Convenient Synthesis of Diaryliodonium Salts for the Production of [^{18}F]F-DOPA

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[^{18}F]F-DOPA is an important radiotracer that is used in the diagnosis of Parkinson's disease and neuroendocrine tu-mours. We describe a simple synthesis for a number of diaryl-iodonium salt precursors that are suitable for the production of [^{18}F]F-DOPA through reaction with no carrier added (n.c.a.) nucleophilic [^{18}F]fluoride. The simple procedure gives bench-stable, complex iodonium precursors in good yields without the need for laborious anhydrous conditions. Further alteration to the precursor counterion can be readily achieved for a range of halides and pseudo halides by a sim-ple modification of the workup. Preliminary "hot" and "cold" fluorination results show the suitability of the compounds for the production of [^{18}F]F-DOPA.

Introduction

The synthesis of radiolabelled compounds is currently an area of great interest, primarily due to their application in positron emission tomography (PET). This highly sensitive and versatile imaging technique allows for the pharmacoki-netic and biodistribution of positron emitters to be studied in vivo, and is crucial to diagnosis and evaluation of dis-eases, including cancers[1] and neurodegenerative diseases such as Parkinson's disease.[2]

[^{18}F]Fluorine is a commonly used radioisotope in the production of such radiotracers. This popularity is due to a number of advantages; it has a relatively long half-life (109.8 min) compared with that of ^{11}C (20.4 min) and ^{13}N (9.98 min), allowing multistep reactions, complex purifica-tions, and even transportation before unacceptable loss of radioactivity. In addition, it is also possible to produce [^{18}F]fluorine in multi-Curie levels with low energy.[3] The strength of the carbon–fluorine bond means that such com-pounds generally show good metabolic stability in vivo. This is especially true of aryl carbon–fluorine bonds, with some aliphatic carbon–fluorine bonds being prone to enzy-matic cleavage.[4]

Numerous methods exist for the incorporation of fluor-ine into molecules at an aryl position with both electro-philic and nucleophilic reagents. Nucleophilic incorporation of [^{18}F]fluoride is the preferred route because of the high specific activity (SA) of no carrier added (n.c.a.) [^{18}F]fluor-ide. Traditional nucleophilic routes for labelling aromatic compounds with [^{18}F]fluoride include Balz–Schiemann and Wallach reactions.[5] Unfortunately, these transformations use harsh conditions and suffer from poor radiochemical yields (RCYs) and a narrow substrate scope. Aromatic nu-cleophilic substitution of halides and other leaving groups (notably NO_2 and N^+Me_3) can be used but, in general, these reactions are limited to aromatic compounds bearing electron-withdrawing groups and regioselectivity remains a significant issue. With these limitations, extending such methodologies to complex systems can be difficult and often requires multistep synthesis.

For more electron-rich aryl moieties, the use of electro-philic fluorine is traditionally more common, utilising [^{18}F]-fluorine gas or reagents produced from this source of the ^{18}F nuclide. However, these methods are avoided if possible because of their numerous disadvantages including low SA and generally poor RCYs. The use of fluorine gas as the source of radioactivity also suffers from handling difficult-ies and a much reduced availability compared with that of n.c.a. [^{18}F]fluoride.

Recently, iodonium salts have generated much interest as precursors for the nucleophilic incorporation of [^{18}F]fluor-ide into electron-rich target molecules. The properties of di-aryliodonium salts make them ideal precursors for aromatic radiotracer synthesis using nucleophilic fluorination. A quick, selective reaction is crucial for short reaction and purification times to increase RCY. This is achieved by the high reactivity of the salts, which is attributed to the "hy-perleaving group ability" of the PhI group, being approxi-mately 10^6 times that of a triflate.[6]

The use of diaryliodonium salts for the formation of [^{18}F]-labelled aromatic compounds was first reported by Pike et al. using both symmetrical and unsymmetrical di-

