conditions in moderate yields (Scheme 3).



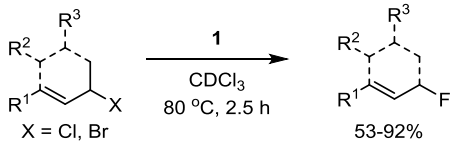
Scheme 3. Nucleophilic fluorination of *N*-bromodifluoromethyl heterocycles.

The complex $(PPh_3)_3CuF$ (**1**) is considered to be the closest analog to CuF[20] and it is a well-known intermediate in the synthesis of the trifluoromethylation reagent $(PPh_3)_3CuCF_3$.[21] Very interestingly, the properties of $(PPh_3)_3CuF$ as fluorinating reagent have received very little attention, as there are only two reports of such type of reaction. The first of them was made by Konovalov and co-workers[22] in 1991, describing the *ipso* fluorination of 1-bromo-2-nitrobenzene. The reaction proceeded in DMF at 150 °C, achieving full conversion to the fluorinated compound (Scheme 4).



Scheme 4. *Ipso*-fluorination of bromonitrobenzene by **1**.

The second study in this context was reported by Szabó and co-workers[23] and describes the fluorination of allyl chlorides and bromides using **1** in good yields and good levels of regio- and stereoselection (Scheme 5).

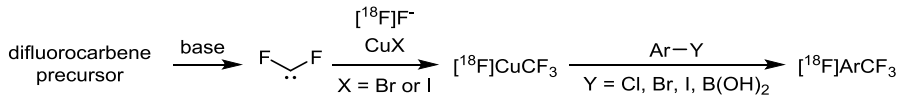


Scheme 5. Fluorination of allylic chlorides and bromides by **1**.

1.2.1.2 Synthesis of fluorine-18-containing trifluoromethyl moieties

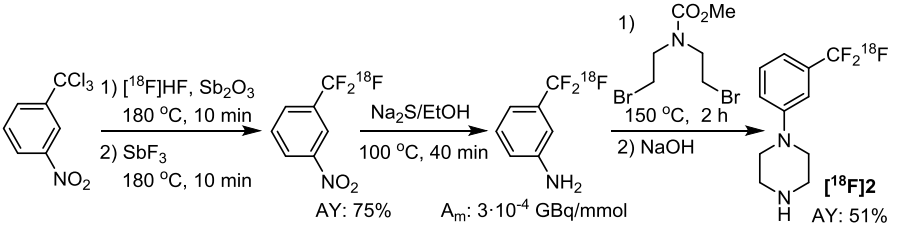
As previously mentioned, research in fluorine chemistry has been significantly expanded owing to the advent of PET. As a result, numerous reactions have been developed, aiming for the late-stage synthesis of fluorine-18 labelled trifluoromethyl moieties.[24] The first synthesis of a fluorine-18 labelled trifluoromethyl arene was reported by Ido and co-workers[25] in 1979 using an isotope exchange method, but the work suffers from low reproducibility and low yields. Furthermore, no molar activity is mentioned, but due to the nature of the process it can be expected to be very low. A more attractive way of introducing these motifs is by nucleophilic

substitution. This can be carried out by two different approaches: halogen exchange on a preformed $-CF_2X$ (X = halogen) unit using [^{18}F]fluoride[26] or by direct introduction of the $-[^{18}F]CF_3$ unit.[27] The latter, developed by Gouverneur and Passchier,[27a] Vugts,[27b] Pannecoucke[27c] and Riss,[27d] relies on the formation of a diflurocarbene and its transformation into $[^{18}F]Cu(I)CF_3$ prior to its coupling to an activated arene (Scheme 6). This methodology, although reliable for the synthesis of labelled trifluoromethyl arenes, suffers from low molar activity values.



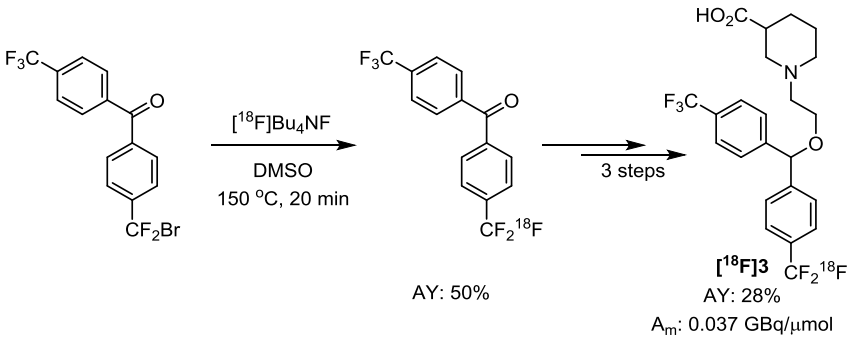
Scheme 6. Synthesis and cross-coupling of $[^{18}F]CuCF_3$.

The first nucleophilic halogen exchange was reported by Shiue and Wolf[26a, 26b] using a mixture of Sb_2O_3 and [^{18}F]HF to furnish fluorine-18 labelled trifluoromethyl arenes from the corresponding trichloroarenes. The authors used this methodology to obtain the labelled serotonin agonist **[^{18}F]2** several steps after the labelling, which took place in 75% activity yield. Interestingly, the molar activity of the final product is not reported. Instead, the authors reported the molar activity of the penultimate labelled precursor, which was $3 \cdot 10^{-4}$ GBq/μmol (Scheme 7).



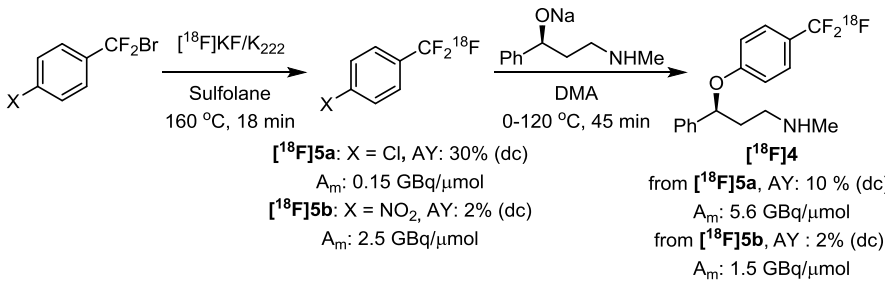
Scheme 7. Labelling of serotonin agonist **[^{18}F]2** by halogen exchange.

Bromodifluoroarenes require milder reaction conditions to undergo halogen exchange than the corresponding chlorinated and fluorinated analogs. The first nucleophilic fluorine-18 substitution on a bromodifluoromethyl arene was reported by Kilbourn and co-workers[26c] in 1990. This methodology requires slightly milder conditions and afforded the labelled trifluoromethyl arene in 50% activity yield. Additional steps allowed for the synthesis of the GABA uptake inhibitor **[^{18}F]3** in 28% overall activity yield. The authors reported an apparent molar activity 0.037 GBq/μmol, as they could not separate the labelled compound from its precursor (Scheme 8).



Scheme 8. Synthesis of fluorine-18 labelled GABA uptake inhibitor **[^{18}F]3** by nucleophilic displacement of bromide.

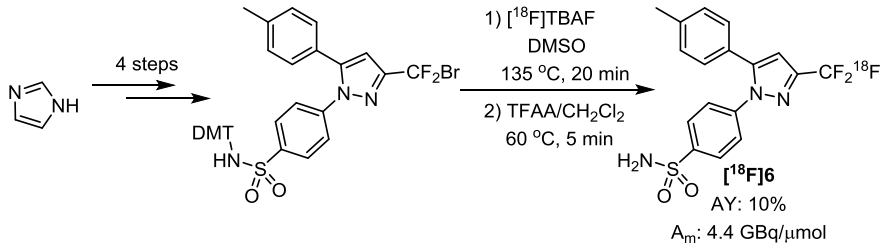
A similar process was employed by Hammadi and co-workers[26d] for the fluorine-18 labelling of the antidepressant Fluoxetine **[^{18}F]4** (Scheme 9). The authors began labelling intermediate **[^{18}F]5a** in 30% activity yield (decay corrected) and a molar activity of 0.15 GBq/μmol. Aromatic nucleophilic substitution using a sodium alkoxide afforded the desired labelled compound in 10% activity yield (decay corrected) and a molar activity of 5.6 GBq/μmol. A similar process was reported by Das, Mukherjee and co-workers[26e] using a *p*-NO_2 substituted precursor. Their labelling procedure afforded the corresponding fluorine-18 labelled trifluoromethyl arene **[^{18}F]5b** in 2% activity yield (decay corrected) and a molar activity of 2.5 GBq/μmol. Subsequent reaction with the same sodium alkoxide afforded **[^{18}F]4** in 2% activity yield (decay corrected) and a molar activity of 1.5 GBq/μmol (Scheme 9).



Scheme 9. Synthesis of [^{18}F]Fluoxetine.

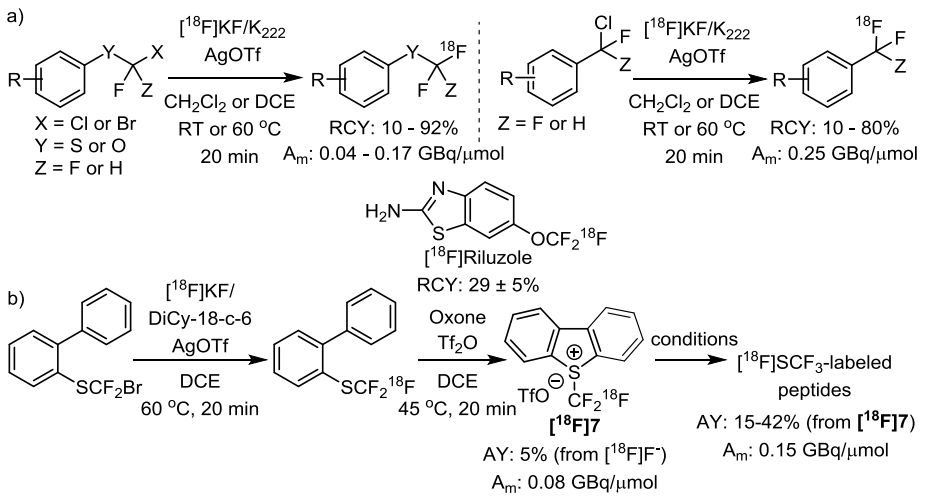
A common feature of these processes is that the labelling step takes place early in the synthesis and the labelled compound is further transformed into the final product. This prosthetic group strategy, although useful, is not ideal. Ideally, the fluorination step takes place last in the synthesis of a radiotracer, as this reduces significantly the activity lost due to decay. The late-stage fluorine-18 fluorination of trifluoromethyl moieties has been illustrated by Kumar and co-workers[26f] in the synthesis of fluorine-18 labelled [^{18}F]Celecoxib **[^{18}F]6** (Scheme 10). In this process, the labelling step took

place last, affording [^{18}F]Celecoxib in 10% activity yield with a molar activity of 4.4 GBq/μmol.



Scheme 10. Late-stage synthesis of [^{18}F]Celecoxib.

Recently, Gouverneur and co-workers[26g, 26h] reported an elegant silver mediated exchange of [^{18}F]fluoride and bromine in order to label [^{18}F]Ar-CF_3, [^{18}F]Ar-CHF_2, [^{18}F]Ar-OCF_3, [^{18}F]Ar-SCF_3 and [^{18}F]Ar-$OCHF_2$ species from the corresponding bromo- and chlorodifluoromethyl arenes (Scheme 11a). The reactions proceeded under mild conditions allowing for the labelling of a broad range of derivatives in moderate to excellent RCY and with a molar activity in the range of 0.04 to 0.25 GBq/μmol. The efficiency of this methodology was demonstrated by the labelling of the anticonvulsant [^{18}F]Riluzole (Scheme 11a). This procedure was later used by the same group as a key step in the synthesis of fluorine-18-labelled Umemoto´s reagent **[^{18}F]7** for its application into the labelling of cysteine-derived peptides (Scheme 11b).[28]



Scheme 11. a) Silver mediated fluorine-18 labelling of aryl-SCF_3, -CHF_2, -CF_3, -OCF_3 and $OCHF_2$. b) Fluorine-18 labelling of Umemoto´s reagent and application into the labelling of peptides.

1.2.2 Electrophilic fluorination

Electrophilic fluorination reactions target electron-rich substrates and are thus complementary to the nucleophilic approach. A common characteristic of these reagents is their ability to accept an electron pair from an incoming nucleophile. As a consequence of the high electronegativity of fluorine, covalently bound fluorine atoms are never positively charged. The reason why these reagents are electrophilic is based on the presence of heteroatoms (X) with relatively high electronegativity (X = O, N, hypervalent I), which decrease the electron density in the fluorine atom.[29] The antibonding MO (*i.e.* σ*) of the covalent X–F bonds has also low energy, which makes it readily accessible for nucleophilic organic substrates.

1.2.2.1 Modern electrophilic fluorine-19 fluorinating reagents

Elemental fluorine (F_2) is the simplest electrophilic fluorination reagent, but it is also the most reactive one. Fluorine is a corrosive and strongly oxidizing gas, which leads to unselective reactions and the necessity of special equipment to handle it. Considerable efforts have been made for the replacement of F_2 with more selective and easy to handle electrophilic fluorination reagents: xenon difluoride, hypofluorites, fluoroxysulfates, perchloryl fluoride and *N*–F reagents.[8f] Of all the reported derivatives, the development of *N*–F reagents such as NFSI (**8**), *N*-fluoropyridinium salts (**9**) and F-TEDA-BF_4 (Selectfluor® **10**) was a pivotal advance in the field of electrophilic fluorination, as they are bench-stable reagents that have allowed for the development of mild, selective and functional-group tolerant fluorination reactions (Figure 6).

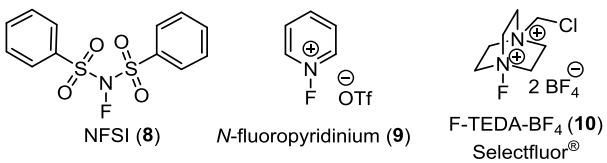


Figure 6. *N*-F electrophilic fluorination reagents.

In early studies, the above-mentioned reagents were applied to the fluorination of main-group organometallic species such as aryl lithium[30] and Grignard[30c, 31] reagents with a narrow substrate scope due to the basicity of the organometallic reagents. This compatibility problem was solved by Ritter, who developed a Pd-[32] and a Ni-mediated[33] procedure using Selectfluor® (**10**) obtaining a wide substrate scope. However, the use of stoichiometric amounts of metal remains a limitation. This issue has been addressed by the development of metal-catalyzed fluorinations, which has received significant attention. The use of transition metals has allowed for the direct C–H electrophilic fluorination of arenes catalyzed by Pd[34] and the silver-catalyzed

fluorination of aryl stannanes.[35] Aliphatic fluorination has also been object of intense study.[36] In this case, stabilized carbanions, often derived from β-ketocarbonylic compounds, are efficiently fluorinated using Pd,[36a-c] Cu,[36d] Ni,[36e] Zn,[36f] Ru[36g] and other transition metals.[36h-j] In these reactions, Selectfluor®, NFSI or other *N*-F derivatives were used as electrophilic fluorine source. These reagents, although mild and selective, require the use of F_2 for their synthesis which, constitutes a potential drawback.

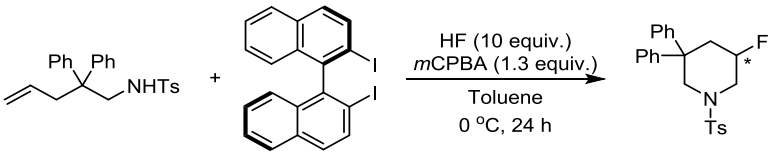
1.2.2.1.1 Fluorination using hypervalent iodine-based reagents

A very attractive alternative to the use of F_2 and F_2-derived reagents is the preparation of electrophilic fluorination reagents by inversion of the polarity of the fluoride anion. In this context, hypervalent iodine-based reagents have attracted considerable attention as mediators in electrophilic halofunctionalization reactions.[37] These versatile reagents display reactivity patterns similar to transition metals, eluding their toxicity and cost.[38] The unique properties of this class of reagents, arising from their structural and bonding features,[39] have opened the path to new reactivities and mechanistic possibilities. The most commonly used hypervalent iodine-containing molecules in organic chemistry are those in which the iodine atom is in oxidation state +3 (λ^3-iodanes) or +5 (λ^5-iodanes). Within the λ^3-iodane family, two different structural classes exist (Figure 7): the open hypervalent iodine species such as $TolIF_2$ (**11**), unstable and hygroscopic compounds with high reactivity, and the more stable and selective cyclic species such as fluoro-benziodoxole **12**.

11 **12**

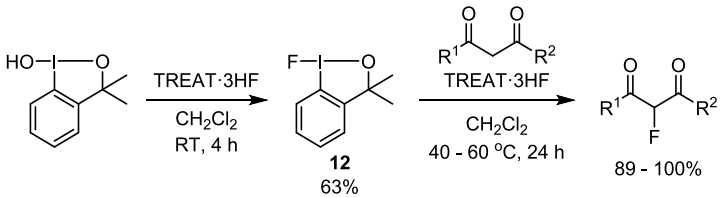
Figure 7. Open and cyclic hypervalent iodine-based electrophilic fluorinating reagents.

Open hypervalent iodine species **11** has been applied by Murphy and co-workers[40] in the fluorination of diazocarbonyl compounds and by Hara and co-workers[41] in the fluorination of silyl enol ethers and in the fluorinative ring expansion of cyclic ethers. Furthermore, these reagents have been applied in asymmetric fluorinat ions using chiral hypervalent iodine reagents by Nevado and co-workers.[42] A very interesting approach to this transformation, developed by Shibata and co-workers,[43] is the *in situ* generation of the asymmetric hypervalent iodine reagent in catalytic amount, a strategy that improves the atom economy of the reaction (Scheme 12).



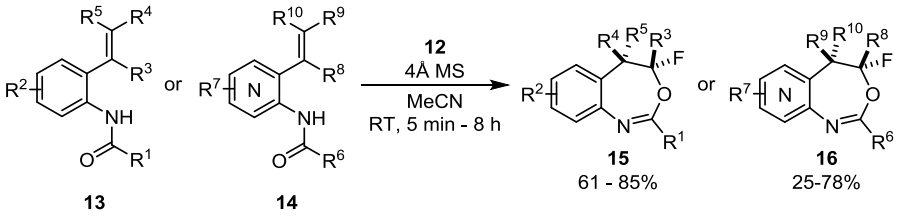
Scheme 12. Catalytic asymmetric fluorination by *in situ* generation of hypervalent iodine.

