Synthesis of 4-[18F]Fluorophenyl-alkenes and -arenes via Palladium-Catalyzed Coupling of 4-[18F]Fluoroiodobenzene with Vinyl and Aryl Tin Reagents

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The cross-coupling reaction of 4-[18F]fluoroiodobenzene 3a with vinyl or aryl tin reagents in the presence of tetrakis(triphenylphosphine)palladium was found to provide a convenient and rapid method for the preparation of 4-[18F]fluorostyrene or 4-[18F]fluorobiphenyl within 45–50 min and 47% or 86% radiochemical yields, respectively, counted from 3a. (E)-N-{3-(4-[18F]fluorophenyl}prop-2-enyl]piperidine 2a was obtained within 45 min and in 80% radiochemical yield from 3a. 4-[18F]Fluorobromobenzene 4a was prepared in 24–48% yield from 2-nitro-5-bromobenzaldehyde and [18F]KF in 95 min.

Positron-emitting radiopharmaceuticals labelled with fluorine-18 are being increasingly used in clinical diagnosis. Although fluorine-18 [β^+ emitter (97%), $E = 0.64$ MeV, $t_{1/2} = 110$ min) is the most attractive radionuclide in the preparation of imaging agents for positron emission tomography, there are few chemical processes suitable for introducing fluorine-18 into organic molecules.[1] Therefore, there is a strong demand for new methods for fluorine-18 radiosynthesis. In practice, for a process to be useful for biological studies, the reactions have to be efficient, regio- and stereo-selective and rapid in the presence of different functional groups. Moreover, in order to prepare samples of high specific activities, 18F-labelled starting materials have to be easily synthesized from 18F-fluoride formed in the 18O(p,n)18F nuclear reaction.

The fluorophenylalkene moiety is a building group for a large variety of molecules of biological interest (i.e. GBR 12936 1, a dopamine reuptake-site inhibitor[2]). Many versatile methods for the introduction of such a group have been investigated. In general, they are based on condensation reactions[3] of an aryl aldehyde (Wittig or Wittig–Horner olefinations,[4] Knoevenagel,[5] Perkin reactions[6]) or on coupling reactions of an organometallic reagent with halides.[7] To our knowledge, the easily

prepared 4-[18F]fluorobenzaldehyde[8] has not been condensed with active methylene group compounds probably because the reaction conditions would require protection and deprotection steps. However, 4-[18F]fluorobenzaldehyde was used in a Wittig reaction for the synthesis of [18F]GBR 12936 1 (overall yield 10–15%).[9] The condensation led to a mixture of Z and E (1:1) stereoisomers. The catalyzed cross-coupling reactions[7,10] being regio- and stereo-selective, in particular when the organometallic compound is a Grignard reagent,[11] a tin (Stille reaction),[12–14] or a boron (Suzuki reaction) derivative,[15] we envisaged the synthesis of the model compound 2 by the routes presented in Scheme 1. In general, with Grignard reagents the preferred path is the catalyzed reaction of an arylmagnesium bromide or iodide with a vinyl halide (route A) due to the low reactivity of vinylmagnesium halides. However, efficient and reproducible syntheses of labelled organometallic species are often difficult under radiosynthesis conditions [nanomolar amount of the labelled precursor, and small solvent volumes (0.5–1 ml)]. Consequently, we have chosen to study route B involving 4-[18F]fluorides 3a or 4a (Scheme 1). The palladium-mediated reactions of stannanes have been successfully used in carbon-11 chemistry to prepare 11C-labelled aryl cyanides,[16] benzamides,[17] ketones,[18] substituted toluenes and [11C]propene.[19]
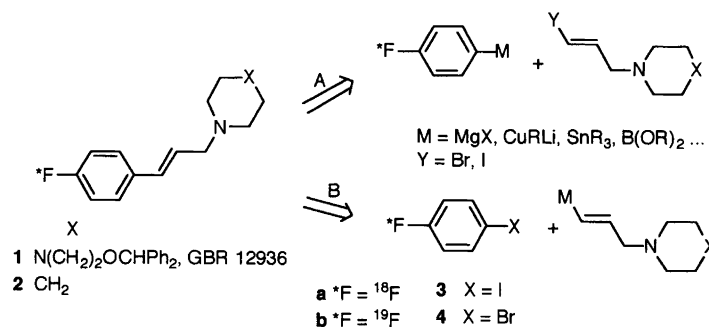
Scheme 1. Different approaches to the synthesis of the amine **2** using a catalyzed cross-coupling reaction.

