^{18}F Fluorination

Deutsche Ausgabe: DOI: 10.1002/ange.201506035
Internationale Ausgabe: DOI: 10.1002/anie.201506035

Organomediated Enantioselective ^{18}F Fluorination for PET Applications

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Abstract: *The first organomediated asymmetric ^{18}F fluorination has been accomplished using a chiral imidazolidinone and [^{18}F]N-fluorobenzenesulfonimide. The method provides access to enantioenriched ^{18}F-labeled α-fluoroaldehydes (>90% ee), which are versatile chiral ^{18}F synthons for the synthesis of radiotracers. The utility of this process is demonstrated with the synthesis of the PET (positron emission tomography) tracer (2S,4S)-4-[^{18}F]fluoroglutamic acid.*

Physiological processes typically show a high degree of chiral discrimination towards exogenous racemic compounds administered in vivo. The effects of enantiomers can be dissimilar as a consequence of their differential interaction with chiral targets, such as receptors, enzymes, and ion channels.[1] In medicinal chemistry, the use of single-enantiomer drugs is therefore advantageous and would be expected to decrease the total dose given to patients, simplify the dose regimen relationship, and minimize side effects (or in some cases toxicity) induced by the inactive enantiomer.[2] Chirality is equally important in the context of positron emission tomography (PET).[3] PET is a widely employed medical imaging technology, which uses radiotracers labeled with positron emitting isotopes, more often ^{18}F ($t_{1/2}$ = 109.8 min), to interrogate biochemical pathways, track changes brought about by disease, or streamline drug research. Several radiotracers used in the clinic are nonracemic chiral entities. Amongst those tracers, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG),[4] 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT),[5] 16-α-[^{18}F]fluoroestradiol ([^{18}F]FES),[6] and 16-β-[^{18}F]fluoro-5α-dihydrotestosterone ([^{18}F]FDHT)[7] stand out as they contain the ^{18}F substituent itself on a stereogenic carbon. With the drive in industry to develop optically pure pharmaceutical drugs, PET is becoming an important tool to study the behavior of enantiomers in living systems. To date, however, the input of nuclear medicine into clinical pharmacology has progressed slowly, a trend underscoring the challenges associated with ^{18}F incorporation,[8] especially when control over stereoselectivity is required. Herein, we report that organocatalysis, one of the current major branches of enantioselective synthesis, is applicable in the context of ^{18}F radiochemistry, an advance opening new opportunities for PET radiotracer development and drug discovery.

Currently, ^{18}F fluorination at a stereogenic carbon is achieved using an enantiomerically pure precursor armed with a leaving group amenable to S_N2 displacement with [^{18}F]fluoride.[9] This method is limited to substrates which tolerate high temperatures, are not prone to elimination, and can resist racemization or epimerization under the harsh reaction conditions required for ^{18}F fluorination. This last criterion also stands true for the newly formed ^{18}F-substituted stereogenic carbon of the product. Incomplete inversion is an additional complication narrowing the scope of conventional S_N2 strategies. In response to these drawbacks, transition metals have been exploited to induce regio- and stereocontrolled ^{18}F fluorination of prefunctionalized precursors;[10] isolated examples of metal-mediated enantioselective ^{18}F fluorination of either *meso*[11] or prochiral precursors[12] have recently appeared but have met with limited success because of a lack of generality in terms of substrate scope and/or low enantiomeric excesses. The benefits of organocatalytic research,[13] offering a range of generic modes of catalyst activation, induction, and reactivity, encouraged us to merge the disconnected fields of organocatalysis and ^{18}F radiochemistry. As a proof of concept, we opted to develop a method converting readily available achiral aldehyde precursors into enantioenriched α-[^{18}F]fluoroaldehydes. These versatile synthons are valuable but notoriously susceptible to epimerization, thus a study to develop an asymmetric ^{18}F-labeling procedure for their preparation and subsequent derivatization provides an ideal platform to establish the field of organomediated ^{18}F radiofluorination (Scheme 1).