The bench-stable and crystalline cyclic hypervalent iodine-based reagent **12** has received much attention as an electrophilic fluorination reagent, being subject of a number of synthetic[44] and computational[39e, 45] studies. This reagent was first reported in 2012 by Legault and Prévost,[44a] who anticipated its potential as an electrophilic fluorination reagent. Since then, this reagent has experimented an astonishing growth in interest, becoming a key intermediate in the synthesis of the well-known trifluoromethylation reagent Togni-I and other hypervalent iodine derivatives.[44b, 46] According to the prediction made by Legault, the competence of **12** as an electrophilic fluorination reagent was rapidly established by Stuart and co-workers[44c, 44d] in the fluorination of several β-ketocarbonyl compounds. In the same publication, a straightforward synthesis using fluoride was reported (Scheme 13). The same group later reported the fluorolactonization of unsaturated carboxylic acids promoted by **12**.[44e]



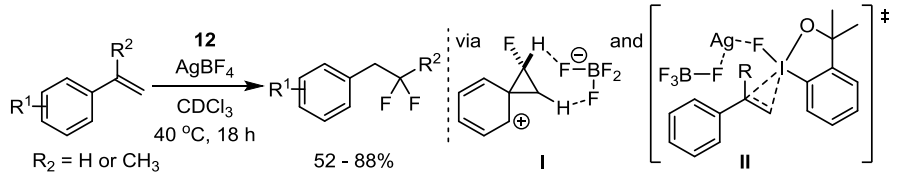
Scheme 13. Synthesis of **12** from fluoride and fluorination of 1,3-dicarbonyl compounds.

Conceptually similar fluorocyclization reactions have been reported by Gulder and co-workers.[44g-i] Starting from readily available *o*-styryl amides **13** or pyridyl styrenes **14**, different fluoro-benzoxazepines **15** and fluoro-azabenzoxazepines **16** were obtained in good yields, regio- and diastereoselectivities (Scheme 14). This process shows a very interesting and complementary regioselective cyclization compared to the reaction with Selectfluor® (**10**), which under the same conditions furnishes fluorinated benzoxazines.[44g, 47] Such selectivity divergency between **10** and **12** was studied computationally by Cheng and co-workers.[45b]



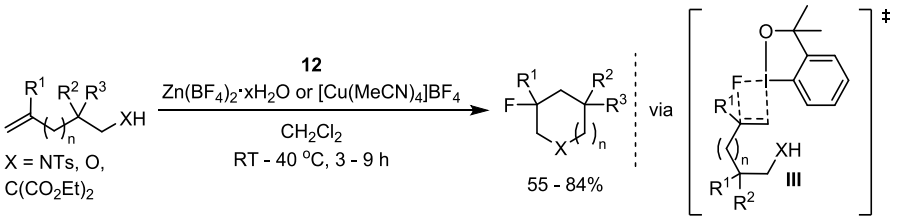
Scheme 14. Synthesis of fluoro-benzoxazepines and fluoro-azabenzoxazepines.

The Szabó group has contributed greatly to the understanding and the expansion of the reactivity profile of **12**.[44j-n] In 2014, our group reported the geminal difluorination of styrenes mediated by **12** and $AgBF_4$. [44j] It was demonstrated that both reagents served as a fluorine source, electrophilic and nucleophilic respectively (Scheme 15). An interesting phenonium ion (**I**) intermediate/aryl migration was proposed as a key feature to explain the rearrangement of the styrene moiety. The mechanism was later examined computationally by Xue, Cheng and co-workers, [45c] finding the proposed 1,2-aryl migration as the rate-limiting step. Their findings include a novel activation mode of the reagents through Lewis acid coordination of the fluorine atom (**II**).



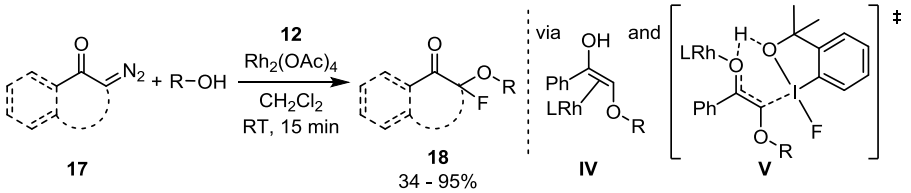
Scheme 15. Silver-mediated difluorination of styrenes.

Our group has also reported the fluorination of aminoalkenes catalyzed by $Zn(BF_4)_2 \cdot xH_2O$, resulting in fluorinated five-, six- and seven-membered nitrogen-containing heterocycles, an important class of compounds widely present in nature. The methodology was extended to the oxyfluorination and carbofluorination of the corresponding alkenes (Scheme 16).[44k] A theoretical investigation by Himo, Szabó and co-workers[45d] provided insight in the mechanism of the reaction, revealing a further activation mode of **12** consisting in the isomerization of the I–F bond towards the apical position (**III**).



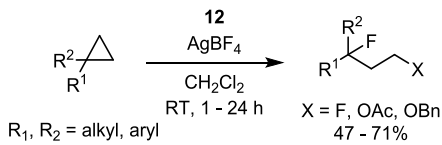
Scheme 16. Zn and Cu-catalyzed aminofluorination, oxyfluorination and carbofluorination.

Difunctionalization reactions are a key process in the chemistry toolbox, as they enable the one-step synthesis of complex and versatile products. In this context, our group has developed a Rh-catalyzed fluorination-based difunctionalization of diazocarbonyl compounds (**17**), introducing fluorine and oxygen moieties to give α-fluoro ethers **18** in one single transformation (Scheme 17).[44l] In a computational study by Himo, Szabó and co-workers,[45e] a key Rh-enol intermediate (**IV**) was found to undergo a concerted proton transfer/electrophilic addition (**V**) involving **12**.



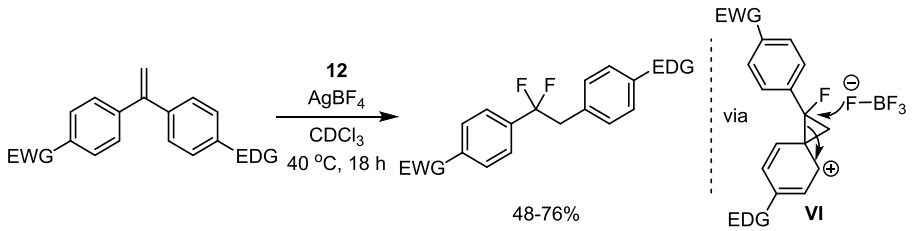
Scheme 17. Rh-catalyzed difunctionalization of diazocarbonyl compounds.

A silver mediated fluorinative opening of cyclopropanes using **12** has been reported by our group.[44m] The reaction features a 1,3-difunctionalization that could be turned from difluorination to fluoroacetoxylation by modifying the ligand on the hypervalent iodine reagent, or to oxyfluorination adding the corresponding alcohol to the reaction mixture (Scheme 18).



Scheme 18. Fluorinative opening and 1,3-functionalization of cyclopropanes.

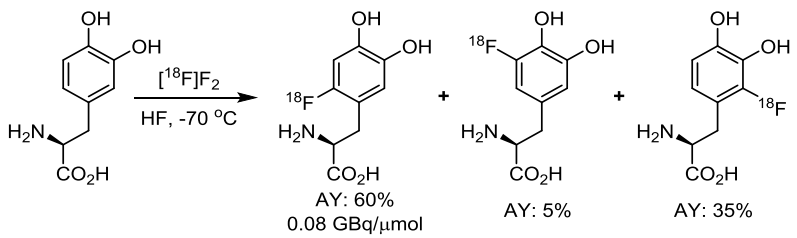
Lastly, our group reported an investigation on the migratory aptitude of α-substituted styrenes mediated by **12** and $AgBF_4$.[44n] This study, based on our previously reported difluorination of styrenes,[44j] reveals a dependence on the electronic properties of the different substituents, being the electron-donating substituted arenes the most prone to migration due to stabilization of the phenonium ion **VI** (Scheme 19).



Scheme 19. Silver mediated rearrangement of α-substituted styrenes.

1.2.2.2 Electrophilic fluorine-18 labelling

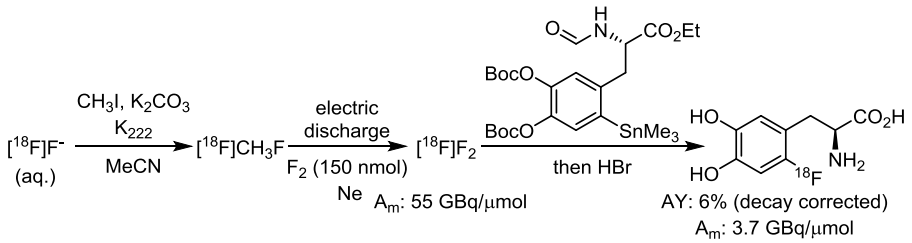
The use of electrophilic reagents in fluorine-18 chemistry is somewhat less developed than its nucleophilic counterparts. The underdevelopment of electrophilic fluorine-18 reagents is based on two main reasons.[6b, 6g, 6j] Firstly, the high reactivity of $[^{18}F]F_2$, the simplest electrophilic fluorination reagent, leads to unselective reactions and mixtures of often inseparable products. Although $[^{18}F]F_2$ has been used in direct C–H fluorination procedures (Scheme 20),[48] considerable (and successful) efforts have been dedicated to its conversion to less reactive species.[49] Reagents such as $[^{18}F]XeF_2$,[49a-f] [^{18}F]AcOF,[49g-l] [^{18}F]pyridinium salts[49m] and other [^{18}F]*N*–F reagents[49n-s] (being [^{18}F]NFSI,[49p, 49q] and [^{18}F]Selectfluor (**[^{18}F]10-OTf**)[49r, 49s] the most commonly used) are among the alternatives. The second problem arises from the fact that only one atom in $[^{18}F]F_2$ is fluorine-18 ($^{18}F–^{19}F$). This imposes a maximum theoretical radiochemical yield of 50% and the obtention of products with low molar activity due to the formation of large amounts of products containing fluorine-19 instead of the desired fluorine-18. Regrettably, the low molar activity of $[^{18}F]F_2$ is transferred to all its derivatives ([^{18}F]Selectfluor **[^{18}F]10-OTf**, [^{18}F]NFSI), strongly limiting their clinical applications.



Scheme 20. Direct fluorination of 6-[^{18}F]fluoro-L-DOPA using $[^{18}F]F_2$.

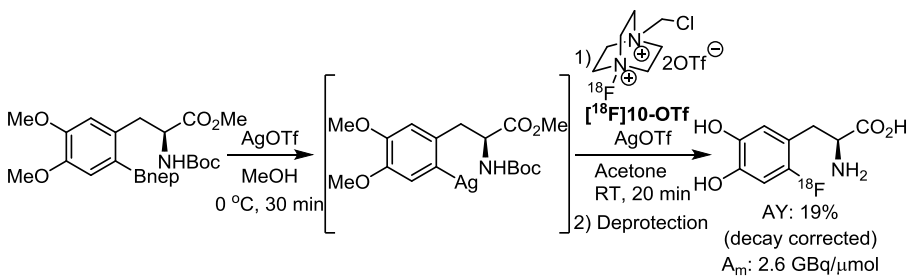
In order to avoid unselective labelling using $[^{18}F]F_2$ for direct C–H fluorination, strategies based on the demetallation of various organometallic precursors have been developed.[49j, 50] These procedures increased the regioselectivity of the labelling, but low molar activities were obtained (0.01-0.4 GBq/μmol). To address the inherent low molar activity of cyclotron-produced $[^{18}F]F_2$, Solin and co-workers[51] developed a method for the post-target synthesis of $[^{18}F]F_2$ using a low amount of carrier F_2. Thus, $[^{18}F]F_2$ was obtained with increased molar activity (55 GBq/μmol vs regular

1 GBq/μmol[52]) and used to synthesize 6-[^{18}F]fluoro-L-DOPA in 3.7 GBq/μmol (Scheme 21).[50a] The method for production of high molar activity was later modified to avoid the use of toxic F_2 as carrier gas.[53]



Scheme 21. Electrophilic synthesis of 6-[^{18}F]fluoro-L-DOPA by demetallation using post-target produced [^{18}F]F_2.

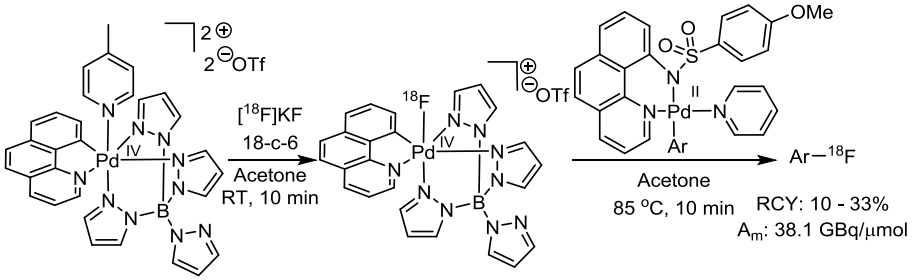
In a recent study, Gouverneur, Solin and co-workers obtained a modified version of [^{18}F]Selectfluor (**[^{18}F]10-OTf**) in high molar activity.[49r] This was accomplished by applying the post-target synthesis of [^{18}F]F_2, developed by Solin and co-workers.[51] The high molar activity [^{18}F]Selectfluor (**[^{18}F]10-OTf**) was used in a silver mediated demetallation strategy affording 6-[^{18}F]fluoro-L-DOPA as a single regioisomer with good molar activity (Scheme 22).[49s]



Scheme 22. Silver mediated labelling of 6-[^{18}F]fluoro-L-DOPA using [^{18}F]Selectfluor prepared from post-target synthesized [^{18}F]F_2.

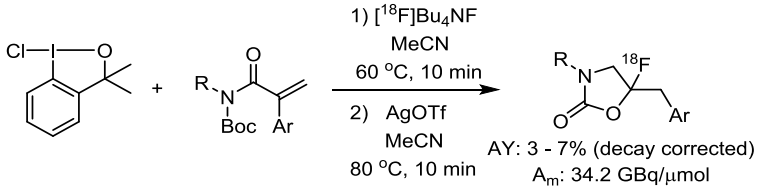
The methods developed by Gouverneur, Solin and co-workers allowed for the electrophilic fluorine-18 fluorination with increased molar activity. However, an inherent limitation of this method is the cumbersome handling of [^{18}F]F_2.

Similarly to fluorine-19, the use of polarity inversion strategies is an attractive option that grants access to a complimentary set of molecules avoiding the drawbacks of [^{18}F]F_2. Ritter and co-workers[54] have elegantly exercised this possibility by transforming [^{18}F]fluoride into highly electrophilic [^{18}F]Pd(IV)–F species. This allowed for the labelling of previously formed Pd-arene complexes in moderate radiochemical yield but most importantly, with a molar activity of 38.1 GBq/μmol (Scheme 23). The process was later adapted to the use of Ni-complexes in aqueous solution.[55]



Scheme 23. Two-step synthesis of aryl fluorides via electrophilic [^{18}F]Pd(IV)-F complex.

The inversion of the polarity of [^{18}F]fluoride has also been accomplished by means of hypervalent iodine reagents. In early 2017 Li, Lu and co-workers[44o] employed the chlorinated derivative of **12** in a two-step labelling of oxazolidine-2-ones mediated by AgOTf and [^{18}F]Bu_4NF (Scheme 24). Albeit the low activity yields (decay corrected), the products are obtained in high molar activity, again demonstrating the usefulness of the polarity inversion strategy.



Scheme 24. Silver mediated fluorine-18 fluorination of unsaturated carbamates.

1.3 Challenges in translational chemistry

The transition of fluorine-19 chemistry into fluorine-18 labelling is a challenging process, as the conditions of fluorine-19 fluorination reactions are most often not directly applicable to fluorine-18 labelling processes. Hence the necessity of translational chemistry, which is not exempt from obstacles. In addition to the inherent difficulties of C–F bond-forming processes (see Section 1.2), there are several challenges that are unique to the development of PET tracers.[6b, 6j, 56]

Firstly, fluorine-18 is produced in extremely small amounts (picomoles to nanomoles) due to its radioactive nature and the limited capacity of hospital cyclotrons. The extreme scale difference with the rest of the reagents (millimoles) alters the reaction kinetics. Under these conditions, side reactions and minor impurities in solvents and reagents (otherwise negligible in fluorine-19 chemistry) can become detrimental.

Secondly, the radioactive decay imposes an important time limitation, especially when high levels of activity are required in the final product. Thus, the timescale of the radiosynthesis (including purification) of fluorine-18 species should not exceed three half-lives (*i.e.* about 5 h). Furthermore, reaction procedures should be robust and operationally simple, as they must be applied by skilled nonspecialist radiochemists.

Thirdly, radiopharmaceuticals need to be obtained in high molar activity, which is of vital importance for occupancy studies and a key aspect of the tracer principle. Isotopic dilution with ambient fluorine-19, use of carrier gases (F_2 for the synthesis of $[^{18}F]F_2$) and the decay of the radioactive isotope are the main causes for the low molar activity of fluorine-18 labelled compounds.

1.4 Aims of this thesis

A large effort has been devoted to the expansion of the chemical toolbox for fluorination reactions. Even though numerous strategies have been developed, the space for improvement and innovation is still considerably large. The aim of this thesis is to broaden the fluorination toolbox, in particular, the fluorine-18 labelling reactions.

The first part of this thesis focuses on the late-stage synthesis of trifluoromethyl moieties, with the ultimate goal of translating the methodology into fluorine-18 labelling.

The second part deals with the exploration of the reactivity of an electrophilic hypervalent iodine-based fluorination reagent. The potential of this reagent as an electrophilic fluorine-18 fluorination reagent will be studied in two different processes: the synthesis of $[^{18}F]$fluoro-benzoxazepines and the rhodium-mediated synthesis of α-$[^{18}F]$fluoroethers. In these two studies, the obtention of high molar activity will be of paramount importance. Furthermore, a palladium-catalyzed iodofluorination of alkenes using the fluorine-19 analog of this reagent is discussed.