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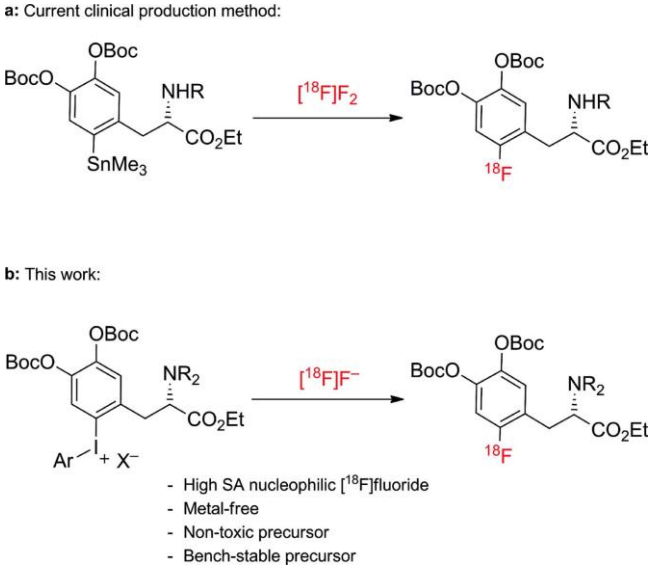
aryliodonium precursors.[7] When an unsymmetrical diaryliodonium salt is used, the aromatic substituent at which the fluorination takes place is dependent on both the electronic and steric properties of the two attached aryl moieties. This allows precursors to be designed for selective fluorination at the desired aromatic position by employing a small, electron-rich aryl group (commonly 2-thienyl and 4-methoxyphenyl) as the "non-participating" aryl ring or other non-participating groups such as a [2,2]paracyclophane moiety.[8] The application of spirocyclic iodonium ylide precursors for such a regioselective fluorination has also been reported to be of great efficacy by Liang et al.[9]

The employment of a diaryliodonium salt precursor for the synthesis of a practical PET tracer was first reported by Suzuki et al. for the synthesis of [^{18}F]DAA1106, a tracer used for imaging peripheral-type benzodiazepine receptor in the brain.[10] The utility of such diaryliodonium salt precursors offers a selective and widely applicable methodology for the introduction of [^{18}F]fluoride into a large number of functionalised arenes. Nevertheless, the use of iodonium salts for the introduction of fluoride cannot be described as general, with a large range of fluorination conditions reported for a range of substrates. The production and fluorination of more complex biomedically relevant iodonium precursors has until recently also been problematic. However, as the understanding and experience in this methodology grows, the use of iodonium salts as precursors to form more complex, electron-rich radiotracers have seen much recent success.[11]

[^{18}F]F-DOPA is a widely used radiotracer most commonly employed in the diagnosis of Parkinson's disease and neuroendocrine tumours (NETs).[1a,2a] The commonly used current synthesis of [^{18}F]F-DOPA (Scheme 1a) proceeds through electrophilic destannylation with [^{18}F]F_2 gas. As expected, the reaction suffers from the disadvantages mentioned above and proceeds with poor RCYs, low SA, and is unavailable to PET centres not equipped with [^{18}F]F_2 gas



Scheme 1. Synthesis of [^{18}F]F-DOPA.

production facilities. An effective [^{18}F]F-DOPA synthesis using a nucleophilic approach would provide a significant improvement to the above synthesis, allowing a more accessible and facile route to this vital radiopharmaceutical.

Recent studies have led to vast improvements in nucleophilic methodology for the synthesis of electron-rich aromatics such as [^{18}F]F-DOPA. Ritter et al. recently reported the production of protected [^{18}F]F-DOPA and other radiolabelled targets by using a nickel complex in the presence of an oxidant.[12] Scott et al. found that copper-catalysed radiofluorination of mesityl iodonium salts could be used to access protected [^{18}F]F-DOPA.[13] Gouverneur et al. have recently shown the utility of boronic esters as precursors for nucleophilic [^{18}F]fluorination also in the presence of a copper catalyst.[14] This method allows access to high SA electron-rich targets including [^{18}F]F-DOPA.

Drawbacks to these advancements in nucleophilic [^{18}F]-fluorination include the use of metals in all cases and the employment of air-sensitive reagents in those reported by Scott and Ritter.

Herein, we report the synthesis of bench-stable diaryliodonium salts that are suitable for the production of [^{18}F]-F-DOPA through reaction with n.c.a. nucleophilic [^{18}F]-fluoride (Scheme 1b). Multiple strategies for salt formation are scrutinised, and preliminary "hot" and "cold" fluorination results are used to show the suitability of the molecules for the production of [^{18}F]F-DOPA.