The enantioselective fluorination of aldehydes employing a chiral secondary amine catalyst and an achiral electrophilic fluorine source was first reported in 2005.[14] Enamine-catalyzed fluorination afforded enantioenriched α-fluoroaldehydes, which can be subjected to a variety of transformations. Preliminary studies indicate that the development of a radiochemical variant presents numerous challenges. The inherently low concentration of the [^{18}F]F^+ reagent with respect to the precursor and the chiral organomediator, which are both employed in equimolar quantities, could induce product racemization. The half-life of the ^{18}F isotope imposes the restriction that reaction times must be kept to a minimum with the radiofluorination proceeding ideally at room temperature, and not at the lower temperatures typically required in

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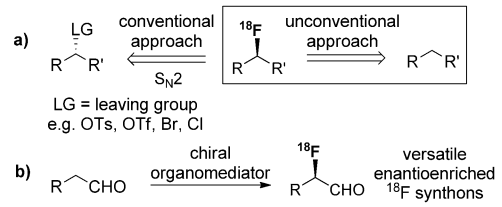
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506035.

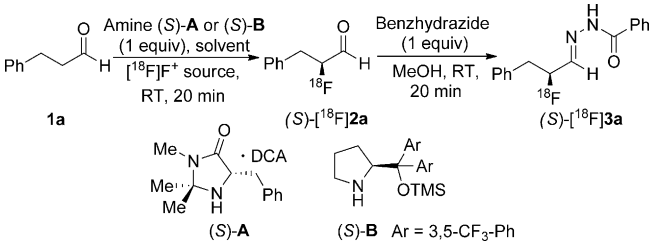


Scheme 1. a) Conventional and unconventional approaches for ^{18}F incorporation at a stereogenic carbon. b) Organomediated enantioselective ^{18}F fluorination affords enantioenriched ^{18}F-labeled α-fluoroaldehydes. OTs = tosylate; OTf = trifluoromethylsulfonate.

enantioselective organocatalysis. Finally, the production and derivatization of α-[^{18}F]fluoroaldehydes should be amenable to a one-pot process, and occur under mild reactions conditions to avoid racemization of the newly formed stereocenter after ^{18}F fluorination. Preliminary studies employed hydrocinnamaldehyde (**1a**) as the model substrate, the chiral imidazolidinone (*S*)-**A** or pyrrolidine (*S*)-**B**, and the [^{18}F]F$^+$ reagent *N*-[^{18}F]fluorobenzenesulfonimide ([^{18}F]NFSI) (Table 1).

[^{18}F]NFSI was synthesized according to a previously reported procedure.[15] This method involved the reaction of sodium bis(phenylsulfonyl)amide in acetonitrile/water with [^{18}F]F_2[16] to afford [^{18}F]NFSI with the theoretical maximum radiochemical yield of 50%, along with 50% of [^{18}F]NaF. Following azeotropic drying, [^{18}F]NFSI was dissolved in the reaction solvent and aliquots were taken for reactions (circa 200 MBq). A 5 min cyclotron irradiation provided [^{18}F]NFSI with a specific activity of 1.9 GBq μmol^{-1}, in line with the short irradiation time applied to the ^{18}O target.[17] Hydrocinnamaldehyde (**1a**) was treated with an aliquot of [^{18}F]NFSI in a THF/isopropanol solvent mixture at room temperature in the presence of amine (*S*)-**A** (1 equiv with respect to **1a**). The resulting α-fluoroaldehyde (*S*)-[^{18}F]**2a** was not isolated but was derivatized in situ with benzhydrazide in MeOH. Analysis of the crude reaction mixture by HPLC[18] indicated that this one-pot process afforded the desired hydrazone (*S*)-[^{18}F]**3a** in 71% radiochemical conversion (RCC)[19] with an enantiomeric excess (*ee*) of 64% (Table 1, entry 1).[20] The use

Table 1: Optimization of the reaction conditions with aldehyde **1**.



Entry	F^+ Source	Amine	Solvent	RCC [%][a]	*ee* [%][b]
1	[^{18}F]NFSI	(*S*)-**A**	THF/IPA[c]	71 ($n=1$)	64 (*S*)
2	[^{18}F]NFSI	(*S*)-**A**	MTBE	62 ($n=5$)	92 (*S*)
3	[^{18}F]NFSI	(*S*)-**B**	MTBE	45 ($n=1$)	92 (*S*)
4	[^{18}F]Selectfluor	(*S*)-**A**	MTBE[d]	0 ($n=2$)	–

[a] RCC of (*S*)-[^{18}F]-**3a** determined by radio-HPLC relative to [^{18}F]F^+ source. [b] Determined by radio-HPLC of isolated (*S*)-[^{18}F]-**3a** on a chiral stationary phase. [c] Ratio 9:1. [d] 5% H_2O. DCA = dichloroacetic acid; TMS = trimethylsilyl.