2 Results and discussion

2.1 Development of new reactions for the late-stage synthesis of fluorine-18 containing trifluoromethyl groups (Papers I and II)

As mentioned in section 1.2.1.1, the introduction of a CF_3 group can be accomplished by the introduction of the CF_3 moiety or by nucleophilic substitution of CF_2Br. This section focuses on the synthesis of CF_3-containing molecules by nucleophilic substitution and their labelling with fluorine-18.

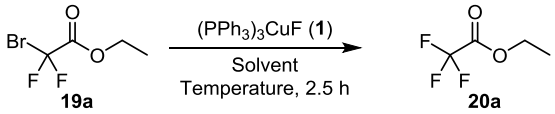
2.1.1 Synthesis of trifluoroacetates, trifluorotoluenes and trifluoroacetamides by Cu(I)-mediated nucleophilic fluorination (Paper I)

The copper complex $(PPh_3)_3CuF$ (**1**) is an efficient, yet relatively unknown, nucleophilic fluorine source that can be easily prepared from CuF_2. We envisioned that this complex would be a suitable reagent for the late-stage synthesis of trifluoromethylated molecules based on a halogen exchange strategy, with the ultimate goal of applying the method into fluorine-18 labelling.

2.1.1.1 Optimization of the reaction conditions

We started our study investigating the reaction between ethyl 2-bromo-2,2-difluoroacetate (**19a**) and **1** in different solvents and temperatures for 2.5 hours (Table 2). When the reaction was performed in $CDCl_3$, only traces of the desired product **20a** could be detected, at 40 ºC or 80 ºC (entries 1 and 2). Changing to ether-type solvents provided a minor improvement in the yield, as the desired product was obtained only in 11% using THF or dioxane at 80 ºC (entries 3 and 4) whereas toluene did not increase the yield (entry 5). Gratifyingly, the yield was considerably increased when the reaction was performed in DMF at 80 ºC, affording **20a** in 69% yield (entry 6). Further increasing the temperature to 100 ºC afforded the desired trifluoroacetate **20a** in 90% yield (entry 7).

Table 2. Reaction conditions screening for fluorination with **1**.[a]



Entry	Solvent	Temperature [°C]	Yield [%][b]
1	$CDCl_3$	40	<1
2	$CDCl_3$	80	5
3	THF	80	11
4	1,4-Dioxane	80	11
5	Toluene	80	3
6	DMF	80	69
7	DMF	100	90

*[a]Substrate **19a** (0.10 mmol) and **1** (0.14 mmol) were dissolved in the corresponding solvent (0.30 mL) under Ar and heated at the indicated temperature for 2.5 h. [b]Determined by ^{19}F-NMR spectroscopy analysis of the reaction crude using α,α,α-trifluorotoluene as internal standard*

2.1.1.2 Substrate scope

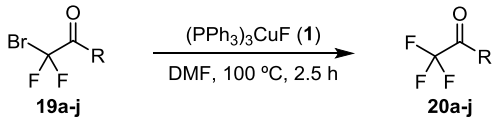
With the optimal conditions in hand, we explored the substrate scope of the reaction (Table 3). All the obtained trifluoromethyl esters (**20a-h**) and trifluoromethyl ketones (**20i-j**) are highly unpolar and therefore very difficult to separate from PPh_3, a by-product of the decomposition of **1**. After careful purification, all product samples contained varying amounts of PPh_3. Since we envisioned that this method would be suitable for fluorine-18 labelling, where final products are purified by semi-preparative HPLC, we identified products **20a-j** and measured their yields by ^{19}F-NMR spectroscopy in the crude reaction mixtures (all the products were synthesized by alternative methods and fully characterized).

2.1.1.2.1 Trifluoroacetates and trifluoromethyl ketones

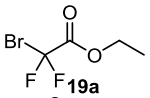
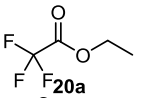
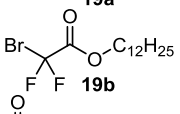
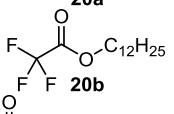
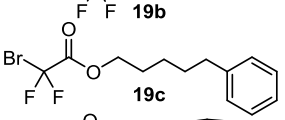
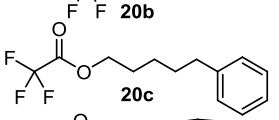
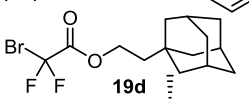
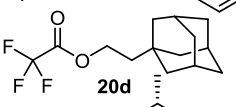
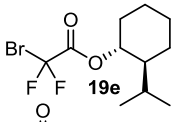
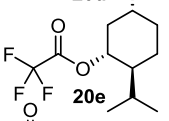
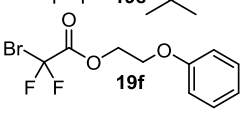
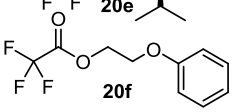
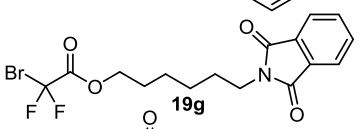
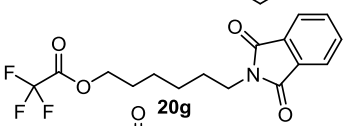
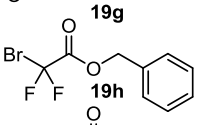
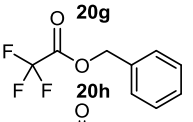
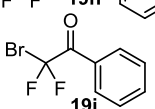
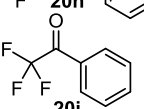
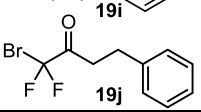
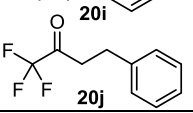
Different 2-bromo-2,2-difluoroacetates bearing alkyl chains were transformed into the corresponding trifluoroacetates **20a-d** in excellent yields, ranging from 89% to 92% (Table 3, entries 1-3). Bulky substituents were very well tolerated, as adamantyl and menthol derivatives **20d** and **20e** were obtained in a comparable 89% and 88% yield respectively (entries 4 and 5). Phenoxy and phthalimide substituents afforded the corresponding trifluoromethylated products **20f** and **20g** in good yields (83% and 68% respectively, entries 6 and 7). Only trifluoroacetate **20h** was obtained in a lower 55% yield (entry 8), along with several fluorinated side-products.[57] Trifluoromethyl ketone **20i** was obtained in the same manner, affording an

excellent yield of 96% (entry 9) whereas **20j** was obtained in very low yield in a complex mixture of side-products, even at lower temperature (entry 10).

Table 3. Substrate scope of trifluoroacetates and trifluoromethyl ketones.[a]



19a-j 20a-j

Entry	Substrate	Product	Yield [%][b]
1	 19a	 20a	90
2	 19b	 20b	89
3	 19c	 20c	92
4	 19d	 20d	89
5	 19e	 20e	88
6	 19f	 20f	83
7	 19g	 20g	68
8	 19h	 20h	55
9	 19i	 20i	96
10	 19j	 20j	16[c]

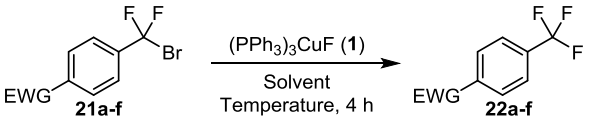
*[a]Unless otherwise stated, **19a-j** (0.10 mmol) and **1** (0.14 mmol) were dissolved in DMF (0.30 mL) under Ar and heated at 100 °C for 2.5 h. [b]Determined by ^{19}F-NMR spectroscopy analysis of the reaction crude using α,α,α-trifluorotoluene as internal standard. [c]In $CDCl_3$ at 70 °C.*

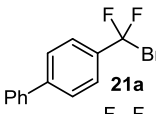
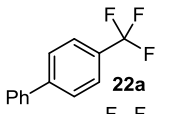
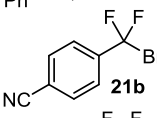
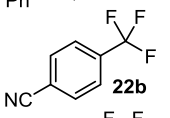
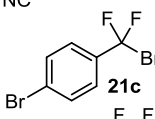
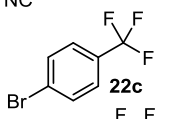
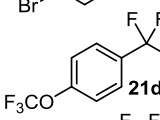
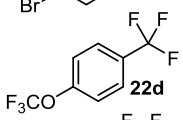
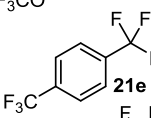
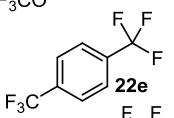
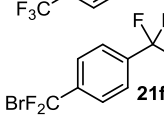
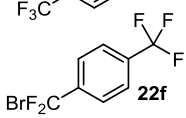
2.1.1.2.2 Trifluoromethyl arenes

Bromodifluoromethyl arenes **21** were also fluorinated using copper complex **1**. These substrates had different reactivity compared to the esters,

and the reaction time had to be increased to 4 hours to achieve full conversion of the precursors. In addition, different solvents and temperatures had to be used in order to obtain good yields of trifluorotoluenes (Table 4). Phenyl substituted trifluoromethyl benzene **22a** was obtained in high 93% yield using $CDCl_3$ as solvent at 70 °C (entry 1). Electron-poor arenes are challenging substrates for this kind of reaction[26g] and therefore arenes **22b-f** required higher reaction temperatures, though only moderate yields could be achieved. When bromodifluoromethyl benzene **21b**, bearing a *p*-CN substituent, was reacted in toluene at 120 °C the corresponding trifluoromethyl benzene **22b** was obtained in 25% yield (entry 2). Substrates bearing *p*-Br or *p*-OCF_3 substituents provided the corresponding trifluoromethyl arenes **22c** and **22d** in 49% and 40% yield respectively in 1,2-dichloroethane at 100 °C (entries 3 and 4). For the strongly electron-withdrawing *p*-CF_3 and *p*-CF_2Br, the solvent had to be changed to DMF in order to obtain **22e** and **22f** in acceptable yields (27% and 40% respectively, entries 5 and 6).

Table 4. Substrate scope of trifluoromethyl arenes.[a]



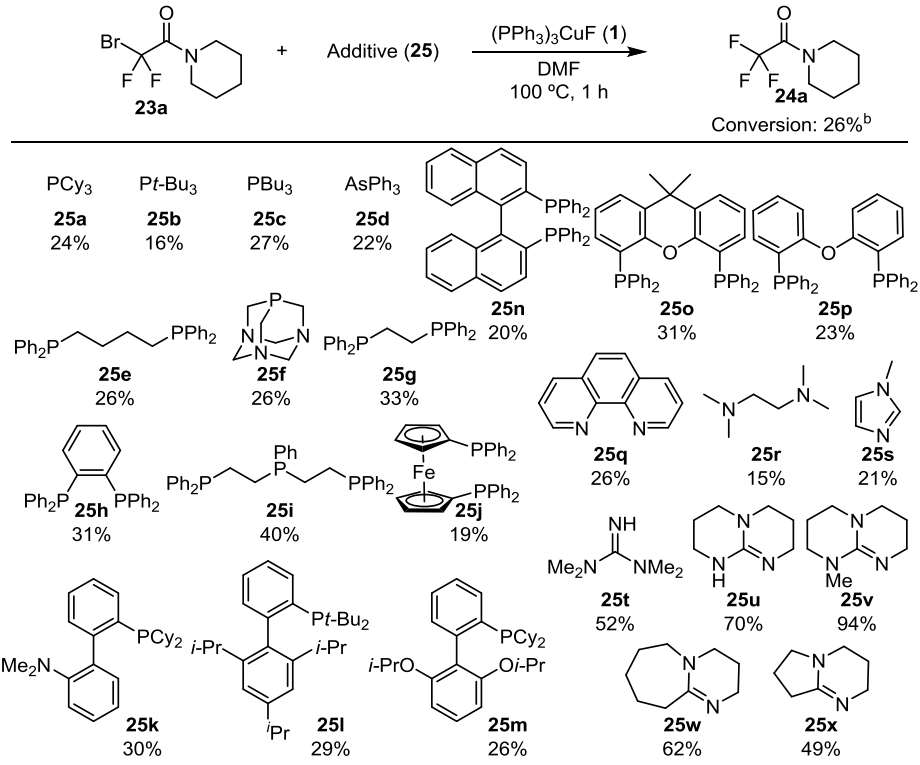
Entry	Substrate	Solvent	Temperature [°C]	Product	Yield [%][b]
1	 **21a**	$CDCl_3$	70	 **22a**	93
2	 **21b**	Toluene	120	 **22b**	25
3	 **21c**	DCE	100	 **22c**	49
4	 **21d**	DCE	100	 **22d**	40
5	 **21e**	DMF	100	 **22e**	27
6	 **21f**	DMF	100	 **22f**	40

*[a]**21a-f** (0.10 mmol) and **1** (0.14 mmol) were dissolved in the indicated solvent (0.30 mL) under Ar and heated at the indicated temperature for 4 h. [b]Determined by ^{19}F-NMR spectroscopy analysis of the reaction crude using α,α,α-trifluorotoluene as internal standard.*

2.1.1.2.3 Trifluoroacetamides

Trifluoroacetamides are important motifs in medicinal chemistry.[58] Despite this importance, their synthesis by late-stage fluorination has been neglected according to the literature. When the reaction between 2-bromo-2,2-difluoroacetamide **23a** and **1** was performed in DMF at 100 ^{o}C for 1 h, 26% conversion to trifluoroacetamide **24a** was observed. In order to increase the reactivity of the copper complex **1** towards 2-bromo-2,2-difluoroacetamides, we examined the effect of various additives **25** (Table 5). Phosphine-type additives (**25a-p**) did not provide any better results, with the sole exception of **25i**, which provided a slightly higher conversion (40%). We then turned our attention to nitrogen-containing additives such as **25q-s**, which did not increase the conversion significantly (26%, 15% and 21% respectively). Gratifyingly, guanidine (**25t-v**) and amidine-type (**25w-x**) additives[59] increased the conversion substantially. Guanidines **25u** (TBD) and **25v** (MTBD) provided the highest conversions (70% and 94% respectively). However, analysis of the reaction crudes by ^{19}F-NMR and ^{1}H-NMR revealed that more than 25% of the starting material **23a** had undergone a hydrodebromination process. Amidine-type additives **25w** (DBU) and **25x** (DBN) provided lower conversions than guanidines (62% and 49% respectively), but no decomposition products were detected. For this reason, DBU (**25w**) was used as an additive in further studies.

Table 5. Additive screening for the fluorination of 2-bromo-2,2-difluoroacetamides.[a]

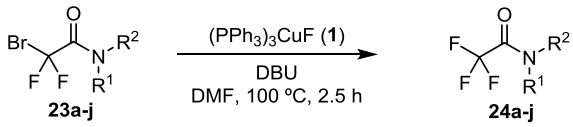


*[a]**23a** (0.10 mmol), **1** (0.14 mmol) and the additive **25** (0.14 mmol) were dissolved in DMF (0.30 mL) under Ar and heated at 100 °C for 1 h. The conversion was determined by analysis of the ^{19}F-NMR of the crude reaction mixture. [b]No additive was added.*

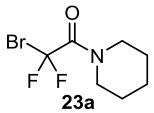
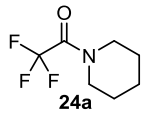
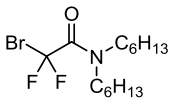
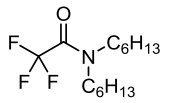
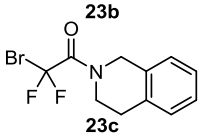
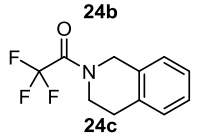
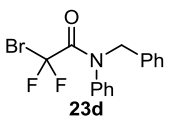
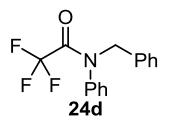
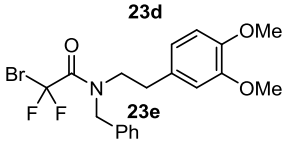
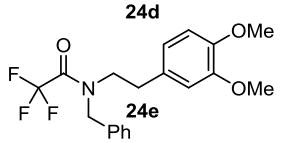
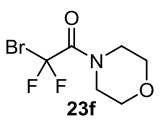
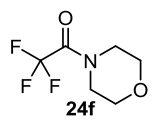
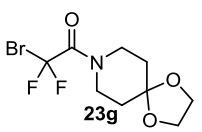
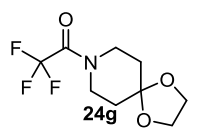
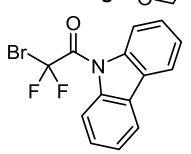
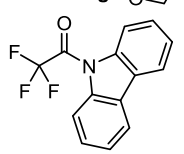
Thus, with the aforementioned additive and increasing the reaction time to 2.5 hours, we were able to obtain **24a** in 74% yield. Applying these conditions, we studied the substrate scope of this transformation (Table 6). Different trifluoroacetamides bearing alkyl groups (**24a-c**) were obtained in high yields (74-87%, entries 1-3). When DBU was not added to the reaction mixture, the yields were considerably lower (34-52%), indicating the important role of DBU in this reaction. The presence of a benzyl substituent did not diminish the yield, as trifluoroacetamides **24d** and **24e** were also obtained in high yield (73% and 81% respectively, entries 4 and 5). Oxygen-containing products, such as morpholine and ketal derivatives **24f** and **24g**, were obtained in good yield (63% and 66% respectively, entries 6 and 7). Interestingly, the presence of DBU diminished the yield of the fluorination of fluorenone and sulfonamide derivatives **24h** and **24i**, which were obtained in 2% and 9% yield respectively (entries 8 and 9). Analysis of the ^{19}F-NMR and ^{1}H-NMR revealed

the formation of large amounts of different by-products, probably caused by the high basicity of DBU. Fortunately, yields of 88% and 56% were obtained in the reaction without DBU (entries 8 and 9). The Weinreb amide derivative **23j** gave a very similar yield with and without DBU, affording **24j** in 40% and 48% yield respectively (entry 10).