Results and Discussion

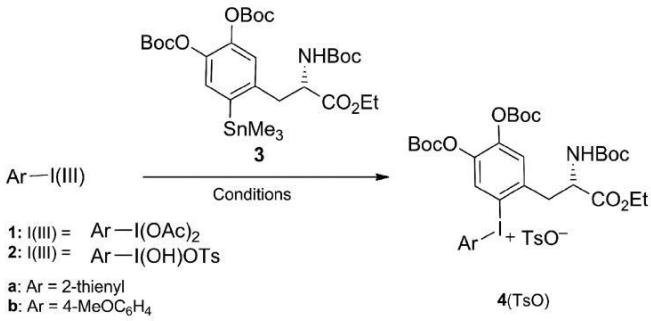
Iodonium Precursor Formation Using Stannylated Protected L-DOPA Ethyl Ester

The reaction of hypervalent iodine(III) reagents of Koser-type [ArI(OH)OTs] with arylstannanes to form iodonium tosylates is well known and provided the starting point for our investigation.[9] The formation of 4-methoxyphenyl- and 2-thienyl-substituted Koser-type reagents was achieved by using reported methods (see the Supporting Information).[15] Alternatively, the reaction can be performed with a Koser-type reagent produced in situ from its corresponding diacetate. (Diacetoxyiodo)arenes were produced by using reported methods (see the Supporting Information).[16] The conditions tested for optimisation of the salt formation are shown in Table 1.

The use of 2,2,2-trifluoroethanol (TFE) as solvent was very detrimental to the reaction (Table 1, Entries 1 and 4) despite being an excellent solvent for the formation of simple diaryliodonium salts.[17] However, when using a method adapted from a procedure reported by Chun et al.,[18] it was found that the reaction proceeded well in a mixture of chloroform and acetonitrile (Table 1, Entry 2). When approximately equimolar amounts of the hypervalent iodine reagent **1** was used, it was found that a significant portion of the stannane remained unreacted.

By increasing the number of equivalents (1.2 and 1.5 equiv.) of the Koser derivative, higher levels of conversion of stannane into the diaryliodonium salt was observed

Table 1. Synthesis of diaryliodonium salts **4**.[a]



Entry	Reagent	Reagent [equiv.]	Solvent	Temperatue [°C]	Yield of **4** [%]
1	**1a**	1.02	CH_2Cl_2/TFE (1:1)	0	0
2	**1a**	1.02	$CHCl_3$/MeCN (5:1)	reflux	24
3	**1a**	1.2	$CHCl_3$/MeCN (5:1)	reflux	37
4	**1a**	1.2	MeCN/CH_2Cl_2/TFE (1:2.5:2.5)	reflux	0
5	**1a**	1.5	$CHCl_3$/MeCN (5:1)	reflux	44
6	**2a**	1.5	$CHCl_3$/MeCN (5:1)	reflux	24
7	**2b**	1.2	CH_2Cl_2/MeCN (1:1)	r.t.	26
8	**1b**	1.2	$CHCl_3$/MeCN (5:1)	reflux	37
9	**1b**	1.5	$CHCl_3$/MeCN (5:1)	50 °C	60
10	**2b**	1.5	$CHCl_3$/MeCN (5:1)	50 °C	30

[a] Reactions were carried out under ambient conditions; reaction time was 18 h.

(Table 1, Entries 3 and 5). The addition of 1.5 equiv. of **1** was found to be optimal; the addition of larger amounts led to difficulties in purification.

Interestingly, the reaction proceeded with higher yields when the stannane was reacted with the Koser reagent produced in situ (compound **1** and *p*-toluenesulfonic acid) rather than preformed Koser reagent (Table 1, Entries 5 vs. 6 and 9 vs. 10).

Conditions reported by Jang et al.[11a] were also investigated, but the combination of dichloromethane and aceto-nitrile as solvent proved to be less fruitful than the op-timised conditions (Table 1, Entry 7).