However, until recently[20] no palladium-promoted cross-coupling reactions involving fluorine-18 compounds have been reported. We present here our results on the formation of compounds containing a carbon-sp^2-carbon-sp^2 bond by reaction of 4-[^{18}F]fluorohalogenobenzene **3a** or **4a** with either Grignard or tin reagents in the presence of a palladium catalyst. The synthesis of the stereodefined 3-(4-[^{18}F]fluorophenyl)allylamine **2a** is also described. This study led us to develop a synthesis of 4-[^{18}F]fluorobromobenzene (**4a**) from 5-bromo-2-nitrobenzaldehyde (**7**).

Results and discussion

Synthesis of [^{18}F]fluorides **3a** *and* **4a**. Because aryl iodides and bromides but not fluorides[21] undergo oxidative addition to palladium complexes at moderate temperatures, **3a** and **4a** are suitable for coupling with organometallic reagents. 4-[^{18}F]Fluoroiodobenzene (**3a**) has been obtained either by hot-atom chemistry[22] or from the triflate **5**[23,24] (Scheme 2). The reaction requires only one step from [^{18}F]potassium fluoride and uses a water-soluble starting material which is easily separated, after radiofluorination, from the [^{18}F]fluoride **3a**. However, in our experiments, the yield of this reaction did not exceed 10–13% (corrected for decay) due to the formation of [^{18}F]fluoromethane via a competitive nucleophilic aliphatic substitution.[25,26] To avoid this side reaction, the synthesis of [^{18}F]fluoride **4a** via decarbonylation of 4-[^{18}F]fluorobromobenzaldehyde (**6a**) was envisaged (Scheme 2). Indeed, the aldehyde group, easily removed in the presence of a catalyst,[27,28] would also make easier the nucleophilic substitution of the nitro group for a fluorine atom in bromonitrobenzaldehyde **7**. This strategy was previously described for the preparation of ^{18}F-fluoromethoxy-substituted benzenes using either Wilkinson catalyst[29] or palladium on charcoal.[30] The benzaldehyde **7** treated by the complex [^{18}F]KF–Kryptofix 222 at 150 °C in dimethyl sulfoxide (DMSO) for 20 min afforded, after purification, the [^{18}F]fluoro aldehyde **6a** in 60–80% yield (50 min, number of runs > 10). The decarbonylation of **6a** in the presence of tris(triphenylphosphine)rhodium(I) chloride was attempted in tetrahydrofuran (THF), toluene, 1,2-

dichloroethane, benzonitrile and 1,4-dioxane. 1,4-Dioxane gave the highest yields of [^{18}F]fluoride **4a**. After purification, the [^{18}F]fluoro bromide **4a** was isolated in 40–66% yield from the aldehyde **6a** and in a 45 min reaction time.

*Reaction of 4-[^{18}F]fluoroiodobenzene (**3a**) with Grignard reagents.* The formation of a Csp^2–Csp^2 bond by reaction of an aryl halide with a Grignard reagent is well documented.[10,31] Nickel or palladium complexes are the catalysts most often used. However, due to the possible reaction of the C–F bond with nickel derivatives,[7] the coupling reactions were studied only in the presence of palladium catalysts. [^{18}F]Fluoride **3a** was treated with phenylmagnesium bromide (**8**) in THF in the presence of tetrakis(triphenylphosphine)palladium. The results are included in Table 1. The optimum conditions for the formation of 4-[^{18}F]fluorobiphenyl (**10a**) required a 5 min reaction time in refluxing THF in the presence of a 0.9% molar ratio of Pd(PPh$_3$)$_4$ to Grignard reagent. **10a** was isolated by HPLC in 53% radiochemical yield from the labelled iodide **3a**. This result compares well with that described in stable isotope chemistry (**10b**: 66% in 30 min reaction time).[32] However, no improvement (data not shown) was observed when the reaction was carried out in the presence of (Ph$_3$P)$_2$Pd(Ph)I, a complex which has been efficient in this type of reaction.[32] All the attempts (data not presented) to carry out the coupling of **3a** with vinylmagnesium bromide **11** in the presence of Pd(PPh$_3$)$_4$ in refluxing THF for 10 or 20 min failed. Radio thin-layer chromatography (radioTLC) did not show the formation of 4-[^{18}F]fluorostyrene (**13a**). A complex mixture was obtained in addition to unchanged starting material (35–40%).