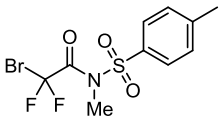
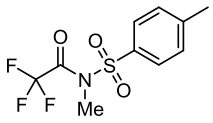
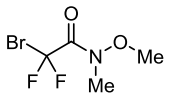
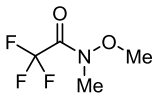
Table 6. Substrate scope of trifluoroacetamides.[a]



23a-j **24a-j**

Entry	Substrate	Product	Yield [%][b]
1	 **23a**	 **24a**	74 (36)[c]
2	 **23b**	 **24b**	87 (34)[c]
3	 **23c**	 **24c**	74 (52)[c]
4	 **23d**	 **24d**	73
5	 **23e**	 **24e**	81
6	 **23f**	 **24f**	63
7	 **23g**	 **24g**	66
8	 **23h**	 **24h**	2 (88)[c]

(table 6 continuation)

9	 **23i**	 **24i**	9 (56)[c]
10	 **23j**	 **24j**	40 (48)[c]

*[a]Unless otherwise stated **23a-j** (0.10 mmol), DBU (0.14 mmol) and **1** (0.14 mmol) were dissolved in DMF (0.30 mL) under Ar and heated at 100 °C for 2.5 h. [b]Determined by ^{19}F-NMR spectroscopy analysis of the reaction crude using α,α,α-trifluorotoluene as internal standard. [c]Yield without DBU.*

2.1.1.3 Conclusions

A reaction protocol for the late-stage synthesis of trifluoromethyl acetates, arenes and acetamides from the corresponding bromodifluoromethyl derivatives has been developed. The reaction proceeds in short reaction times at high temperatures using the complex $(PPh_3)_3CuF$ as nucleophilic fluorine source. In order to provide good yields, substrates with low reactivity required the presence of DBU as activator. We envisioned that this process is a good candidate to be translated into a fluorine-18 labelling procedure.

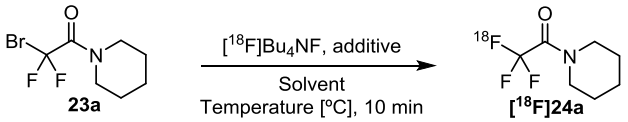
2.1.2 Synthesis of fluorine-18 labelled trifluoroacetamides (Paper II)

As previously mentioned, trifluoroacetamides are relevant moieties in medicinal chemistry. With the goal of translating the methodology developed in section 2.1.1 into a fluorine-18 labelling process, we devoted our efforts to the synthesis of the fluorine-18 labelled copper complex **[^{18}F]1**. Initial attempts to label trifluoroacetamides using **[^{18}F]1** were unsuccessful but fortunately, we encountered that they could be labelled using [^{18}F]Bu_4NF. [^{18}F]Bu_4NF is a readily available nucleophilic fluorine-18 source that can be easily prepared in high molar activity from cyclotron-produced [^{18}F]fluoride. This section describes the metal-free fluorine-18 labelling of trifluoroacetamides using [^{18}F]Bu_4NF.

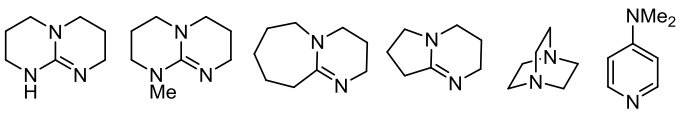
2.1.2.1 Optimization of the reaction conditions

We started our investigation by reacting 2-bromo-2,2-difluoroacetamide **23a** and [^{18}F]Bu_4NF at different temperatures in different solvents (Table 7). Traces of the desired product **[^{18}F]24a** were obtained when the reaction was performed in MeCN at 60 ^{o}C or in DCE at 85 ^{o}C (3%, entries 1 and 2), whereas DMSO at 170 ^{o}C provided a radiochemical yield of 29% (entry 3). As we expected, the reaction in DMF provided the highest radiochemical yield (35%, entry 4). Interestingly, when the reaction was performed using the system [^{18}F]KF/K_{222}, a common combination in nucleophilic fluorine-18 labelling, a lower radiochemical yield of 22% was obtained (entry 5). We also examined the influence of metal activators.[26g, 26h] To our disappointment, this afforded only trace amounts of the desired product (entries 6-8). In light of these results and of our previous studies (section 2.1.1), we investigated the effect of nitrogen-containing additives. TBD (**25u**) and MTBD (**25v**) provided very high radiochemical yield (81% and 76% respectively, entries 9 and 10), but the reactions resulted in considerable decomposition of the starting material. DBU (**25w**) provided a radiochemical yield of 71% (entry 11) in a clean reaction with no decomposition products. Again, a lower radiochemical yield was obtained when [^{18}F]KF/K_{222} was used as labelling reagent (entry 12). DBN (**25x**), DABCO (**25y**) and DMAP (**25z**) provided lower radiochemical yields (40-59%, entries 13-15), whereas pyridine provided a radiochemical yield close to that of DBU (68%, entry 16). Based on these results, we decided to continue the study of the labelling reaction using DBU (**25w**) as additive, as it cleanly provided the labelled product in good radiochemical yield.

Table 7. Screening of reaction conditions for the fluorine-18 labelling of trifluoroacetamides.[a]



Entry	Solvent	Temperature [°C]	Additive	RCY [%][b]
1	CH_3CN	60	-	3 ± 1 (*n* = 2)
2	DCE	85	-	3 ± 2 (*n* = 2)
3	DMSO	170	-	29 ± 5 (*n* = 2)
4	DMF	100	-	35 ± 13 (*n* = 3)
5[c]	DMF	100	-	22 ± 6 (*n* = 3)
6	DMF	100	$(PPh_3)_3CuOAc$	<1 (*n* = 2)
7	DCM	RT	AgOTf	2 ± 0 (*n* = 2)
8	DCE	80	AgOTf[d]	4 ± 1 (*n* = 2)
9	DMF	100	TBD **(25u)**	81 ± 8 (*n* = 3)
10	DMF	100	MTBD (**25v**)	76 ± 12 (*n* = 3)
11	DMF	100	DBU (**25w**)	71 ± 8 (*n* = 3)
12[c]	DMF	100	DBU (**25w**)	65 ± 13 (*n* = 2)
13	DMF	100	DBN (**25x**)	40 ± 7 (*n* = 3)
14	DMF	100	DABCO (**25y**)	41 ± 7 (*n* = 3)
15	DMF	100	DMAP (**25z**)	59 ± 16 (*n* = 3)
16	DMF	100	Pyridine	68 ± 9 (*n* = 3)



25u **25v** **25w** **25x** **25y** **25z**

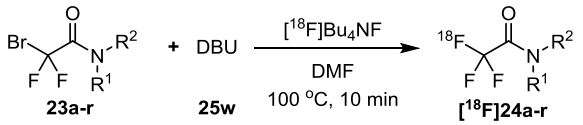
*[a]Unless otherwise stated: **23a** (60 μmol) and the indicated additive (60 μmol) were dissolved in the appropriate solvent (0.30 mL) containing [18F]Bu4NF and stirred at the indicated temperature. [b]Estimated by radio-HPLC analysis of the crude reaction mixture. [c]Using KF/K222. [d]2.0 equiv.*

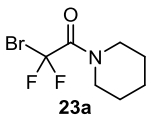
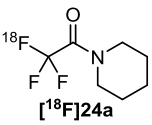
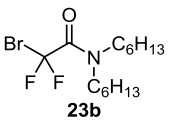
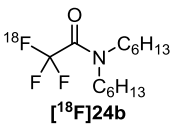
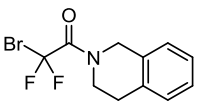
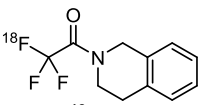
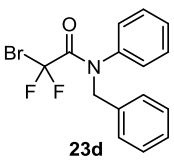
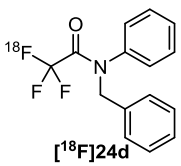
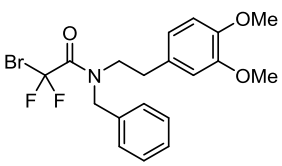
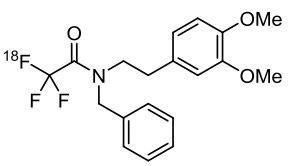
2.1.2.2 Substrate scope

With the optimal reaction conditions in hand, we studied the structural scope of this labelling reaction. Starting with tertiary bromodifluoroacetamides **23**, several tertiary trifluoroacetamides **[18F]24** were obtained in high radiochemical yield (Table 8). Cyclic and acyclic alkyl chains were well tolerated, affording products **[18F]24a** and **[18F]24b** in good radiochemical yield (71% and 68% respectively, entries 1 and 2). Benzylic derivatives such as **[18F]24c-e** were also obtained in high radiochemical yield (61-89%, entries 3-5). The reaction conditions proved to be equally adequate for oxygen-containing moieties, as the morpholine (**[18F]24f**, 72%), ketal

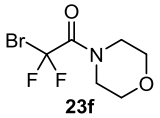
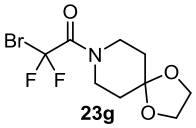
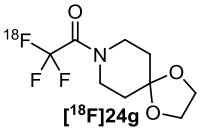
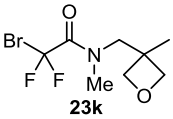
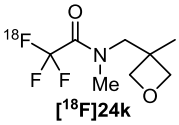
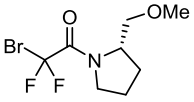
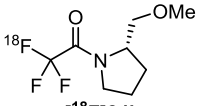
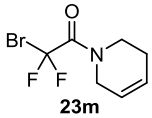
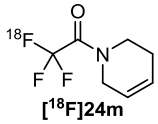
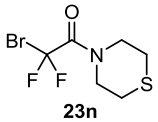
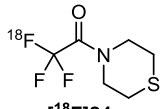
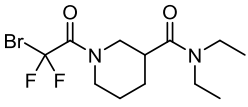
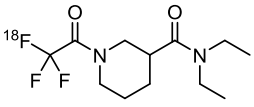
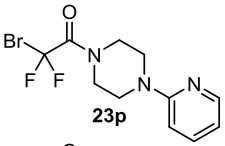
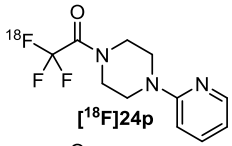
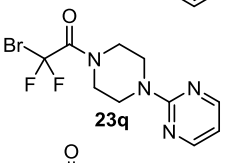
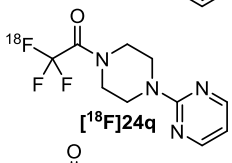
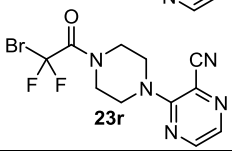
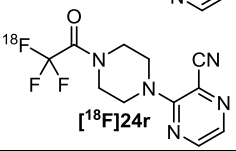
([^{18}F]**24g**, 92%), oxetane ([^{18}F]**24k**, 90%) and proline ([^{18}F]**24l**, 91%) derivatives were obtained in very good radiochemical yields (entries 6-9). An alkene functionality was also tolerated, as **[^{18}F]24m** was obtained in 84% radiochemical yield (entry 10). The presence of sulfur is often problematic in metal-catalyzed reactions, as it tends to coordinate to the metal and inhibit its catalytic activity. Using our metal-free process, sulfur-containing amide **[^{18}F]24n** was obtained in 84% radiochemical yield (entry 11). An additional amide and nitrogen-containing heterocycles were also tolerated, and products **[^{18}F]24o-r** were obtained in very high radiochemical yield (75-90%, entries 12-15).

Table 8. Substrate scope in the fluorine-18 labelling of tertiary trifluoroacetamides.[a]



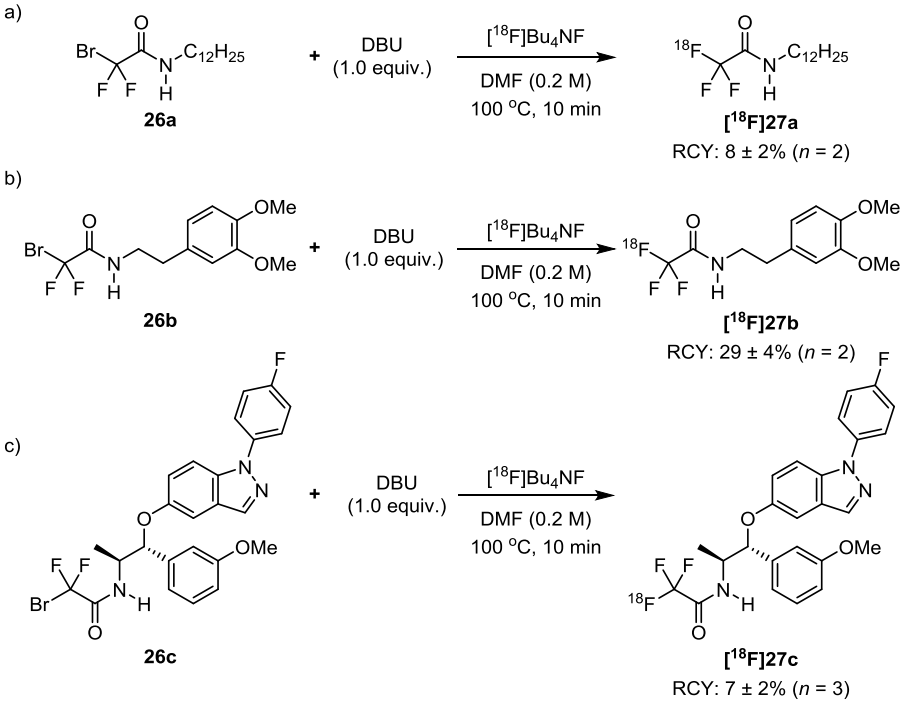
Entry	Substrate	Product	RCY [%] (n = 3)[b]
1	 **23a**	 **[^{18}F]24a**	71 ± 8
2	 **23b**	 **[^{18}F]24b**	68 ± 3
3	 **23c**	 **[^{18}F]24c**	61 ± 1
4	 **23d**	 **[^{18}F]24d**	89 ± 8
5	 **23e**	 **[^{18}F]24e**	77 ± 12

(table 8 continuation)

6	 **23f**	 **[^{18}F]24f**	72 ± 4
7	 **23g**	 **[^{18}F]24g**	92 ± 2
8	 **23k**	 **[^{18}F]24k**	90 ± 1
9	 **23l**	 **[^{18}F]24l**	91 ± 2
10	 **23m**	 **[^{18}F]24m**	84 ± 1
11	 **23n**	 **[^{18}F]24n**	84 ± 2
12	 **23o**	 **[^{18}F]24o**	77 ± 5
13	 **23p**	 **[^{18}F]24p**	90 ± 3
14	 **23q**	 **[^{18}F]24q**	75 ± 3
15	 **23r**	 **[^{18}F]24r**	80 ± 2

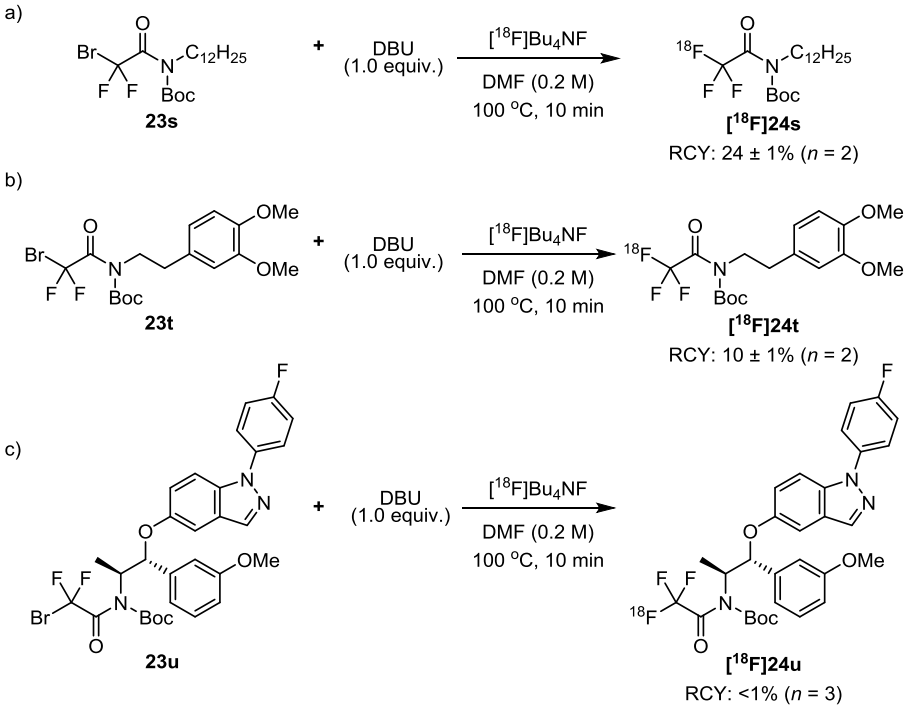
*[a]**23a-r** (60 μmol) and DBU (60 μmol) were dissolved in DMF (0.30 mL) containing [^{18}F]Bu$_4$NF and stirred at 100 °C for 10 minutes. [b]Estimated by radio-HPLC analysis of the crude reaction mixture.*

Secondary amides undergo basic hydrolysis more easily than their tertiary counterparts. When substrates **26a-c** were subjected to the labelling reaction conditions, secondary amides **[^{18}F]27a-c** were obtained in poor radiochemical yields (8-29%) and substantial decomposition of the starting materials was observed (Scheme 25).



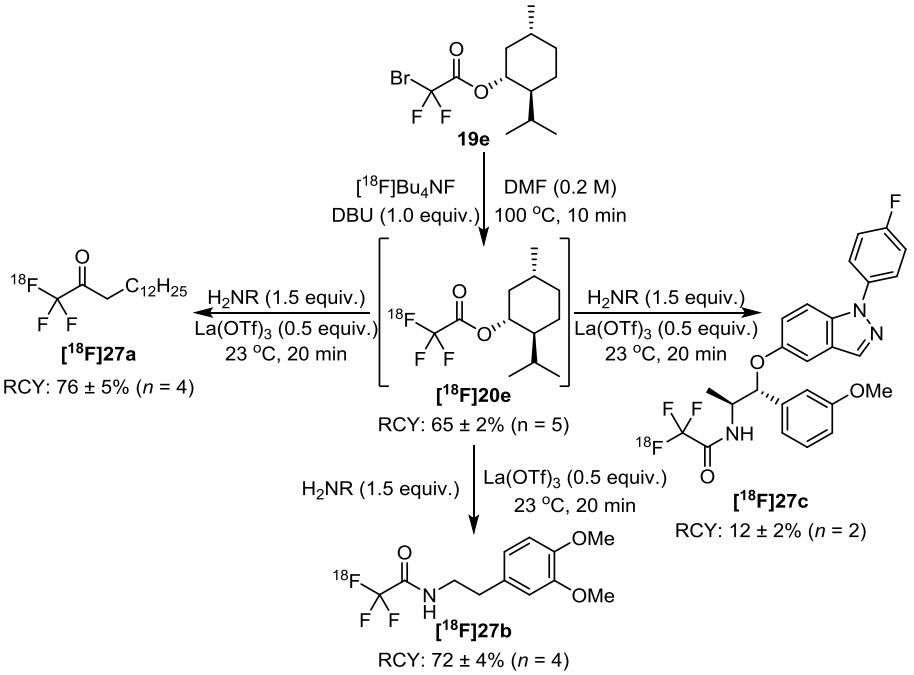
Scheme 25. Fluorine-18 labelling of secondary trifluoroacetamides.