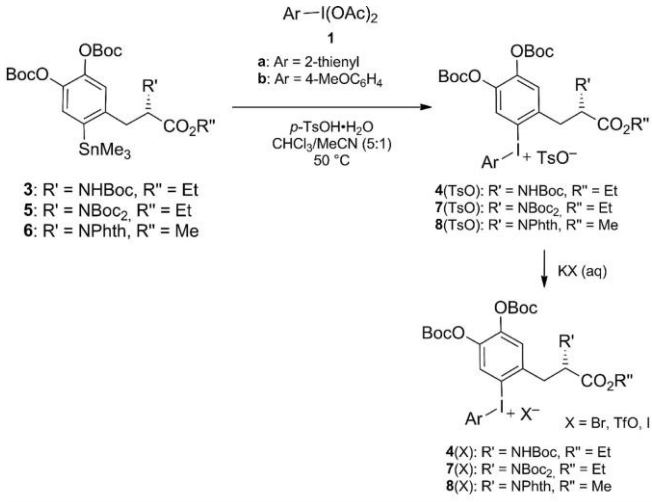
Under the optimised conditions the reaction proceeded with good yields for both 2-thienyl and 4-methoxyphenyl Koser reagents, with the highest yields being observed with the latter derivative (Table 1, Entries 5 and 9).

Significant improvements to the product purity were observed when the solution of the crude salt in dichlorometh-ane was washed with water before trituration. The use of the optimised reaction conditions for the formation of diaryliodonium salts with different protecting groups is shown in Table 2.

The formation of diaryliodonium salts **4a** and **7a** pro-ceeded in reasonable yields (Table 2, Entries 1 and 2). Yields could be improved by increasing the number of equivalents of diacetate **1** and *p*-toluenesulfonic acid. However, when the tetra-Boc-protected stannyl precursor was treated with more than 1.5 equiv. of *p*-toluenesulfonic acid, deprotection of one of the *N*-Boc groups occurred to yield the tri-Boc-protected iodonium salt (**4a**).

Surprisingly, reaction of the phthalimide-protected aryl-stannane **6** with the 2-thienyl Koser reagent produced in situ proceeded very poorly, and a pure product could not

Table 2. Synthesis of diaryliodonium salts with different nitrogen protections and counterions.



Entry	Ar	R9	R99	Yield [%]
1	**4a**(OTs)	NHBoc	Et	44
2	**7a**(OTs)	$NBoc_2$	Et	28
3	**8a**(OTs)	NPhth	Me	0
4	**4b**(OTs)	NHBoc	Et	60
5	**7b**(OTs)	$NBoc_2$	Et	26
6	**8b**(OTs)	NPhth	Me	29

be isolated. However, the reaction did proceed satisfactorily with the 4-methoxyphenyl Koser reagent produced in situ. The reasons for this unexpected change in reactivity are not clear at present.

When the salt was washed with a saturated aqueous solution of a potassium salt then a simple counterion exchange

occurred for salts including KI, KOTf and KBr. Yields for the counterion exchange to the iodonium bromide were quantitative and performed for all compounds shown in Table 2. Conversion into the iodonium triflate was also quantitative, and conversion into the iodonium iodide proceeded with 95 % yield. These counterion exchange processes were performed with compounds **4a**(OTs) and **4b**(OTs).

It was found that conversion from the iodonium tosylate into the iodonium perchlorate could not be performed by using this method but was achieved by using the procedure reported by Dinkelborg et al.[11c] Thus, the iodonium salt was charged on a reverse-phase C-18 cartridge before eluting with an aqueous solution of perchloric acid through the cartridge. Following this, water was passed through the cartridge before a gradient of acetonitrile and water was used to elute the iodonium perchlorate (see the Supporting Information).

"Cold" Fluorination Reactions

After the successful formation of different iodonium precursors, it was important to assess their suitability for the production of F-DOPA. Different conditions for the fluorination of iodonium salts have been reported.[19] We started our investigations by performing fluorinations using tetramethylammonium fluoride (TMAF) in a range of solvents. Acetonitrile, *N*,*N*-dimethylformamide DMF) and dimethyl sulfoxide (DMSO) are commonly used in the fluorination of iodonium salts, and these were investigated first. Recent work by DiMagno et al. has shown that non-polar aprotic solvents such as benzene and toluene can also be used; they reported that thermal decomposition of the iodonium fluoride in such solvents can dramatically improve the fluorination yields.[20] Therefore, fluorinations with TMAF were carried out in acetonitrile, DMF, DMSO and toluene, as shown in Table 3.