of methyl *tert*-butyl ether (MTBE) as a solvent led to a similar RCC (62%) but pleasingly increased the *ee* value to 92% (Table 1, entry 2). Amine (*S*)-**B** also gave 92% *ee* but a lower RCC of 45% (Table 1, entry 3). The use of [^{18}F]Selectfluor bis-triflate[21] instead of [^{18}F]NFSI was unsuccessful, likely because of the poor solubility of this reagent in the solvent system employed (Table 1, entry 4). This study highlights the dramatic influence of the [^{18}F]F^+ source on the reaction outcome and underscores the importance of [^{18}F]F^+ reagent diversity for radiofluorination. Significant differences were observed between experiments conducted with [^{19}F]F^+ or [^{18}F]F^+ reagents.[18,22] Three representative aldehydic substrates responded well to ^{18}F fluorination under our optimized conditions, as shown in Figure 1. The enantiomeric excesses measured for all ^{18}F-labeled α-fluoroaldehydes (*S*)-[^{18}F]**3b**, (*S*)-[^{18}F]**3c**, and (*S*)-[^{18}F]**3d** were found to be greater than 90%.

The success of the first asymmetric organomediated ^{18}F fluorination encouraged further derivatization of the chiral α-[^{18}F]fluoroaldehyde (*S*)-[^{18}F]**2a** into a range of additional high value ^{18}F-labeled molecules (Scheme 2).

Oxidation leading to the formation of 2-fluoro-3-phenylpropanoic acid ((*S*)-[^{18}F]**4**) was investigated first. With this in mind, (*S*)-[^{18}F]**2a** was prepared in MTBE applying the optimum procedure (Table 1, entry 2) and was directly treated with a range of oxidants. No product of oxidation was observed upon addition of either oxone in DMF or potassium permanganate in methanol/water. Pleasingly, the Pinnick–Lindgren oxidation[23] performed with sodium hypochlorite in acetonitrile afforded (*S*)-[^{18}F]**4** with 75% RCC[19]

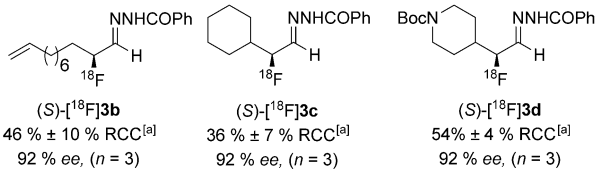
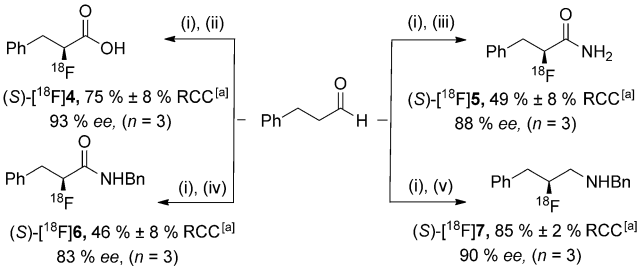


Figure 1. Enantioselective α-^{18}F fluorination: substrate scope. [a] RCC determined by radio-HPLC relative to [^{18}F]NFSI.