Considering that that **[^{18}F]24e** (which is the benzylated analog of **[^{18}F]27b**) was obtained in 77% radiochemical yield (Table 8, entry 5) we attempted a protecting group strategy. We selected the easily removable Boc protecting group to protect our secondary amides against deprotonation by DBU. However, applying the optimized conditions to the Boc-protected bromodifluoroacetamides **23s-u**, only **[^{18}F]24s** was obtained in higher radiochemical yield (24%, Scheme 26a) whereas **[^{18}F]24t** and **[^{18}F]24u** were obtained in lower radiochemical yield (10% and <1% respectively, Scheme 26b and c).



Scheme 26. Attempted fluorine-18 labelling of Boc-protected secondary trifluoroacetamides.

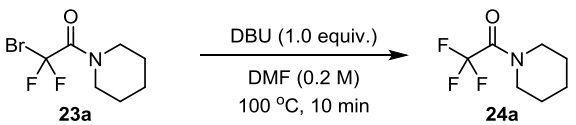
To achieve the labelling of secondary amides **[^{18}F]27a-c** in higher radiochemical yield, the procedure was modified to include a labelled ester intermediate **[^{18}F]20e** (Scheme 27). We envisioned that this labelled ester could be transformed into the desired secondary amides using the appropriate primary amines.[60] Labelled trifluoroacetate **[^{18}F]20e** was obtained in 65% radiochemical yield from its precursor **19e**. Treatment of this labelled ester with the corresponding primary amine and $La(OTf)_3$ at room temperature allowed us to obtain secondary trifluoroacetamides **[^{18}F]27a-b** in high radiochemical yield (Scheme 27). Furthermore, the utility of this methodology was demonstrated by the labelling of **[^{18}F]27c** (AZD5423), a non-steroidal glucocorticoid agonist developed against respiratory disease.[58, 61] This labelled pharmaceutical was obtained in 12% radiochemical yield under non-optimized conditions.



Scheme 27. Fluorine-18 labelling of secondary trifluoroacetamides via labelled ester intermediate.

2.1.2.3 Measurement of molar activity and activity yield

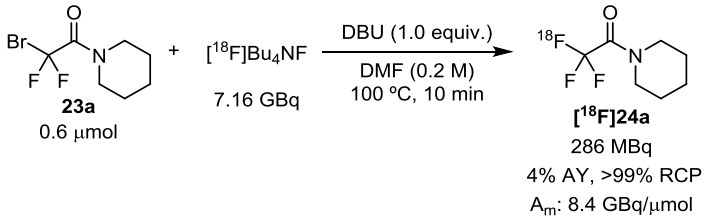
In order to determine the activity yield (AY) and the molar activity (A_m) of an isolated product, **[^{18}F]24a** was isolated by semi-preparative HPLC. Starting from 762 MBq of [^{18}F]Bu_4NF, 334 MBq of **[^{18}F]24a** were isolated (44% AY). The measured molar activity was 0.10 GBq/μmol 70 minutes after the end of the bombardment. Although this value is high enough to perform microdosing studies (determine the distribution of the tracer), it is insufficient for drug-target engagement studies. Surprisingly, we found that when [^{18}F]Bu_4NF was not added to the reaction mixture, a part of the starting material **23a** was transformed into the product **24a**. This indicated that the natural isotope of fluorine in **23a** assists in the formation of unlabelled **24a** (Scheme 28) which probably leads to the formation of **[^{18}F]24a** with a low molar activity.



Scheme 28. Starting material-assisted formation of **24a**.

We envisioned that decreasing the amount of starting material **23a** would increase the molar activity of the isolated product. Gratifyingly, a 100-fold decrease of the amount of **23a** (from 60 μmol to 0.6 μmol) and increasing the

amount of starting [^{18}F]Bu$_4$NF to 7.16 GBq allowed us to obtain 286 MBq of **[^{18}F]24a** in (4% activity yield with over 99% radiochemical purity) and a molar activity of 8.4 GBq/μmol (Scheme 29).



Scheme 29. Labelling and isolation of **[^{18}F]24a**.

2.1.2.4 Mechanistic studies to explore the role of DBU

In order to determine the role of the DBU activator, we monitored the interaction between amide **23a** and DBU by ^{13}C-NMR in DMF-d_7 at 100 °C (Figure 8), simulating the reaction conditions of the fluorine-18 labelling studies. Measuring the ^{13}C-NMR at room temperature, only a mixture of unreacted **23a** and DBU was observed. Upon heating the NMR probe to 100 °C (Figure 8a) systematic changes were observed in certain signals of DBU: the signals at 38.1 ppm (C6, purple) and 46.5 ppm (C11, orange) shifted upfield to 33.6 ppm and 40.5 ppm respectively. A substantial broadening of the signals was also observed. This change in the chemical shifts indicated that the chemical environment of C6 and C11 was significantly different when **23a** was present at 100 °C compared to pure DBU at 100 °C (Figure 8b), suggesting a covalent interaction between **23a** and DBU. A possible reason for the broadening of the signals could be attributed to the presence of rotamers or to the long-range coupling between C6 and C11 and the fluorine atoms in **23a**.

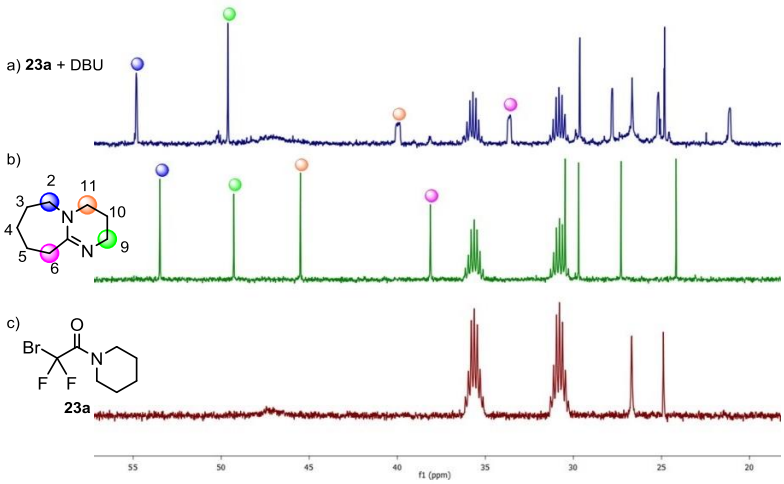
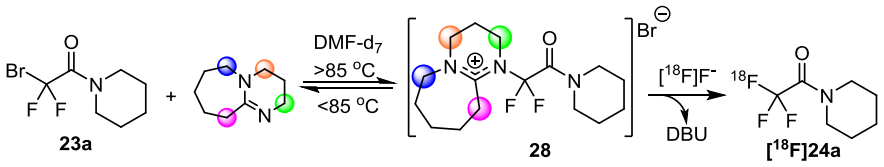


Figure 8. a) ^{13}C-NMR spectrum of **23a** + DBU in DMF-d_7 at 100 °C. b) ^{13}C-NMR spectrum of DBU in DMF-d_7 at 100 °C. c) ^{13}C-NMR spectrum of **23a** in DMF-d_7 at 100 °C.

Based on these experiments, we concluded that **23a** and DBU must form adduct **28** by displacement of bromine[59b] (Scheme 30). Thus DBU would act as an organocatalyst, activating the substrate prior to the fluorine-18 fluorination. In adduct **28**, the C(F_2)–N bond is very weak and the amidinium ion can be easily displaced by [^{18}F]F$^-$. Interestingly, when the reaction mixture was cooled below 85 °C, **28** decomposed to a mixture of **23a** and DBU. Adduct **28** was detected again when the mixture was heated to 100 °C, indicating that this process is reversible.



Scheme 30. Suggested mechanism and role of DBU.

2.1.2.5 Conclusions

This study has demonstrated that tertiary trifluoroacetamides can be efficiently labelled using [^{18}F]Bu_4NF in the presence of nitrogen-containing nucleophilic activators. Secondary trifluoroacetamides were labelled using a modified procedure via a labelled trifluoroacetate intermediate. Large-scale experiments allowed for the isolation of a labelled product in moderate activity yield and good molar activity. The role of the DBU additive was determined to be the activation of the substrate through the formation of a covalently bonded C(F_2)–N center.

2.2 Development of new electrophilic fluorination reactions (Papers III-V)

2.2.1 Preparation, purification and application of [^{18}F]fluoro-benziodoxole, a no-carrier-added electrophilic fluorine-18 fluorination reagent (Paper III)

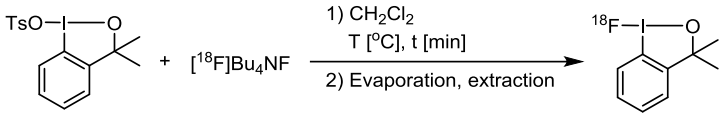
As stated in section 1.2.2.2, most of the electrophilic fluorine-18 fluorination reagents have an important drawback: they are derived from [^{18}F]F_2. As a result of the nature of [^{18}F]F_2 and its production, a maximum of 50% radiochemical yield and a low molar activity can be obtained. This section describes our efforts to prepare an electrophilic fluorine-18 reagent without the use of [^{18}F]F_2.

2.2.1.1 Synthesis and purification of [^{18}F]fluoro-benziodoxole

As a result of the time constraint and the limited amount of fluorine-18 sources available, the synthesis of **12** reported by Stuart[44c] (Section 1.2.2.1.1, Scheme 13) is not suitable in a labelling process. In addition, the typical analytical chromatographic techniques in radiochemistry (radio-HPLC and radio-TLC) cannot be used on [^{18}F]fluoro-benziodoxole **[^{18}F]12** (or on **12**), due to its instability towards silicon-based materials. We anticipated that the purification reported by Stuart (evaporation of the reaction solvent and extraction in warm *n*-hexane) would be suitable to assess the performance of the reaction, as the solubility of [^{18}F]Bu_4NF in *n*-hexane should be minimal. Thus, if any activity is extracted it must belong to [^{18}F]fluoro-benziodoxole **[^{18}F]12**.

We started investigating the transformation of tosyl-benziodoxole **29** into [^{18}F]fluoro-benziodoxole **[^{18}F]12** using [^{18}F]Bu_4NF at different temperatures and reaction times (Table 9). When the reaction was performed at 70 ^{o}C for 40 minutes, 47% of the total activity was extracted (entry 1). Gratifyingly, reducing the reaction time to 20 minutes did not decrease significantly the percentage of extracted activity (40%, entry 2). Increasing the amount of precursor gave a similar result (42%, entry 3) and decreasing the amount of solvent did not cause any significant difference (entry 4), as 37% of the activity was extracted. Increasing the amount of solvent provided higher extraction (56%, entry 5) but the prolonged evaporation time renders this impractical. We were very surprised to observe that performing the reaction at room temperature for 20 minutes provided a similar extraction of activity (40%, entry 6) and even more surprised when we obtained the same value reducing the reaction time to 5 minutes (41%, entry 7).

Table 9. Optimization of the reaction conditions for the synthesis of **[^{18}F]12**.[a]



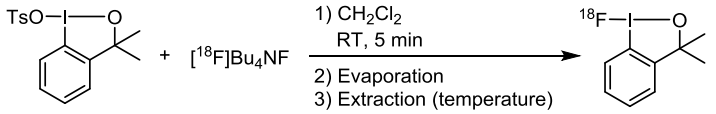
29 **[^{18}F]12**

Entry	T [°C]	t [min]	29 [mg]	Extracted activity [%] (n = 2)[b]
1	70	40	5	47 ± 3
2	70	20	5	40 ± 7
3	70	20	20	42 ± 6
4[c]	70	20	5	37 ± 1
5[d]	70	20	5	56 ± 1
6	RT	20	5	40 ± 3
7	RT	5	5	41 ± 1

*[a]The indicated amount of precursor **29** and [^{18}F]Bu$_4$NF were stirred in CH_2Cl_2 (0.50 mL) at the indicated temperature and time. The solvent was removed under a stream of N_2. The obtained solid residue was extracted with* n-*hexane (0.50 mL) at 70 °C for 1 minute. [b]Percentage of the activity soluble in* n-*hexane compared to the unsoluble activity. [c]0.25 mL of solvent used. [d]1.0 mL of solvent used.*

Our following task was to determine whether [^{18}F]Bu$_4$NF is indeed not soluble in *n*-hexane (Table 10). When tosyl-benziodoxole precursor **29** was not present in the reaction, 7% of the activity was extracted, indicating poor solubility of [^{18}F]Bu$_4$NF in *n*-hexane (entry 1). Decreasing the temperature of the extraction to 40 °C or to room temperature (entries 3 and 5) did not prevent the extraction of some [^{18}F]Bu$_4$NF and only caused a decrease in the extracted activity when tosyl-benziodoxole **29** was present (entries 2 and 4). Therefore, we concluded that performing the reaction at room temperature for 5 minutes and the extraction for 1 minute at 70 °C (Table 9, entry 7) afforded the best result, and thus those were the conditions used in further studies.

Table 10. Evaluation of the extraction temperature.[a]



29 **[^{18}F]12**

Entry	29 [mg]	Extraction T [°C]	Extracted activity [%] (n = 2)[b]
1	0	70	7 ± 1
2	5	40	23 ± 3
3	0	40	10 ± 4
4	5	RT	20 ± 5
5	0	RT	5 ± 2

*[a]The indicated amount of precursor **29** and [^{18}F]Bu$_4$NF were stirred in CH_2Cl_2 (0.50 mL) at RT for 5 minutes. The solvent was removed under a stream of N_2. The obtained solid residue was extracted with* n*-hexane (0.5 mL) at the indicated temperature for 1 minute. [b]Percentage of the activity soluble in* n*-hexane compared to the unsoluble activity.*

As mentioned above, [^{18}F]fluoro-benziodoxole **[^{18}F]12** cannot be analyzed by common methods in radiochemistry. In every radiochemical process, starting at the production of fluorine-18 in the cyclotron, there is contamination by ambient fluorine-19 fluoride. Since both isotopes are chemically equivalent, both will be incorporated in any reaction. In order to ascertain the formation of [^{18}F]fluoro-benziodoxole **[^{18}F]12**, an extracted sample containing **[^{18}F]12** was allowed to decay and afterwards analyzed by ^{19}F-NMR and HRMS. A comparison of the ^{19}F-NMR spectrum of an extracted sample of **[^{18}F]12** that had been allowed to decay (blue), a reference sample of fluoro-benziodoxole **12** and a reference sample of Bu$_4$NF is shown in Figure 9. The decayed sample showed a sharp singlet at -143.15 ppm, matching the chemical shift of reference **12** (-143.12 ppm). The presence of the non-labelled analog in the reaction mixture of a fluorine-18 labelling reaction serves as a positive indication for the formation of the labelled compound.[49r] Thus, the presence of the signal of fluoro-benziodoxole **12** in the extracted decayed sample confirms the formation of **[^{18}F]12**. Furthermore, the experiment confirmed that the extracted sample was not significantly contaminated with Bu$_4$NF (broad singlet at -122.93 ppm).

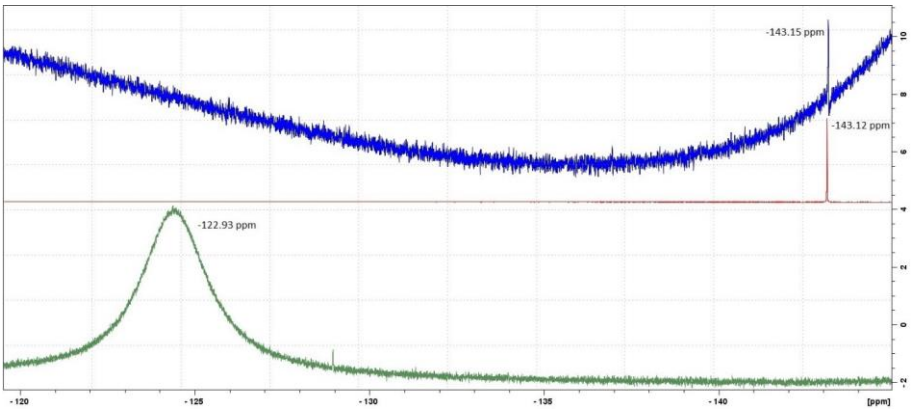


Figure 9. Comparison of the ^{19}F-NMR spectra of the decayed extracted sample (blue), reference sample of **12** (red) and reference sample of Bu_4NF (green).

In addition, the HRMS analysis also indicated the presence of fluoro-benziodoxole **12** in the decayed sample (Figure 10). We observed the Na-adduct of **12** at m/z = 302.9656 m.u (arrow) as well as the benziodoxole fragment at m/z = 260.9754 as a result of the thermal lability of the I–F bond.

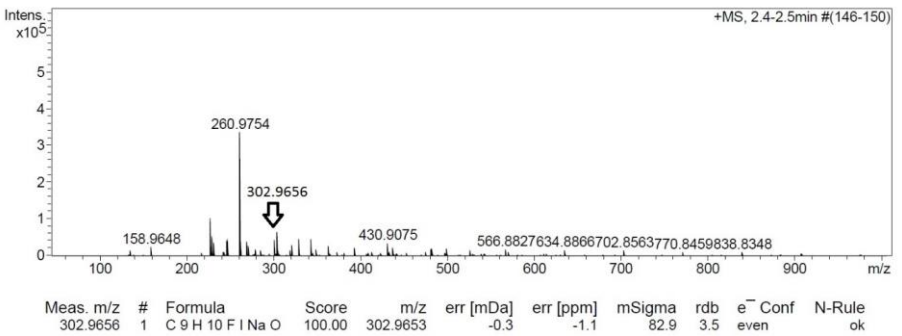


Figure 10. HRMS of the decayed sample after extraction. The arrow indicates the Na-adduct of **12**.