The reactions of tetraphenylstannane **9** or tributylvinylstannane **12** with aryl halides under a variety of conditions using a palladium catalyst have been widely studied.[10,13,14] The couplings usually proceed under neutral conditions and are generally not particularly sensitive to water and oxygen. However, their efficiency, both in terms of times and yields, is strongly dependent on the palladium catalyst, the added ligand, the solvent and eventually the added salts. The reactions are usually
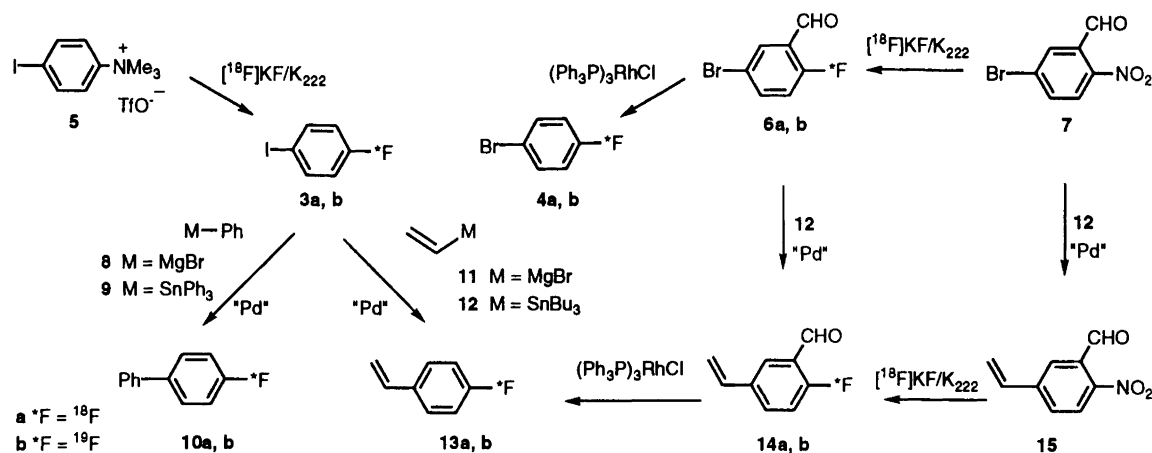
Scheme 2. Catalyzed cross-coupling reactions of iodo or bromo ^{18}F-fluoroaromatics with different organometallics.

Table 1. Cross-coupling reactions of [^{18}F]fluoroiodobenzene (**3a**) with Grignard and tin reagents.[a]

Entry	Substrate	Catalyst(s)	Ratio[b]	Solvent	t/min	T/°C	Product	Yield (%)[c]
1	PhMgBr	Pd(PPh$_3$)$_4$	1.9	THF	20	Reflux	4-[^{18}F]fluorobiphenyl	20
2	PhMgBr	Pd(PPh$_3$)$_4$	0.9	THF	5	Reflux		53
3	PhSnPh$_3$	BnPdCl(Ph$_3$P)$_2$	0.7	THF	5	Reflux		(15)[d]
4	PhSnPh$_3$	Pd(PPh$_3$)$_4$	0.7	HMPA	5	120		86
5	PhSnPh$_3$	BnPdCl(Ph$_3$P)$_2$	0.7	HMPA	5	120		80
6	H$_2$C=CH-SnBu$_3$	Pd$_2$(dba)$_3$, AsPh$_3$	2:16	Toluene	30	60	4-[^{18}F]fluorostyrene	26 (37)[d]
7	H$_2$C=CH-SnBu$_3$	Pd$_2$(dba)$_3$, AsPh$_3$, CuI	2:16:8	Toluene	5	60		42–53
8	H$_2$C=CH-SnBu$_3$	Pd$_2$(dba)$_3$, AsPh$_3$, CuI	2:16:8	DMF	30	60		47 (70)[d]