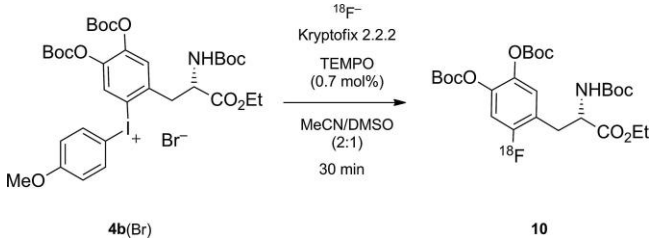
The formation of the fluorinated product was observed in all reactions by ^{19}F NMR and HPLC analyses, except for the reaction performed in DMSO (Table 3, Entry 1). The formation of the iodonium fluoride intermediate **4**(F) was observed by ^{19}F NMR spectroscopic analysis in all cases (see the Supporting Information). The thermal decomposition of iodonium fluoride **4**(F) in DMSO, however, did not proceed to give the fluorinated product (Table 3, Entry 1). It should be noted that no production of 4-fluoroanisole or 2-fluorothiophene was observed in any of these reactions.

The reaction proceeds with both the thiophene- and the anisole-derived iodonium salts, with neither "non-participating" arene showing a clear advantage over the other, with all yields (determined by HPLC analysis) being between 2 and 5 % (Table 3).

"Hot" Fluorination Reactions

After the success of the cold fluorinations, further investigation into the suitability of the precursors for production of [^{18}F]F-DOPA was carried out. Reactions were performed with an automated Eckert & Ziegler system in a hot cell.

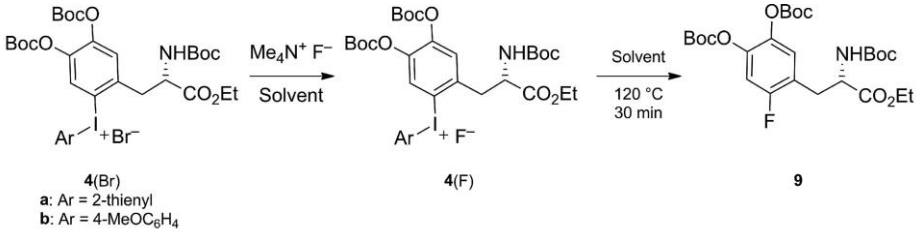
Reaction of iodonium bromide **4b**(Br) with azeotropically dried [^{18}F]KF·Kryptofix 222·K_2CO_3 salt gave the ^{18}F-labelled, protected DOPA compound **10** (Scheme 2).



Scheme 2. Synthesis of hot [^{18}F]F-DOPA.

Although the reaction proceeded with poor conversion of [^{18}F]fluoride into the labelled product, it was found that

Table 3. Fluorinations of diaryliodonium salts **4** with TMAF.



Entry	Ar	Fluorination solvent	Yield [%][a]
1	**4b**(Br)	DMSO	0
2	**4b**(Br)	DMF	2
3	**4b**(Br)	MeCN	5
4[b]	**4b**(Br)	toluene	2
5	**4a**(Br)	MeCN	3
6[b]	**4a**(Br)	toluene	5

[a] Yields were calculated based on HPLC analysis. [b] Iodonium fluoride **4a**(F) was produced in acetonitrile before removal of the solvent. Compound **4a**(F) was then redissolved in toluene and passed through a filter into a clean vessel for thermal decomposition to **9**.

the reaction performed in a mixture of DMSO and acetonitrile proceeded very cleanly. Interestingly, the reaction did not proceed in DMSO alone, and reactions in either DMF or acetonitrile alone proceeded less cleanly, with the formation of a number of unidentified radiolabelled products. In all cases, the conversion of fluoride into any products was low, with , 1 % RCY.

Isolation of the [^{18}F]fluorinated product could be achieved by using semipreparative HPLC purification to give the product in . 95 % radiochemical purity.

Alternative protecting strategies for the amine showed no advantages under the current conditions. No product formation was observed when using the iodonium bromide **8b**(Br) (phthalimide protected amine) as the precursor.

Iodonium bromide **7b**(Br) (di-Boc-protected amine) gave the corresponding ^{18}F-labelled, protected DOPA moiety, but the reaction did not proceed cleanly.