In order to study the possibility of purification using solid-phase extraction cartridges, we studied the behavior of [^{18}F]fluoro-benziodoxole **[^{18}F]12** and [^{18}F]Bu_4NF in three different adsorbents: silica (120 mg, Waters), alumina (280 mg, Waters) and Celite® (77 mg, hand-packed glass pipette). In the first experiment, the crude reaction mixture of [^{18}F]fluoro-benziodoxole **[^{18}F]12** was passed through the solid absorbents. We observed that the silica and alumina cartridges retained 97% of the activity, whereas celite retained 62% of the activity. This retained activity was not eluted when the adsorbents were rinsed with MeCN. This observation indicated that **[^{18}F]12** had decomposed and the radioactive material had irreversibly bound to the solid

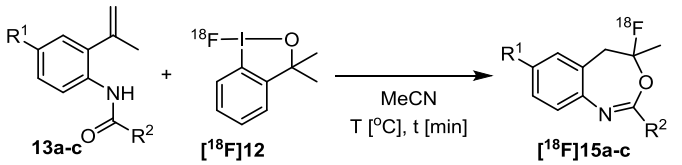
adsorbent. Interestingly, the results were similar when we repeated the experiments using [^{18}F]Bu_4NF. In these cases, 74-81% of the activity was retained in the absorbent, indicating that filtration through these materials is not a suitable procedure for the purification of [^{18}F]fluoro-benziodoxole **[^{18}F]12**. Therefore, we concluded that solid-phase extraction is not a suitable method for the separation of [^{18}F]fluoro-benziodoxole **[^{18}F]12** from unreacted [^{18}F]Bu_4NF.

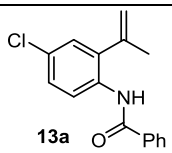
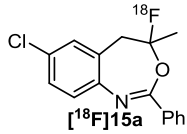
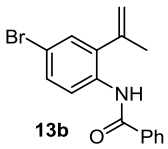
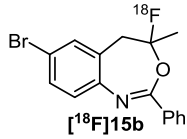
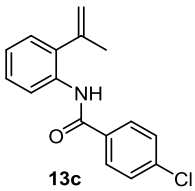
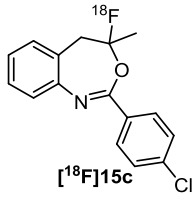
2.2.1.2 Synthesis of [^{18}F]fluoro-benzoxazepines

To demonstrate the utility of [^{18}F]fluoro-benziodoxole **[^{18}F]12** as labelling reagent, we selected the formation of fluoro-benzoxazepines developed by Gulder[44g] (Section 1.2.2.1.1, Scheme 14). This cyclization is a simple and fast reaction that takes place in short time and, therefore, is a good candidate for fluorine-18 labelling. We began our study with the electron-deficient *o*-styryl amide **13a**, as we envisioned that it would react easily according to the proposed activation mode.[45b]

Following the conditions reported by Gulder,[44g] we obtained fluoro-benzoxazepine **[^{18}F]15a** in an encouraging 9% radiochemical yield (Table 11, entry 1). Neither increasing the temperature to 50 ^{o}C nor decreasing the reaction time to 7 minutes affected the radiochemical yield (entries 2 and 3) but when we increased the reaction temperature to 90 ^{o}C, the radiochemical yield increased to 76% (entry 4). Prolongation of the reaction time did not improve the radiochemical yield (entry 5). Applying these conditions, the brominated analog **13b** and the regioisomer **13c** reacted similarly, affording the corresponding [^{18}F]fluoro-benzoxazepines **[^{18}F]15b** and **[^{18}F]15c** in 57% and 88% yield respectively (entries 6 and 7).

Table 11. Substrate scope of electron-poor [^{18}F]fluoro-benzoxazepines.[a]



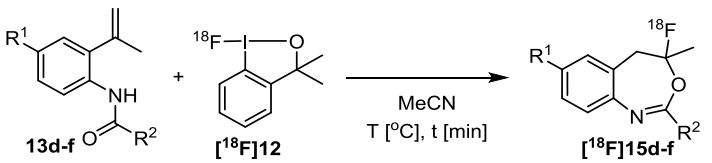
Entry	Precursor	T [°C]	t [min]	Product	RCY [%] (n = 2)[b]
1	 **13a**	RT	40	 **[^{18}F]15a**	9 ± 2
2	**13a**	50	40	**[^{18}F]15a**	7 ± 2
3	**13a**	50	7	**[^{18}F]15a**	12 ± 1
4	**13a**	90	7	**[^{18}F]15a**	76 ± 2
5	**13a**	90	15	**[^{18}F]15a**	74 ± 4
6	 **13b**	90	7	 **[^{18}F]15b**	57 ± 1
7	 **13c**	90	7	 **[^{18}F]15c**	88 ± 6

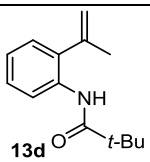
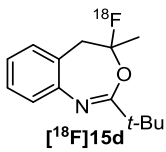
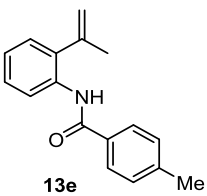
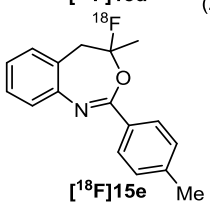
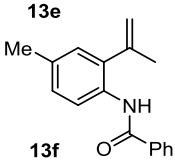
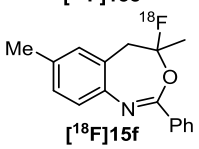
*[a]To a solution of precursor **13a-c** (0.4 μmol) in MeCN (25 μL) was added **[^{18}F]12** in n-hexane (50-100 μL). The solvent was evaporated before dissolving in MeCN (0.50 mL) and heating at the indicated temperature and time.* *[b]Estimated by radio-HPLC analysis of the crude reaction mixture.*

Styryl amides bearing electron-donating substituents also underwent the labelling process, but milder conditions were required (Table 12). When **13d** was reacted under the same conditions (90 °C, 7 min), [^{18}F]fluoro-benzoxazepine **[^{18}F]15d** was obtained in 54% radiochemical yield along with an unidentified labelled impurity in 28% radiochemical yield (entry 1). The origin of this impurity is probably the low chemical stability of [^{18}F]fluoro-benzoxazepine **[^{18}F]15d**. Reducing the reaction time to 2 minutes decreased the amount of impurity to 20%, but the radiochemical yield of **[^{18}F]15d** dropped to 19% (entry 2). Decreasing the reaction temperature to 70 °C, we could maintain the radiochemical yield of **[^{18}F]15d** to 50% and

decrease the amount of impurity to 20% (entry 3). When **13e**, having a more electron-rich amide compared to **13c**, was reacted under the original conditions (90 °C, 7 min) a very low radiochemical yield was obtained (10%, entry 4). Probably, [^{18}F]fluoro-benzoxazepine **[^{18}F]15e** is not as stable at high temperatures as **[^{18}F]15c**, hence the lower radiochemical yield. Fortunately, decreasing the reaction time to 2 minutes afforded **[^{18}F]15e** in 90% radiochemical yield (entry 5). The thermal stability of isomer [^{18}F]fluoro-benzoxazepine **[^{18}F]15f** is even lower: when the reaction was performed at 90 °C for 2 minutes, a moderate radiochemical yield of 46% was obtained (entry 6). However, lowering the temperature to 70 °C increased the radiochemical yield of **[^{18}F]15f** to 74% (entry 7).

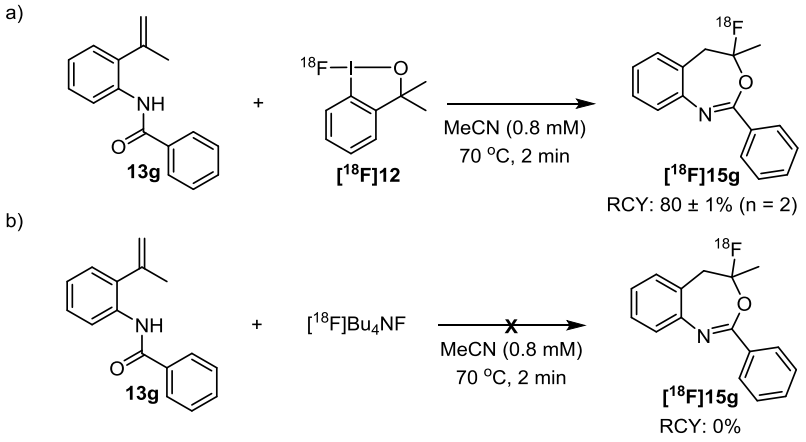
Table 12. Substrate scope of electron-rich [^{18}F]fluoro-benzoxazepines.[a]



Entry	Precursor	T [°C]	t [min]	Product	RCY [%] (n = 2)[b]
1	 **13d**	90	7	 **[^{18}F]15d**	54 ± 4 (28% impurity)
2	**13d**	90	2	**[^{18}F]15d**	19 ± 6 (20% impurity)
3	**13d**	70	7	**[^{18}F]15d**	50 ± 6 (20% impurity)
4	 **13e**	90	7	 **[^{18}F]15e**	10 ± 1
5	**13e**	90	2	**[^{18}F]15e**	90 ± 1
6	 **13f**	90	2	 **[^{18}F]15f**	46 ± 3
7	**13f**	70	2	**[^{18}F]15f**	74 ± 3

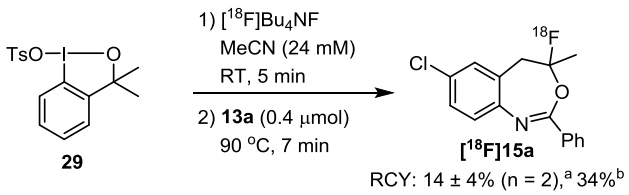
*[a]To a solution of the precursor **13d-f** (0.4 μmol) in MeCN (25 μL) was added **[^{18}F]12** in n-hexane (50-100 μL). The solvent was evaporated before dissolving in MeCN (0.50 mL) and heating at the indicated temperature and time.*
[b]Estimated by radio-HPLC analysis of the crude reaction mixture.

The unsubstituted *o*-styryl amide also reacted under these conditions, affording [^{18}F]fluoro-benzoxazepine **[^{18}F]15g** in 80% radiochemical yield (Scheme 31a). To confirm that [^{18}F]Bu_4NF is unable to perform the labelling reaction, we reacted **13g** with [^{18}F]Bu_4NF under the same conditions (Scheme 31b). In this experiment [^{18}F]fluoro-benzoxazepine **[^{18}F]15g** was not detected, thus confirming that the electrophilic reagent [^{18}F]fluoro-benziodoxole **[^{18}F]12** is the labelling reagent in this process.



Scheme 31. a) Labelling of unsubstituted [^{18}F]fluoro-benzoxazepine **[^{18}F]15g**. b) Attempted labelling using [^{18}F]Bu_4NF.

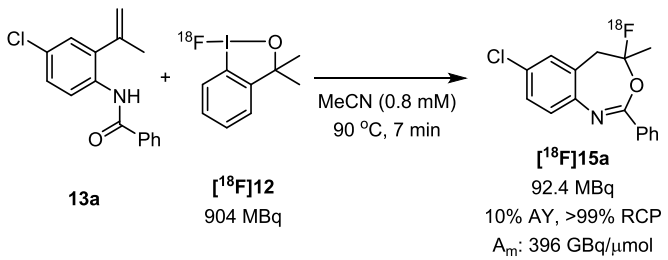
Due to the limited life-span of fluorine-18, we attempted the labelling reaction without isolating [^{18}F]fluoro-benziodoxole **[^{18}F]12** (Scheme 32). When we performed the labelling reaction following a one-pot sequential-addition protocol, the reaction time was shortened by about 5 minutes. In these non-optimized conditions, the radiochemical yield of [^{18}F]fluoro-benzoxazepine **[^{18}F]15g** was reduced to 14% (based on [^{18}F]Bu_4NF). Assuming that the formation of [^{18}F]fluoro-benziodoxole **[^{18}F]12** proceeded in 41% radiochemical yield, this corresponds to 34% radiochemical yield based on **[^{18}F]12**. This confirms that superior results were obtained when [^{18}F]fluoro-benziodoxole **[^{18}F]12** was purified by extraction, compared to the *in situ* generated **[^{18}F]12**.[44o]



Scheme 32. One-pot synthesis of **[^{18}F]15g**. [a]Based on [^{18}F]Bu_4NF as limiting reagent. [b]Based on **[^{18}F]12** as limiting reagent assuming it formed in 41% RCY.

2.2.1.3 Measurement of molar activity and activity yield

The optimized protocol for the cyclization of **13a** was used in a large-scale experiment to determine the activity yield and molar activity (Scheme 33). Thus, 3.93 GBq of [^{18}F]Bu_4NF were reacted with tosyl-benziodoxole **29**, affording 904 MBq of [^{18}F]fluoro-benziodoxole **[^{18}F]12** after purification by extraction. This amount of **[^{18}F]12** was used in a labelling reaction with **13a** at 90 ^{o}C for 7 minutes. After purification by semi-preparative HPLC, 92.4 MBq of [^{18}F]fluoro-benzoxazepine **[^{18}F]15a** were obtained (10% activity yield) with over 99% radiochemical purity. This value corresponds to a molar activity of 396 GBq/μmol, measured 130 minutes after the end of the bombardment. This molar activity is orders of magnitude higher than those reported for electrophilic labelling based on [^{18}F]F_2.[6]



Scheme 33. Isolation and molar activity measurement of **[^{18}F]15a**.

2.2.1.4 Conclusions

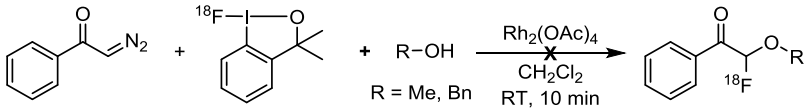
In this project, we have developed the radiosynthesis of an electrophilic fluorine-18 labelling reagent with [^{18}F]Bu_4NF as fluorine source, thus avoiding the use of [^{18}F]F_2. Rapid purification afforded [^{18}F]fluoro-benziodoxole free from its nucleophilic precursor. The utility of this labelling reagent has been demonstrated by the synthesis of [^{18}F]fluoro-benzoxazepines in high radiochemical yields in short reaction times. A preparative-scale experiment afforded an activity yield of 10% and a molar activity of 396 GBq/μmol, much higher than the typical values in electrophilic fluorine-18 fluorination.

2.2.2 Rhodium-mediated electrophilic fluorine-18 oxyfluorination of diazoketones (Paper IV)

Diazocarbonyl compounds are versatile metal-carbene precursors that can be applied in multiple coupling processes with various transition metal complexes.[62] These interesting and functional molecules have been previously used in fluorine-18 labelling by Gouverneur[63] and Doyle,[64] using nucleophilic fluorine-18. Our group[44l] has previously reported a Rh-catalyzed geminal oxyfluorination of diazoketones using **12** (Section 1.2.2.1.1, Scheme 17). This chapter describes our work in the translation of this Rh-catalyzed reaction into an electrophilic fluorine-18 labelling using [^{18}F]fluoro-benziodoxole **[^{18}F]12**.

2.2.2.1 Optimization of the reaction conditions

We began our investigations by applying the conditions previously reported by our group: diazocompound **17a** reacted in the presence of $Rh_2(OAc)_4$ with fluoro-benziodoxole **12** and an alcohol substrate. However, when this reaction was performed using [^{18}F]fluoro-benziodoxole **[^{18}F]12**, no fluorine-18 oxyfluorinated product **[^{18}F]18a** was detected (Scheme 34).



17a **[^{18}F]12** **[^{18}F]18a**

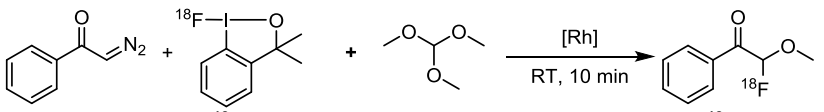
Scheme 34. Attempted fluorine-18 oxyfluorination of diazoketone **17a** using alcohols.

After extensive variation of the reaction conditions and the application of different alcohols, the desired product **[^{18}F]18a** was not detected. As mentioned previously (section 1.3), fluorine-18 is used in extremely small quantities compared to the rest of the reagents. This extreme scale difference can give rise to side reactions that are otherwise negligible in regular fluorine-19 chemistry (see section 1.3). According to our hypothesis, the minuscule amount of [^{18}F]fluoro-benziodoxole **[^{18}F]12** reacted with the huge excess of alcohol and fully decomposed. This type of reaction takes place very slowly using equimolar amounts of fluoro-benziodoxole **12** and alcohol substrates (and therefore this side reaction is not problematic in fluorine-19 chemistry).

To avoid this detrimental reaction between [^{18}F]fluoro-benziodoxole **[^{18}F]12** and the alcohol, we employed orthoformate **30**, a much less nucleophilic species, as coupling partner (Table 13). Gratifyingly, when we performed the same reaction between **17a** and **[^{18}F]12** using $Rh_2(OAc)_4$ as catalyst and **30** as solvent, we observed **[^{18}F]18a** in 90% radiochemical yield (entry 1). Changing the catalyst to $Rh_2(OPiv)_4$ increased the radiochemical yield of **[^{18}F]18a** to 98%, probably due to the increased solubility of this

catalyst in **30** (entry 2). Using MeOH as solvent completely inhibited the formation of **[^{18}F]18a** (entry 3), which is in accordance with our previous findings. Surprisingly, when we used benzyl alcohol, traces of the corresponding bezyloxylated product were detected (entry 4). The importance of using **30** as solvent is demonstrated in entry 5, in which no product was obtained when a 1:1 mixture of **30** and DCM was used. Using other catalysts in trimethyl orthoformate (**30**), such as $Rh_2(esp)_2$ or $Rh_2(TPA)_4$, significantly decreased the radiochemical yield (21% and 26% respectively, entries 6 and 7). The presence of a rhodium catalyst is however essential, as no product was formed when no catalyst was added to the reaction mixture (entry 8). To demonstrate the necessity of an electrophilic fluorine-18 fluorine source, we performed the reaction using [^{18}F]Bu_4NF, which did not result in the formation of **[^{18}F]18a** (entry 9). Based on these results, we decided to continue our studies using $Rh_2(OPiv)_4$ in neat **30**. The use of trimethyl orthoformate **30** as nucleophile is beneficial compared to methanol, as it is much less nucleophilic and thus it does not destroy [^{18}F]fluoro-benziodoxole **[^{18}F]12**. However, the use of orthoformates also imposes some limitations to the synthetic scope of the reaction. For example, labelling reactions using orthoformates with other alkyl chains (such as triethyl orthoformate) did not provide any fluoro-ethoxy analog of **[^{18}F]18**. The reason for this is probably the decreased nucleophilicity caused by the increased steric bulk of the alkyl chain, compared to that of trimethyl orthoformate.