[a] Reactions were carried out with 10–14 μmol of substrate in 1 ml solvent except entries 1 and 2, respectively, 460 and 600 μmol. [b] In % based on the substrate. [c] Radiochemical yield, corrected for decay of isolated compound after HPLC based on 4-[^{18}F]fluoroiodobenzene ($n \geq 2$); radiochemical purity $\geq 98\%$. [d] Values given within parentheses refer to the ratio (from radioTLC) of the expected product in the crude reaction mixture.

highly chemo- and regio-selective, retention of configuration with respect to the vinyl bond being observed.[33]

*Reaction of **3a** with non-functionalized stannanes.* The reaction of the labelled iodide **3a** with tetraphenylstannane (**9**) (Table 1, entries 3–5) or tributylvinylstannane **12** (Table 1, entries 6–8) was studied under different conditions. Benzylchlorobis(triphenylphosphine)palladium(II) [BnPdCl(Ph$_3$P)$_2$], described as the catalyst of choice for the coupling of tetraorganotin compounds with aryl halides,[34] in particular with those containing electron-withdrawing substituents, was also satisfactory in promoting the reaction of the [^{18}F]fluoride **3a** with tetraphenylstannane (**9**) in hexamethylphosphoramide (HMPA) (entry 5). Pd(PPh$_3$)$_4$, although air sensitive,[14b] was found to have a similar efficiency (Table 1, entry 4). No oxygen effect was observed but the choice of the solvent appeared crucial to reach high yields quickly. In toluene at 120 °C for 5 min using either Pd(PPh$_3$)$_4$ or BnPdCl(Ph$_3$P)$_2$ (catalyst:stannane 0.7% molar ratio, data not shown) no reaction was observed. In refluxing THF, using Pd(PPh$_3$)$_4$, polar compounds were the only compounds detected by radioTLC. Under the same conditions, but using BnPdCl(Ph$_3$P)$_2$ (Table 1, entry 3), the analysis of the crude product showed the formation

of **10a** along with unchanged starting material (ratio = 15:85).

The standard Stille coupling conditions[13] [Pd(PPh$_3$)$_4$ in toluene or DMF (data not shown)] failed to give any **13a** from the stannane **12** and [^{18}F]fluoride **3a**. However, when the reaction was carried out in the presence of tris(dibenzylideneacetone)dipalladium(0) [Pd$_2$(dba)$_3$] and triphenylarsine,[35] **13a** was isolated in 47% radiochemical yield from **3a**. A significant effect on the yield was observed when copper(I) iodide[36] was added to the reaction mixture (Table 1, entries 6–8). These results are in good agreement with faster rates of the Stille coupling associated with ligands of low donicity and addition of a second metal.[37]

4-[^{18}F]Fluorostyrene (**13a**) *from 4-[^{18}F]fluorobromobenzaldehyde* (**6a**). The previous synthesis of **13a** was compared with that using [^{18}F]fluorovinylbenzaldehyde (**14a**). The latter compound was prepared in 25–30% radiochemical yield by reaction of [^{18}F]KF-Kryptofix 222 in DMSO with nitroaldehyde **15**. The decarbonylation of the aldehyde **14a** in benzonitrile was carried out in the presence of Wilkinson catalyst and by heating for 3 min in a kitchen microwave oven. 4-[^{18}F]Fluorostyrene (**13a**) was isolated in 40–65% from **14a** after 25 min.

This approach showed the advantage of using the aldehyde **15** over the trimethylarylammonium triflate **5** to synthesize **13a**.

Reaction of [^{18}F] fluorides **3a** *or* **4a** *with the allyl amine* **16E.** Regio- and stereo-selective palladium cross-coupling reactions of various electrophilic reagents with N,N-bis(trimethylsilyl)-[38] or N-BOC-[39] protected or unprotected[40] tributylstannylallyl amines have been reported. This prompted us to synthesize the amine **16E** as a model compound in the cross-coupling reaction of ^{18}F-labelled aryl halides with functionalized tributylvinylstannanes.