Decay-corrected RCYs were calculated by measurement of the activity of the isolated [^{18}F]labelled products in a well counter, because conversions calculated from analytical HPLC proved to be inaccurate (see the Supporting Information). We would thus recommend caution when using HPLC analysis for monitoring the success of labelling reactions.

To confirm the production of ^{18}F-labelled, protected DOPA in the successful reactions, the corresponding ^{19}F compound was co-eluted during HPLC analysis. No chiral HPLC analysis has yet been performed to assess the chiral integrity of the product.

Conclusions

Different iodonium salt precursors for the synthesis of [^{18}F]F-DOPA have been synthesised in reasonable to good yields by using a robust and facile route with no need for laborious inert conditions. The complex iodonium precursors are bench-stable molecules. Further exchange of the precursor counterion can be readily achieved with a range of halides and pseudo halides by a simple alteration of the workup. The use of such precursors for the formation of both ^{19}F- and ^{18}F-protected DOPA has been studied, showing the utility of the iodonium salts as precursors for the nucleophilic synthesis of this valuable radiotracer. The poor conversion of [^{18}F]fluoride into the labelled product means that the current conditions are not suitable for useful production of [^{18}F]F-DOPA. Hence, further investigations into the "hot" fluorination reaction are ongoing. Investigation into any possible racemisation during the [^{18}F]labelling reaction also needs to be undertaken.

Experimental Section

General Procedure for the Formation of Diaryl Iodonium Salts Suitable for [^{18}F]F-DOPA Production from Diacetate: To a stirred suspension of either 2-(diacetoxy)iodothiophene or 4-(diacetoxy)-iodoanisole (0.44 mmol) in acetonitrile (5 mL) at 0 °C, was added *p*TsOH·H_2O (0.44 mmol) before immediate dilution with chloroform (25 mL). The appropriate protected 6-(trimethylstannyl)-l-DOPA reagent (0.29 mmol) in chloroform (5 mL) was added dropwise. The reaction mixture was heated to 50 °C and stirred for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with water/saturated KX (X = Br, I, OTf) solution (3 3 40 mL). The organic layer was passed through a phase separator and concentrated under reduced pressure to give the crude product as a yellow oil. The product was triturated with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). The precipitate was collected on a Telos phase separator and washed with hexane. The collected precipitate was removed from the phase separator with CH_2Cl_2. The CH_2Cl_2 was removed before the product was triturated once more with hexane from a minimum amount of CH_2Cl_2 and diethyl ether (1:1). Removal of the solvent under reduced pressure gave the product as a white solid.

General Procedure for No-Carrier-Added [^{18}F]Fluoride Incorporation Using Iodonium Salts: [^{18}F]Fluoride delivered from the cyclotron as an aqueous solution was trapped on a pretreated QMA cartridge to remove the ^{18}O-enriched water. The [^{18}F]fluoride was eluted with a Kryptofix 2.2.2 carbonate solution (0.6 mL) (0.3 mL of MeCN, 0.3 mL of H_2O, 22.8 mg of Kryptofix 2.2.2, 8.4 mg of K_2CO_3) into a 5 mL V-shaped vial. The mixture was dried under a flow of nitrogen and reduced pressure at 120 °C for 440 s. The residue was azeotropically dried twice with the addition of acetonitrile (2 3 1 mL). Distillation was achieved by heating at 120 °C under a flow of nitrogen for 440 s. To the dried [^{18}F]-KF·Kryptofix 222·K_2CO_3 salt were added iodonium precursor (0.03 mmol) and TEMPO (0.021 mmol) in acetonitrile and DMSO (1.5 mL) (2:1). The reaction mixture was heated at 90 °C for 30 min before being cooled to room temperature. The reaction mixture was ejected into a sterile vial, and the activity was measured in a well counter to calculate the radiochemical recovery (RCR). The reaction mixture was loaded onto the HPLC sample loop. Reverse-phase purification was performed using a semipreparative Agilent 1200 column [4 mL/min, 70 % MeCN in H_2O (0.01 % formic acid)]. The γ-peak was collected (retention time: 7.5–8.5 min), and the activity of the isolated product was measured with a Campitec CRC-25PET well counter. A 100 μL sample was taken for HPLC analysis to confirm the product as the protected [^{18}F]F-DOPA.

Supporting Information (see footnote on the first page of this article): All synthetic methods including spectroscopic data and analytical data.

Acknowledgments

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