Table 13. Optimization of reaction conditions for the synthesis of α-[^{18}F]fluoroethers.[a]



17a **[^{18}F]12** **30** **[^{18}F]18a**

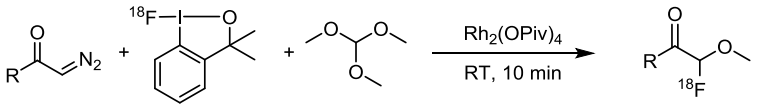
Entry	[Rh]	Solvent	RCY [%] (n = 2)[b]
1	$Rh_2(OAc)_4$	**30**	90 ± 2
2	$Rh_2(OPiv)_4$	**30**	98 ± 1
3	$Rh_2(OPiv)_4$	MeOH instead of **30**	0
4	$Rh_2(OPiv)_4$	BnOH instead of **30**	2 ± 2[c]
5	$Rh_2(OPiv)_4$	DCM/**30** 1:1	0
6	$Rh_2(esp)_2$	**30**	21 ± 1
7	$Rh_2(TPA)_4$	**30**	26 ± 9
8	None	**30**	0
9[d]	$Rh_2(OAc)_4$	**30**	0

*[a]Unless otherwise stated, to a mixture of the Rh catalyst (0.8 μmol) and **[^{18}F]12** was added a solution of **17a** (14 μmol) in **30** (0.50 mL). The reaction was stirred for 10 minutes at room temperature. [b]Estimated by radio-HPLC analysis of the crude reaction mixture. [c]The corresponding benzyloxylated product was formed. [d]Using [^{18}F]Bu_4NF instead of **[^{18}F]12**.*

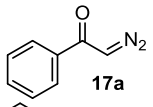
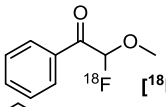
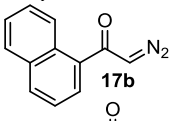
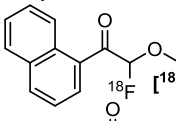
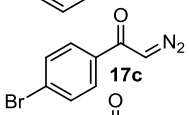
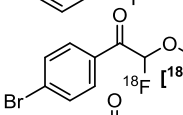
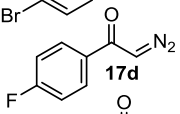
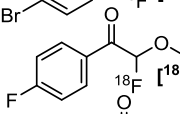
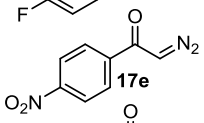
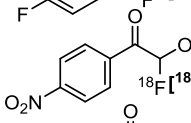
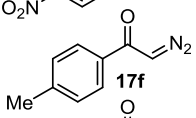
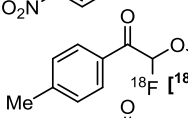
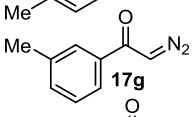
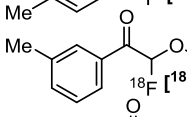
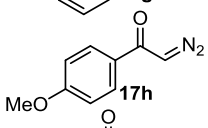
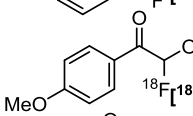
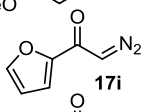
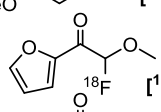
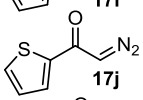
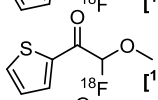
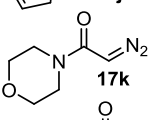
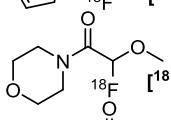
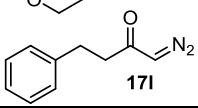
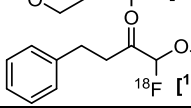
2.2.2.2 Substrate scope

With the optimal conditions in hand, we explored the substrate scope of the reaction using different diazoketones **17** (Table 14). Naphtyl-substituted diazoketone **17b** provided **[^{18}F]18b** in a similarly high radiochemical yield (94%, entry 2). The reaction tolerated diazoketones with electron-withdrawing groups such as bromine and fluorine as products **[^{18}F]18c** and **[^{18}F]18d** were obtained in 91% and 96% radiochemical yield respectively (entries 3 and 4). However, the presence of a *p*-NO_2 functionality was detrimental for the reaction, as **[^{18}F]18e** was obtained in 26% radiochemical yield (entry 5). Diazoketones bearing electron-donating substituents provided good results. Diazoketone **17f**, with a *p*-Me group, reacted to give **[^{18}F]18f** in high radiochemical yield (98%, entry 6) whereas the isomer **[^{18}F]18g** was obtained in lower radiochemical yield (67%, entry 7). Diazoketone **17h**, which bears a *p*-OMe group afforded the fluorine-18 labelled product **[^{18}F]18h** in 79% radiochemical yield (entry 8). The reaction could be applied to heteroaromatic diazoketones, although with varying results. Furane derivative **[^{18}F]18i** was obtained in very high radiochemical yield (95%, entry 9) whereas thiophene analog **[^{18}F]18j** was obtained in only 49% radiochemical yield (entry 10). A possible reason for this is the tendency of sulfur to coordinate irreversibly to metal catalysts, thus inhibiting the reaction. In addition, we were able to use morpholine-derived diazoamide **17k** as substrate (entry 11). This diazoamide was less reactive than its aromatic diazoketone counterparts and the temperature had to be increased to 90 ^{o}C to obtain **[^{18}F]18k** in 16% radiochemical yield. Unfortunately, oxyfluorination of aliphatic diazoketones could not be achieved in this process. We attempted to prepare **[^{18}F]18l** without success. This was a surprising result, as the reaction using equimolar amounts of diazoketone **17l** and fluoro-benziodoxole **12** (with the natural fluorine isotope) afforded **18l**.

Table 14. Substrate scope for the fluorine-18 oxyfluorination of diazo compounds.[a]



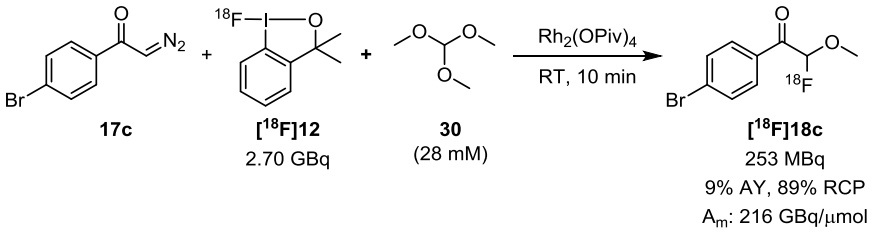
17 [18F]12 30 [18F]18

Entry	Diazocompound	Product	RCY [%] (n = 2)[b]
1	 17a	 [18F]18a	98 ± 1
2	 17b	 [18F]18b	94 ± 5
3	 17c	 [18F]18c	91 ± 2
4	 17d	 [18F]18d	96 ± 1
5	 17e	 [18F]18e	26 ± 6
6	 17f	 [18F]18f	98 ± 1
7	 17g	 [18F]18g	67 ± 8
8	 17h	 [18F]18h	79 ± 9
9	 17i	 [18F]18i	95 ± 4
10	 17j	 [18F]18j	49 ± 4
11[c]	 17k	 [18F]18k	16 ± 3
12	 17l	 [18F]18l	0

*[a]To a mixture of the Rh catalyst (0.8 μmol) and **[18F]12** was added a solution of **17a-l** (14 μmol) in **30** (0.50 mL). The reaction was stirred for 10 minutes at room temperature. [b]Estimated by radio-HPLC analysis of the crude reaction mixture. [c]The reaction was performed at 90 °C.*

2.2.2.3 Measurement of molar activity and activity yield

We measured the activity yield and the molar activity of a large-scale experiment using bromine-substituted diazoketone **17c** (Scheme 35). We envisioned that the resulting labelled product **[^{18}F]18c** could be used as a prosthetic group.[6d, 6g, 65] Thus, starting from 2.70 GBq of **[^{18}F]12** we obtained 253 MBq of **[^{18}F]18c** after purification by semi-preparative HPLC (9% activity yield, 89% radiochemical purity). The molar activity was determined to be 216 GBq/μmol, 110 minutes after the end of the bombardment. This value is in the range of our previous measurement using **[^{18}F]12** and much higher than those obtained using reagents derived from **[^{18}F]F$_2$**.[6]



Scheme 35. Isolation and molar activity measurement of **[^{18}F]18c**.

2.2.2.4 Proposed mechanism

Based on our previous experimental[44l, 66] and DFT modelling[45e, 67] studies, we proposed a catalytic cycle for the reaction of diazoketones with **30** and **[^{18}F]12** (Figure 11). The first step is the formation of the Rh-carbene **VIII** through intermediate **VII**.[68] Nucleophiles react readily with electrophilic rhodium carbenes such as **VIII** to form onium ylids[69] as **IX**, which is formed by the attack of **30** on carbene **VIII**. Onium ylide **IX** is converted to **X** by decomposition of the orthoester moiety and **X** is subsequently isomerized to enolate **XI**. The addition of [^{18}F]fluoro-benziodoxole **[^{18}F]12** to intermediate **XI** is a key step in the reaction, which leads to the formation of **XII**. After isomerization of the I–F bond to form **XIV**, [^{18}F]fluorine displaces iodine and fluorine-18 labelled product **[^{18}F]18** is formed.

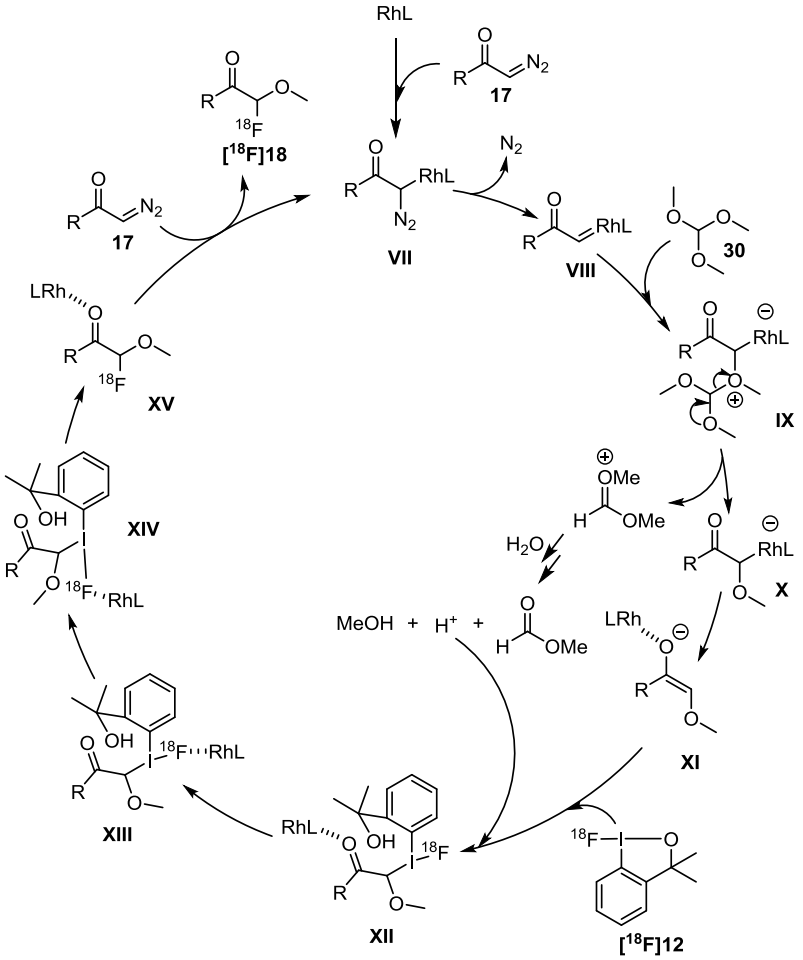


Figure 11. Proposed catalytic cycle for the fluorine-18 oxyfluorination of diazoketones.

2.2.2.5 Conclusions

An efficient fluorine-18 labelling of diazoketones using **[^{18}F]12** has been developed. Short reaction times and mild reaction conditions afforded α-[^{18}F]fluoroethers in moderate to high radiochemical yields. A preparative-scale experiment afforded an isolated compound in 9% activity yield with a molar activity of 216 GBq/μmol, a higher value than the typically obtained values using electrophilic fluorine-18 fluorination reagents derived from [^{18}F]F_2.

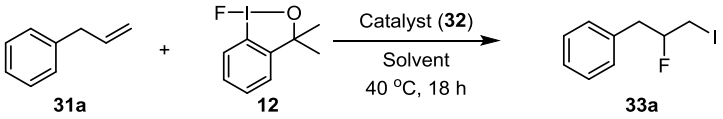
2.2.3 Palladium-catalyzed iodofluorination of alkenes (Paper V)

Fluorine-based difunctionalization reactions are useful transformations that allow for the simultaneous installation of two functional groups in the same molecule (see also section 2.2.2). Iodofluorinated molecules are interesting and useful compounds that can be further transformed using iodine as a handle. Classical iodofluorination methods require the use of hazardous reagents (HF, $ArIF_2$) and external iodine and/or fluorine sources,[70] which makes the process poorly atom economical. This section describes a Pd-catalyzed iodofluorination of alkenes using hypervalent iodine reagent **12**.

2.2.3.1 Optimization of the reaction conditions

During the Szabó group's studies on difluorination of styrenes (Section 1.2.2.1.1, Scheme 15), it was found that when the silver mediator was replaced by a catalytic amount of Pd the styrene underwent iodofluorination instead of difluorination.[44j] Interestingly, both iodine and fluorine atoms arose from fluoro-benziodoxole **12**. To fully develop the iodofluorination reaction by reagent **12**, we studied the effect of different Pd catalysts and solvents (Table 15). We started reacting allyl benzene **31a** and **12** in the presence of 5 mol% of $Pd(MeCN)_4(BF_4)_2$ (**32a**) in $CDCl_3$ at 40 ºC for 18 h, obtaining iodofluorinated product **33a** in 61% yield (entry 1). Increasing the amount of catalyst to 20 mol% enhanced the yield to 76% (entry 2). Other catalysts such as $PdCl_2(PhCN)_2$ (**32b**), $Pd(TFA)_2$ (**32c**) or $Pd(OAc)_2$ (**32d**) provided lower yields (entries 3-5) whereas $PdCl_2$(*t*-BuCN)$_2$ (**32e**), $PdCl_2(DMSO)_2$ (**32f**) or $PdCl_2$(dppe) (**32g**) afforded only traces of the desired product (entry 6). Changing the solvent to 1,4-dioxane provided only 38% yield (entry 7) and other solvents such as THF, MeCN or MeOH failed to provide any product (entry 8). Thus, we selected $CDCl_3$ as solvent and $Pd(BF_4)_2(MeCN)_4$ (**32a**) as catalyst to continue the study.

Table 15. Optimization of the reaction conditions for the iodofluorination of allylbenzene.[a]



31a + 12 → 33a

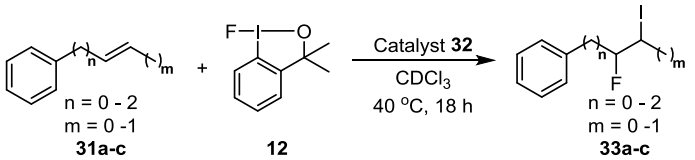
Entry	Catalyst	Solvent	Yield [%][b]
1	$Pd(MeCN)_4(BF_4)_2$ (**32a**)[c]	$CDCl_3$	61
2	$Pd(MeCN)_4(BF_4)_2$ (**32a**)	$CDCl_3$	76
3	$PdCl_2(PhCN)_2$ (**32b**)	$CDCl_3$	40
4	$Pd(TFA)_2$ (**32c**)	$CDCl_3$	68
5	$Pd(OAc)_2$ (**32d**)	$CDCl_3$	15
6	$PdCl_2$(*t*-BuCN)$_2$ (**32e**),$PdCl_2(DMSO)_2$ (**32f**) or $PdCl_2$(dppe) (**32g**)	$CDCl_3$	< 5
7	$Pd(MeCN)_4(BF_4)_2$ (**32a**)	1,4-Dioxane	38
8	$Pd(MeCN)_4(BF_4)_2$ (**32a**)	THF, MeCN or MeOH	< 5

*[a]Unless otherwise stated, substrate **31a** (0.10 mmol), **12** (0.10 mmol) and the indicated Pd catalyst **32** (20 mol%) were dissolved in the indicated solvent (0.50 mL) and stirred at 40 °C for 18 h. [b]Isolated yield. [c]5 mol%.*

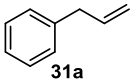
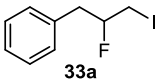
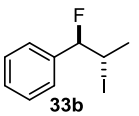
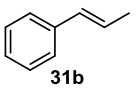
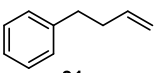
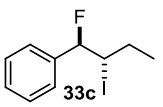
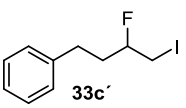
2.2.3.2 Substrate scope

As previously mentioned, reacting allyl benzene **31a** and **12** with 20 mol% $Pd(MeCN)_4(BF_4)_2$ provided **33a** in 76% yield (Table 16, entry 1). Interestingly, using the same starting material but changing to $PdCl_2(MeCN)_2$ (**32h**), the isomerized product **33b** was obtained as a single regio- and diastereoisomer in 71% yield (entry 2). When the reaction was performed with **31b** (the allylic isomer of **31a**) and fluoro-benziodoxole **12** using $PdCl_2(MeCN)_2$ (**32h**), the same product **33b** was obtained in 77% yield (entry 3). This indicated an interesting allylic isomerization depending on the ligands of the catalyst. The homoallylic isomer **31c** underwent a similar process when catalyst **32h** was used, affording isomerized product **33c** in 86% yield as a single regio- and diastereoisomer (entry 4). Contrarily, when $Pd(OAc)_2$ (**32d**) was used as catalyst, no isomerization was observed, and product **33c´** was obtained (58% yield, entry 5).