Among the different methods described to prepare vinyltrialkylstannanes,[41] three different approaches to the synthesis of the amine **16E** were studied (Scheme 3): addition of tributyltin hydride to the N-propargylamine **17** under radical conditions (path A),[42] or via a higher order cuprate (path B),[43] and alkylation of piperidine with a preformed vinyltin derivative **18E** (path C). A comparison of the results is presented in Table 2. The isomers **16E**, **16Z** and **16R** (regioisomer) were formed in the relative ratio 71:14:15. The high selectivity of the tributyltin hydride addition to bis(trimethylsilyl)prop-

argylamine,[38] was not observed here, probably because of the lack of steric hindrance. The results are in good agreement with the selectivity usually observed in radical additions. The tin derivative **16E** was isolated in 15% yield but attempts to obtain the pure stereoisomers **16Z** and **16R** failed. The reaction of the higher order cuprate (Bu$_3$Sn)(Bu)Cu(CN)Li$_2$ (path B, Scheme 3), under mild conditions, although not completely regioselective (**16E**:**16R** 91:9), afforded compound **16E** in 50–56% yield. To avoid the formation of the amine **17** which occurs in 46% yield by reaction of piperidine with propargyl bromide, the alkylation of piperidine was carried out using as the reagent the chloride **18**[44] as a mixture of **18E**, **18Z** and **18R** isomers. Indeed, when the alkylation was carried out in refluxing ethanol, the tributylstannylamine **16E** was the only product isolated in 35% yield after purification. No traces of the stereoisomer **16Z** and the regioisomer **16R** were detected in the NMR spectrum of the crude product (Table 2, entries 11–13).

The cross-coupling reactions of tributylstannylallylamines with aryl halides have been studied only with aryl bromides in the presence of Pd(PPh$_3$)$_4$.[38,40] These
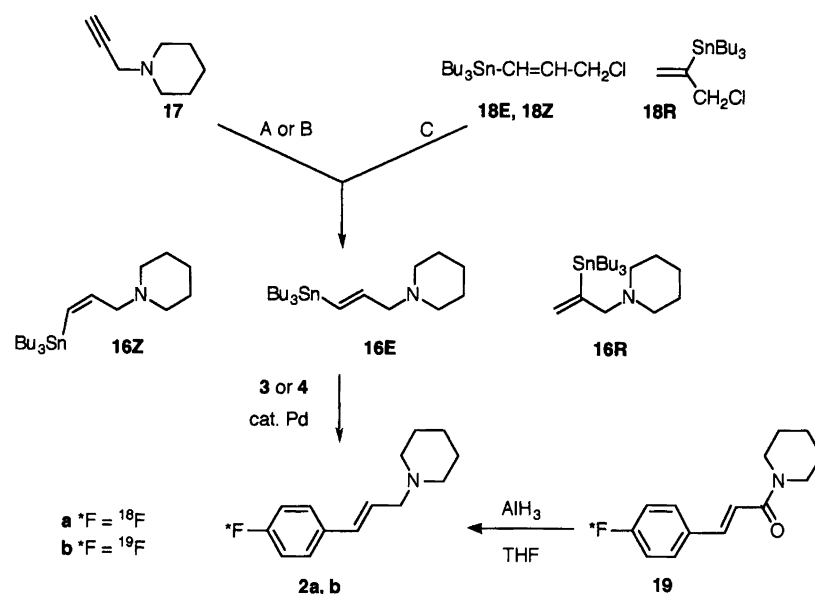
Scheme 3. Synthesis of fluorophenylallylamines **2a** and **2b**. A = Bu$_3$SnH, AIBN, reflux; B = (Bu$_3$Sn)(Bu)Cu(CN)Li$_2$, −78°C; C = piperidine, ethanol, reflux.

Table 2. Preparation of the tributylstannylamine **16E**. Comparison of the different methods (Scheme 3).

Entry	(Method) Reagents	Solvent	$t/°C$	T/h	Isomer ratio (%)[a]			Yield (%)[b] **16E**
					16E	**16Z**	**16R**	
9	(A) **17**, Bu$_3$SnH, AIBN	Toluene	110	4	71	14	15	15
10	(B) **17**, Bu$_3$Sn(Bu)Cu(CN)Li$_2$	THF	70	0.5	91	0	9	50–56
11	(C) piperidine, **18E**:**Z**:**R**^{s} (81:9:10)	EtOH	78	15	100	—	—	35
12	(C) piperidine, **18E**:**Z**:**R**^{s} (37:15:48)	EtOH	78	15	90	10	—	12
13	(C) piperidine, **18E**:**Z**:**R**^{s} (20:8:72)	EtOH	78	15	99	1	—	13

[a] Determined in the crude NMR spectra. [b] Isolated yield based on Bu$_3$SnCH=CHCH$_2$Cl.