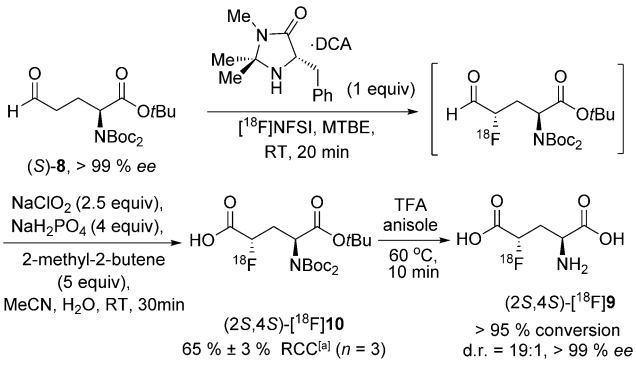


Scheme 2. One-pot radiosynthesis of carboxylic acid (*S*)-[^{18}F]**4**, amides (*S*)-[^{18}F]**5** and (*S*)-[^{18}F]**6**, and amine (*S*)-[^{18}F]**7** from hydrocinnamaldehyde. Conditions: i) [^{18}F]NFSI, MTBE, amine (*S*)-**A** (1 equiv), RT, 20 min; ii) $NaClO_2$ (2.5 equiv), NaH_2PO_4 (4 equiv), 2-methyl-2-butene (5 equiv), MeCN, H_2O, RT, 30 min; iii) $NH_2CH(p\text{-}OMePh)_2$ (1.5 equiv), 2-methyl-2-butene (5 equiv), toluene, RT, 5 min then $NaClO_2$ (2.5 equiv), NaH_2PO_4 (4 equiv), H_2O, RT, 30 min then TFA, anisole, 60 °C, 10 min; iv) benzylamine (1.5 equiv), 2-methyl-2-butene (5 equiv), toluene, RT, 5 min then $NaClO_2$ (2.5 equiv), NaH_2PO_4 (4 equiv), H_2O, RT, 30 min; v) benzylamine (2 equiv), DCE, RT, 5 min then $NaBH(OAc)_3$ (4 equiv), RT, 30 min. [a] RCC determined by radio-HPLC relative to [^{18}F]NFSI.[19] Bn = benzyl.

and 93% *ee*. This reaction required sodium dihydrogen phosphate and 2-methyl-2-butene acting as a scavenger of hypochlorous acid generated in situ. Next, we successfully developed the oxidative amidation[24] of (*S*)-[^{18}F]**2a** as a route to the secondary amide (*S*)-[^{18}F]**6** directly from hydrocinnamaldehyde. The aldehyde (*S*)-[^{18}F]**2a** was generated first and stirred with benzylamine in toluene for 5 min. Subsequent Pinnick–Lindgren oxidation of the resultant imine afforded amide (*S*)-[^{18}F]**6** in 46% RCC over three steps, all carried out in one pot, with a slightly decreased *ee* value of 83%. Alternatively, the treatment of (*S*)-[^{18}F]**2a** with $NH_2CH(p\text{-}OMePh)_2$[25] followed by Pinnick oxidation (30 min) then addition of trifluoroacetic acid (TFA; 10 min) afforded the primary α-fluoroamide (*S*)-[^{18}F]**5** in 49% RCC[19] and 88% *ee*. Finally, the formation of the chiral β-fluoroamine (*S*)-[^{18}F]**7** was also possible from (*S*)-[^{18}F]**2a** by imine formation in dichloroethane (DCE) followed by reduction with sodium triacetoxyborohydride.[26] This reductive amination was achieved affording (*S*)-[^{18}F]**7** in 85% RCC[19] and 90% *ee*.

After establishing these conditions for the synthesis and transformation of aldehyde (*S*)-[^{18}F]**2a**, we focused on the labeling of (2*S*,4*S*)-4-fluoroglutamic acid, a radiotracer difficult to access as a single stereoisomer applying known methods. Glutamine and glutamate play key roles in the metabolism of tumors and may act as a useful alternative radiotracer for [^{18}F]FDG negative tumors.[27] After deamidation of glutamine, glutamate is transaminated to 2-oxoglutarate, which is channeled into the tricarboxylic acid cycle. We opted to focus on 4-[^{18}F]fluoroglutamic acid ([^{18}F]**9**) since preclinical trials indicate that this tracer has potential in breast and lung tumor imaging as a result of high uptake in these cell lines.[28] Previous syntheses of 4-[^{18}F]fluoroglutamic acid involve S_N2 ^{18}F fluorination of stereochemically pure starting materials. This method has provided access to (2*S*,4*R*)-4-[^{18}F]fluoroglutamic acid but access to the alternative diastereomer (2*S*,4*S*) proved difficult because of epimerization at one of the stereocenters under the ^{18}F fluorination conditions; time-consuming purification by HPLC on a chiral stationary phase was therefore required prior to imaging studies.[29] We envisaged a radiosynthesis of (2*S*,4*S*)-[^{18}F]**9** starting from the enantiopure aldehyde precursor (*S*)-**8** applying our optimized electrophilic ^{18}F fluorination, a process that would be stereocontrolled by the chiral amine activator. Aldehyde (*S*)-**8** was synthesized from L-glutamic acid in five facile steps.[18] In a one-pot process, (*S*)-**8** was reacted with [^{18}F]NFSI followed by Pinnick oxidation under the optimum reaction conditions (Scheme 3). The resulting protected ^{18}F-labeled glutamic acid (2*S*,4*S*)-[^{18}F]**10** was formed in 65% RCC. Following removal of the solvent, deprotection was effected by heating in a TFA/anisole solution for 10 min; this process provided 4-[^{18}F]fluoroglutamic acid (2*S*,4*S*)-[^{18}F]**9** (more than 95% conversion) with a d.r. value of 19:1, the stereochemical outcome of the ^{18}F fluorination being controlled by the chiral amine. Careful analysis of this product confirmed that no racemization occurred at the C2 position during ^{18}F fluorination and deprotection (*ee* > 99%).