Table 16. Substrate scope for the iodofluorination of allyl benzenes.[a]



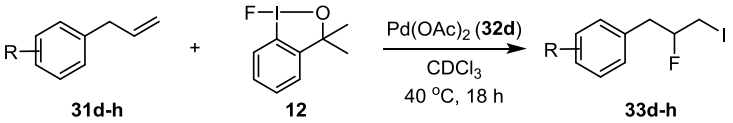
31a-c **12** **33a-c**

Entry	Substrate	Catalyst	Product	Yield [%]
1	 **31a**	$Pd(MeCN)_4(BF_4)_2$ **32a**	 **33a**	76
2	**31a**	$PdCl_2(MeCN)_2$[b] **32h**	 **33b**	71
3	 **31b**	$PdCl_2(MeCN)_2$ **32h**	**33b**	77
4	 **31c**	$PdCl_2(MeCN)_2$ **32h**	 **33c**	86
5[c]	**31c**	$Pd(OAc)_2$ **32d**	 **33c´**	58

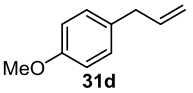
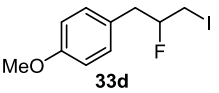
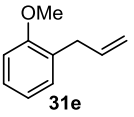
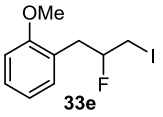
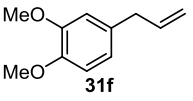
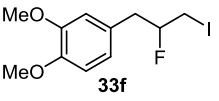
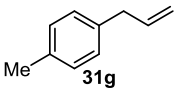
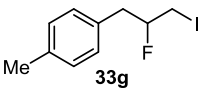
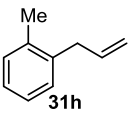
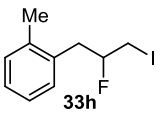
*[a]Unless otherwise stated, substrate **31a-c** (0.10 mmol), **12** (0.10 mmol) and the indicated Pd catalyst **32** (20 mol%) were stirred in $CDCl_3$ (0.50 mL) under Ar at 40 °C for 18 h. Isolated yields are given. [b]5 mol%. [c]The reaction was performed at 50 °C.*

Allyl benzenes bearing electron-donating substituents were very reactive and thus $Pd(OAc)_2$ (**32d**) was used as catalyst (Table 17). When *p*-OMe substituted allyl benzene **31d** was reacted, **33d** was obtained in 78% yield (entry 1). The regioisomer **33e** was obtained in lower yield (53%), probably because of steric reasons (entry 2). Disubstituted allyl benzene **31f** reacted to afford **33f** in 64% yield (entry 3). Methyl-substituted iodofluorinated product **33g** was obtained in a moderate 51% yield and its isomer **33h** in a similar 48% yield. We determined the yield of the *o*-Me substituted product **33h** by ^{19}F-NMR spectroscopy, indicating a value much higher than the isolated yield (76% *vs* 48%). This difference can be attributed to the volatility of the product and the difficulty of its isolation.

Table 17. Substrate scope for the iodofluorination of electron-rich allyl benzenes.[a]



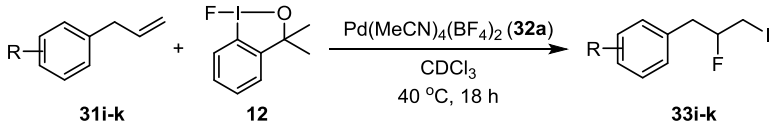
31d-h 12 33d-h

Entry	Substrate	Product	Yield [%]
1	 31d	 33d	78
2	 31e	 33e	53
3	 31f	 33f	64
4	 31g	 33g	51
5	 31h	 33h	48 (76)[b]

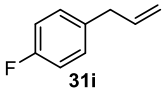
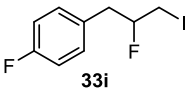
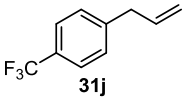
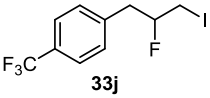
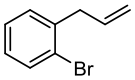
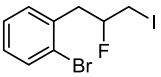
*[a]Substrate **31d-h** (0.10 mmol), **12** (0.10 mmol) and Pd catalyst **32d** (20 mol%) were stirred in $CDCl_3$ (0.50 mL) under Ar at 40 °C for 18 h. Isolated yields are given. [b]The yield was determined by ^{19}F-NMR spectroscopy using α,α,α-trifluorotoluene as internal standard.*

On the other hand, electron-poor alkenes had a relatively low reactivity with **12** and the corresponding reactions proceeded with low yields in the presence of $Pd(OAc)_2$ as catalyst. Using the more active catalyst $Pd(BF_4)_2(MeCN)_4$ (**32a**), iodofluorinated products **33i-k** were obtained in 48-53% yield (Table 18). The NMR yield of the *p*-CF_3 substituted product **33j** was 78%, much higher than the isolated one (48%). The volatility of the product and difficulty in the isolation was probably the reason for this large difference in the yields. Product **33k** contains three different halogen substituents, making it a good candidate for further transformations such as elimination reactions,[70g] substitutions[71] or Suzuki-Miyaura cross-coupling reactions.[72]

Table 18. Substrate scope for the iodofluorination of electron-poor allyl benzenes.[a]



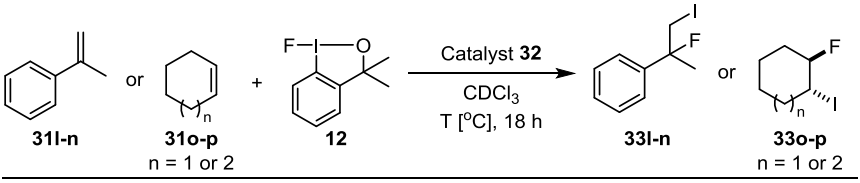
31i-k 12 33i-k

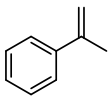
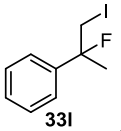
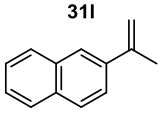
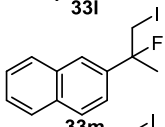
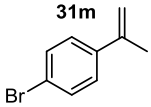
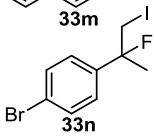
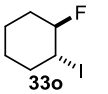
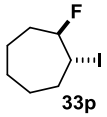
Entry	Substrate	Product	Yield [%]
1	 31i	 33i	53
2	 31j	 33j	48 (78)[b]
3	 31k	 33k	53

*[a]Substrate **31i-k** (0.10 mmol), **12** (0.10 mmol) and Pd catalyst **32a** (20 mol%) were stirred in $CDCl_3$ (0.50 mL) under Ar at 40 °C for 18 h. Isolated yields are given. [b]The yield was determined by ^{19}F-NMR spectroscopy using α,α,α-trifluorotoluene as internal standard.*

As mentioned previously, styrenes undergo iodofluorination when Pd catalysts are used in the presence of **12**.[44j] Using $Pd(OAc)_2$ (**32d**) product **33l** was obtained in 61% yield (Table 19, entry 1) while the bulkier styrene **31m** required the use of the more active $PdCl_2(MeCN)_2$ (**32h**) to obtain the corresponding iodofluorinated product **33m** in 54% yield. In both cases, the reaction temperature was increased to 50 °C to achieve complete conversion of the styrene (entries 1 and 2). Compound **33n**, which contains three halogens (F, Br, I), was obtained in 64% yield using $PdCl_2(MeCN)_2$ (**32h**) at 60 °C (entry 3). The reaction was also extended to cycloalkenes **31o-p**, which afforded the corresponding iodofluorinated products **33o-p** in moderate yields (40% and 50% respectively, entries 4 and 5). Similarly to internally iodofluorinated products **33b** and **33c**, iodofluorinated cycloalkanes **33o-p** were obtained as single diastereoisomers. Again, the yield of **33o** determined by ^{19}F-NMR (96%) was higher than the isolated yield (40%) because of the volatility of the product.

Table 19. Substrate scope for the iodofluorination styrenes and cycloalkenes.[a]

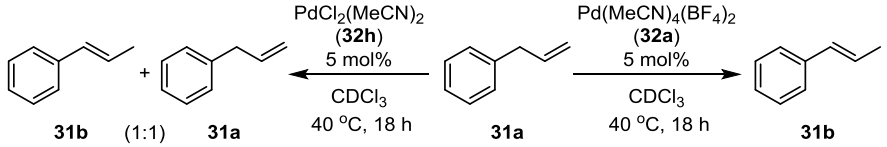


Entry	Substrate	Catalyst	T [°C]	Product	Yield [%]
1	 31l	$Pd(OAc)_2$ **32d**	50	 33l	61
2	 31m	$PdCl_2(MeCN)_2$ **32h**	50	 33m	54
3	 31n	$PdCl_2(MeCN)_2$ **32h**	60	 33n	64
4	 31o	$PdCl_2(MeCN)_2$ **32h**	60	 33o	40 (96)[b]
5	 31p	$PdCl_2(MeCN)_2$ **32h**	60	 33p	50

*[a]Substrate **31l-p** (0.10 mmol), **12** (0.10 mmol) and the indicated Pd catalyst **32** (20 mol%) were stirred in $CDCl_3$ (0.50 mL) under Ar at the indicated temperature for 18 h. Isolated yields are given. [b]The yield was determined by ^{19}F-NMR spectroscopy using α,α,α-trifluorotoluene as internal standard.*

2.2.3.3 Isomerization studies and proposed mechanism

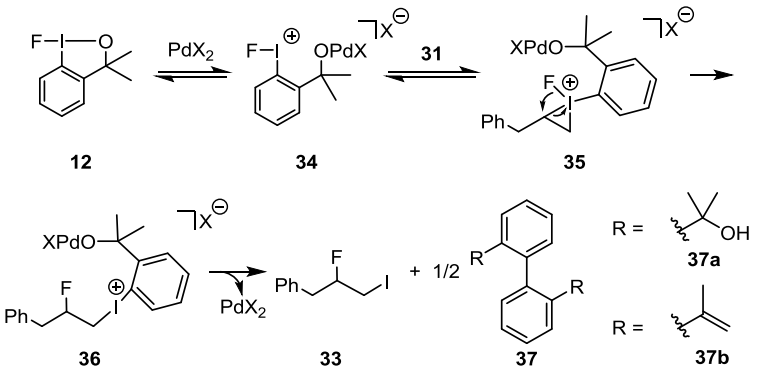
We briefly studied the regioselectivity of the reaction as a function of the different Pd catalysts. It is well documented that allyl benzenes undergo allylic isomerization in the presence of Pd(II) species.[73] When we reacted **31a** with 5 mol% $Pd(MeCN)_4(BF_4)_2$ (**32a**) in $CDCl_3$ at 40 °C for 18 h, full isomerization to **31b** was observed. Contrarily, when the reaction between **31a** and $PdCl_2(MeCN)_2$ (**32h**) was performed, an equimolar mixture of **31a** and **31b** was obtained (Scheme 36).



Scheme 36. Pd-catalyzed isomerization of allyl benzene.

Based in this observations and considering the regioselectivity of the reaction with **12**, we concluded that in the presence of $Pd(MeCN)_4(BF_4)_2$ (**32a**) the iodofluorination is faster than the isomerization, as only the externally iodofluorinated product **33a** was obtained (Table 16, entry 1). Contrarily, $PdCl_2(MeCN)_2$ (**32h**) performs a tandem isomerization/iodofluorination affording the internally iodofluorinated product **33b**. It is noteworthy to mention that mixtures of internally and externally functionalized products were not detected in the crude reaction mixtures, indicating a highly selective process.

According to our previous studies,[44j, 44k] we suggested a mechanism based on the activation of **12** similar to the one established for the structurally similar Togni´s reagent.[74] Activation of **12** by the Pd-catalyst may give rise to activated complex **34**. This complex would undergo electrophilic addition to the double bond in **31** to form iodonium intermediate **35**. The opening of the iodonium intermediate **35** by fluorine transfer results in **36**, which evolves through an intriguing $C(sp^2)$–I bond cleavage. GC/MS studies indicated the presence of biphenyl **37** in the reaction mixture. Biphenyl **37** is a product of the dimerization of the aromatic ring arising from **12** (Scheme 37).



Scheme 37. Proposed mechanism for the iodofluorination reaction.

The intriguing selectivity of the $C(sp^2)$–I cleavage over the $C(sp^3)$–I bond is a key feature in this process. Unfortunately, the fact that the $C(sp^2)$–I cleavage takes place after the I–O and the I–F bond cleavage obstructs the mechanistic study of this interesting step. Besides our previous report,[44j] we have only found one study in which benziodoxoles serve as iodine source.[75] Using a structurally related reagent for C–H iodination, Rao proposed a Pd(II)/Pd(IV) oxidative addition/reductive elimination process to introduce

the iodine atom. Based on this previous report and in the presence of **37**, we believe that a similar process might take place in our reaction.

2.2.3.4 Conclusion and outlook

With this study, we have shown that fluoro-benziodoxole **12** is an efficient reagent for the iodofluorination of alkenes. Both the iodine and fluorine atoms arise from the same reagent, making this process more atom-economical than previously reported methodologies. The regioselectivity of the process depends on the Pd catalyst, cleanly affording externally or internally functionalized products. The reaction involves the formation of a $C(sp^3)$–I bond with subsequent cleavage of a $C(sp^2)$–I bond.

The translation of the iodofluorination of alkenes to a fluorine-18 labelling process was also attempted. Different activators, solvents and substrates were examined, but no fluorine-18 iodofluorinated products were detected. Further studies are necessary for the development of an iodofluorination method for fluorine-18 labelling.

3 Closing remarks

The studies in this thesis have been focused on the development of new fluorination reactions.

A new method for the late-stage nucleophilic synthesis of trifluoroacetates, trifluorotoluenes and trifluoroacetamides has been developed. This methodology was translated into a fluorine-18 labelling protocol, in which tertiary and secondary trifluoroacetamides were efficiently labelled using a nucleophilic fluorine-18 source.

The use of mild and selective fluorine-18 electrophilic fluorination reagents is a very attractive research topic. In this field, we have demonstrated that an electrophilic fluorine-18 fluorination reagent can be synthesized avoiding $[^{18}F]F_2$ as primary fluorine source. This reagent was applied to two different labelling processes: a metal-free synthesis of [^{18}F]fluoro-benzoxazepines and a Rh-mediated synthesis of α-[^{18}F]fluoroethers. High molar activities were achieved in both cases, indicating that this labelling reagent can potentially be applied to the synthesis of radiotracers for PET studies. Furthermore, an atom-economical Pd-catalyzed iodofluorination reaction was developed using the fluorine-19 analog of the reagent. This methodology will be adapted to fluorine-18 labelling in the near future.

4 Sammanfattning på svenska

I denna avhandling presenteras nya metoder inom området fluorineringsreaktioner samt deras applikationer inom radiokemi med fluor-18 ($t_{1/2}$= 109.8 min).

I den första delen av denna avhandling presenteras nya metoder för sen inkorporering (s.k. ”late-stage”) av fluor via nukleofil fluorinering av trifluorometylestrar, arener och amider. Vidare har dessa reaktioner anpassats till att innefatta fluor-18 där flera trifluoroacetamider har inmärkts med denna radioisotop.

Den andra delen av denna avhandling fokuserar på elektrofila fluorineringsreaktioner. Den hypervalenta jodföreningen [^{18}F]fluoro-beziodoxol syntetiserades med fluor-18 som fluorkälla och användes sedan i två olika radiokemiska inmärkningsmetoder. I den första av dessa inmärktes [^{18}F]fluorobenzoxazepiner via en direkt elektrofil reaktion och i den andra användes rhodium för att mediera inmärkandet av α-[^{18}F]fluoroetrar. I båda fallen kunde höga utbyten och hög molär aktivitet erhållas vilket visar metodens potential inom PET radiokemi. En liknande metod med en korresponderade fluor-19-analog utvecklades också och användes i syntesen av fluorojoderade föreningar.

Appendix A: Contribution list

Author´s contribution to each publication (referred to by their roman numerals).

I. Participated in the synthesis of starting materials and reference compounds (30%) and in the study of the substrate scope. Participated in writing the manuscript and the supporting information.

II. Participated in the synthesis of the precursors and reference compounds (40%). Performed, together with A.B.G., the mechanistic studies. Wrote parts of the supporting information.

III. Performed the synthesis and characterization of the precursors and reference compounds. Performed the fluorine-18 labelling experiments. Wrote the manuscript and the supporting information.

IV. Performed the synthesis and characterization of 90% of the precursors and reference compounds. Performed 90% of the fluorine-18 labelling experiments. Wrote the manuscript and the supporting information.

V. Participated in the optimization of the reaction conditions and in the isolation of the final products (30%). Assisted N.I. writing the manuscript. Wrote the supporting information.

Appendix B: Reprint permissions

Reprint permissions were kindly granted by the publishers for each publication (referred to by their roman numerals):

I. A. Bermejo Gómez, M. A. Cortés González, M. Lübcke, M. J. Johansson, M. Schou, K. J. Szabó, *J. Fluorine Chem.* **2017**, *194*, 51-57.
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II. A. Bermejo Gomez, M. A. Cortés González, M. Luebcke, M. Johansson, C. Halldin, K. J. Szabó, M. Schou, *Chem. Commun.* **2016**, *52*, 13963-13966.
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III. M. A. Cortés González, P. Nordeman, A. Bermejo Gomez, D. N. Meyer, G. Antoni, M. Schou, K. J. Szabó, *Chem. Commun.* **2018**, *54*, 4286-4289.
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IV. M. A. Cortés González, X. Jiang, P. Nordeman, G. Antoni, K. J. Szabó, *Chem. Commun.* **2019**, *55*, 13358-13361.
Open access article licensed under a Creative Commons Attribution 3.0 Unported Licence.

V. N. O. Ilchenko, M. A. Cortés, K. J. Szabó, *ACS Catal.* **2016**, *6*, 447-450.
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