Table 3. Formation of 4-[^{18}F]fluorophenylallylamine **2a** by cross-coupling reactions of [^{18}F]fluoride **3a** with the tributylstannyl-allylamine **16E**[a] in the presence of BnClPd(PPh$_3$)$_2$ and CuI.

Entry	Ratio BnPdCl(Ph$_3$P)$_2$: CuI[b]	Solvent	*t*/min	*T*/°C	Yield (%)[c,d]
14	5:7	DMF	20	80	54 (63)
15	5:7	HMPT	20	80	(64)
16	10:20	DMF	20	80	44
17	5:10	DMF	20	80	55
18	5:10	DMF, dioxane[e]	5	120	(80)
19	5:10	DMF, dioxane[e]	10	120	90

[a] Reactions were carried out in 1 ml of solvent with 10–14 μmol of substrate except entry 17 (24 μmol). [b] In % based on the substrate. [c] Isolated radiochemical yield corrected for decay and relative to [^{18}F]fluoride **3a**. [d] Values within parentheses refer to the ratio of compound **2a** in the crude reaction mixture and obtained from radioTLC. [e] Ratio 1:1.

reactions being relatively slow (reaction times >24 h) and the aryl iodides more reactive, we have studied the cross-coupling reaction of the stannyl amine **16E** with [^{18}F]fluoride **3a**. The results are summarized in Table 3. Using the conditions described [Pd(PPh$_3$)$_4$ in toluene, 15 or 30 min at 110 °C],[36] radioTLC (or ^{1}H NMR in stable isotope chemistry) of the crude reaction product did not show the formation of the amine **2a** (or **2b**). The catalysts which gave high yields in our previous experiments [Pd$_2$(dba)$_3$, AsPh$_3$, CuI] or in the reaction of electrophiles with *N*-BOC-protected allylamines [PdCl$_2$(PhCN)$_2$][39] gave no amine **2a** or poor yields. The best results were obtained using BnPdCl(Ph$_3$P)$_2$ (entry 19) in the presence of copper(I) iodide in a mixture DMF–dioxane at 120 °C. A measure of the yield as a function of time showed that, under these conditions (Table 3, entries 18 and 19) after 5 min and 10 min reaction times, the crude reaction mixture contained 80% and 90%, respectively, of amine **2a** with unchanged starting material. This percentage did not increased significantly with increasing reaction times (90% after 15 or 20 min) but about 10% of polar compounds were detected. Under the conditions described (entry 19) the labelled fluorophenylamine **2a** was isolated in 90% yield from **3a** (55 min).

The coupling reaction was also studied using the [^{18}F]fluoride **4a**. The stannylallylamine **16E** was heated for 5 min in a 1:1 mixture of DMF–dioxane at 120 °C

with the labelled bromide **4a** in the presence of BnPdCl(PPh$_3$)$_2$ and CuI (5:10 relative ratio in % from **16E**) yielded [^{18}F]fluorophenylallylpiperidine (**2a**) in 41% radiochemical yield. RadioTLC analysis showed that the reaction was not complete and that labelled polar compounds were formed. Although this coupling reaction was less efficient and the overall process more time demanding (Table 4), this route gave higher yields of amine **2a**.

The identity of the ^{18}F-labelled compounds was assessed by radioTLC (in two different eluents), by HPLC of products before and after addition of unlabelled reference substances and by the different synthetic approaches. Furthermore, amide **19** was prepared by independent synthesis.[45–47] The selective reduction of the amide function was achieved in 76% yield using alane (AlH$_3$) as the reducing agent.

In conclusion, we have shown that [^{18}F]fluoro-phenylalkenes, arenes and allylamines can be efficiently prepared by a palladium-promoted reaction of [^{18}F]fluorides **3a** or **4a** with vinyl (or aryl) stannanes in less than 150 min (Table 4). The success of reactions is strongly dependent on the catalyst, the best results being obtained with the fluoride **4a** and with the catalyst bearing ligands which are poor donors. 4-[^{18}F]Fluoro-bromobenzene **4a** can be prepared in moderate to good yields in a two-step procedure starting from 2-bromo-5-nitrobenzaldehyde.

Table 4. Radiochemical yields of ^{18}F-fluoro compounds and overall synthesis time from [^{18}F]KF.