Further experiments studied the possible match/mismatch effect between the chiral imidazolidinone and the chiral



Scheme 3. One-pot radiosynthesis of 4-[^{18}F]fluoroglutamic acid (2*S*,4*S*)-[^{18}F]**9**. [a] RCC determined by radio-HPLC relative to [^{18}F]NFSI.[19] BOC = *tert*-butoxycarbonyl.

aldehydic substrate (*S*)-**8**. When the ^{18}F fluorination was performed with amine (*R*)-**A** applying the reaction sequence shown in Scheme 3, 4-[^{18}F]fluoroglutamic acid was formed in 47% ± 5% RCC and a d.r. of 7:3 favoring the formation of diastereomer (2*S*,4*R*)-[^{18}F]**9**; this result indicates that a mismatch effect operates between (*S*)-**8** and the chiral amine (*R*)-**A**.

In conclusion, we report that enamine catalysis, one of the main activation modes of organocatalysis, allows for the enantioselective ^{18}F fluorination of aldehydes in high radiochemical conversion and with *ee* values reaching 93%. These versatile synthons can be transformed into ^{18}F-labeled carboxylic acids, amides, and amines in a one-pot process directly from the achiral aldehydic precursor. We have further demonstrated the utility of this method with the synthesis of (2*S*,4*S*)-4-[^{18}F]fluoroglutamic acid. This radiochemistry is significant as it merges for the first time the fields of organocatalysis and ^{18}F fluorination, opening the door to a myriad of opportunities for labeling with the ^{18}F isotope or with alternative imaging-appropriate isotopes.

Experimental Section

General procedure for asymmetric fluorination of aldehyde: To an Eppendorf vial containing a stirrer bar and (*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid (1.7 mg, 5.0 μmol) was added a solution of aldehyde (5.0 μmol) in MTBE (50 μL). The reaction was stirred for 10 min prior to the addition of an aliquot of [^{18}F]NFSI in MTBE (250 μL, circa 200 MBq). The reaction was stirred at room temperature for 20 min. Reagents for derivatization were added and stirred for reaction times as described, followed by analysis by analytical HPLC. The peak corresponding to ^{18}F-labeled product was collected and analyzed by reverse-phase HPLC on a chiral stationary phase.

Acknowledgements

Financial support was provided by the BBSRC (F.B.), GE Healthcare (F.B.), the Academy of Finland Grant Agreement 266891 (A.K.K., S.F.), the EC (FP7-PEOPLE-2012-ITN-RADIOMI-316882 to A.K. and T.K.) and Advion. V.G. holds a Royal Society Wolfson Research Merit Award (2013–2018).

Keywords: asymmetric synthesis · enamines · fluorine-18 · organocatalysis · positron emission tomography

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13366–13369
Angew. Chem. **2015**, *127*, 13564–13567

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[17] A short initial irradiation time on the ^{18}O target (5 min bombardment) was applied to minimize the amount of ^{18}F, thereby minimizing radioactive exposure. Longer target irradiation time can provide $[^{18}F]F_2$ with specific activity of up to 55 GBq μmol^{-1}, see Ref. [16].
[18] See the Supporting Information for all experimental details.
[19] An aliquot from the crude reaction mixture was diluted in MeOH or MeCN/H_2O (1:1) for analysis by reverse-phase analytical HPLC. RCC from [^{18}F]NFSI was measured by integration of all organic peaks (see the Supporting Information for the HPLC spectra) and reported with the standard deviation of the mean for *n* reactions. All RCC values calculated from [^{18}F]NFSI are omitting the initial inherent 50% loss encountered for its preparation.
[20] Measurement of *ee* values was carried out by collection of the peak corresponding to the product during the analytical HPLC run and injection directly onto an appropriate reverse-phase chiral column (see the Supporting Information for HPLC spectra).
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Received: July 1, 2015
Revised: July 30, 2015
Published online: September 11, 2015