^{18}F-Fluoroaromatic derivatives	Reagents[a]	RCY (%)[b]	Total synthesis time/min
Fluoroiodobenzene (**3a**)	[^{18}F]KF, **5**	10–12	45
Fluorobromobenzaldehyde (**6a**)	[^{18}F]KF, **7**	60–80	50
Fluorobromobenzene (**4a**)	**6a**	24–48	95
Fluorobiphenyl (**10a**)	**3a, 8**	5–6.5	95
Fluorobiphenyl (**10a**)	**3a, 9**	8.5–10	80
Fluorostyrene (**13a**)	**3a, 12**	4–6	75
Fluoro-5-vinylbenzaldehyde (**14a**)	[^{18}F]KF, **15**	24–30	45
Fluorostyrene (**13a**)	**14a, 12**	9.5–19.5	85
Fluorophenylallylamine (**2a**)	**3a, 16E**	9	100
Fluorophenylallylamine (**2a**)	**4a, 16E**	24	140

[a] Reagents used in the final (or single) step of the synthesis. [b] Radiochemical yields, counted from [^{18}F]KF and corrected for decay, of the ^{18}F-compounds isolated by HPLC.

Experimental

General. Palladium acetate, tetrakis(triphenylphosphine)-palladium, tris(dibenzylideneacetone)dipalladium(0), benzylchlorobis(triphenylphosphine)palladium(II), tri-phenylphosphine, tris(triphenylphosphine)rhodium chloride, triphenylarsine, copper(I) cyanide, tetraphenyl-tin, *N,N*-dimethylacetamide (DMAc), Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexa-cosane), 4-fluorocinnamic acid and 2-fluoro-5-bromo-benzaldehyde (6b) were purchased from Aldrich or Acros and were used as received. Phenylmagnesium bromide,[48] vinylmagnesium bromide,[49] bis(triphenylphosphine)phen-ylpalladium iodide,[21] CuI,[50] 4-fluorobiphenyl (10b),[33] and 4-iodophenyltrimethylammonium triflate (5)[23] were prepared according to described procedures. 5-Bromo-2-nitrobenzaldehyde (7) was prepared in 72% yield by nitration of 3-bromobenzaldehyde using sulfuric acid–potassium nitrate.[51] 2-(Tributylstannyl)-3-chloro-1-propene (18) was synthesized in 75% yield by reaction of 3-(tributylstannyl)-2-propenol[52] with thionyl chloride. The compounds 7 and 18 were characterized by compar-ison of their spectral properties with those previously described (Refs. 53 and 44, respectively).

The solvents were freshly distilled under nitrogen prior to use: light petroleum (b.p. 45–55 °C), 1,4-dioxane from sodium, *N,N*-dimethylformamide (DMF) and aceto-nitrile from calcium hydride, tetrahydrofuran (THF) from sodium benzophenone ketyl. All reactions were run under a nitrogen atmosphere.

Melting points were recorded on an Reichert micro-scope and are uncorrected. ^{1}H and ^{13}C NMR spectra of samples in deuteriochloroform were run on a Bruker AC instrument (250 MHz and 62.89 MHz, respectively) using tetramethylsilane (TMS) as an internal standard. The chemical shifts are recorded in parts per million (ppm) from TMS. ^{19}F and ^{119}Sn NMR spectra were obtained on a Bruker WP 80 SY3 instrument (75.4 MHz and 29.88 MHz, respectively) using CFCl$_3$ and (CH$_3$)$_4$Sn as internal references. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), and m (multiplet). IR spectra were recorded on a spectrophotometer Perkin–Elmer 684. Mass spectra were obtained on a Nermag R10 (electron impact, ionizing voltage 70 eV). High resolution mass spectra were recorded on a Jeol AX 500 instrument. Liquid chromatography was performed on 70–230 mesh silica gel 60 (Merck) column. The Sep-Paks were purchased from Millipore Waters. The C-18 cartridges were washed with methanol (5 ml), then water (5 ml) prior to use. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F$_{254}$ analytical plates. TLC conditions were varied and are specified individually, with R_f values, for each compound below. A Berthold LB 284/285 instrument was used to detect the radioactive spots. High performance liquid chromato-graphy (HPLC) was performed on a Waters system equipped with an injector U6K and a multiple wave-length UV detector (M490, λ=254 nm) connected in series with a radioactivity detector (Kipp & Zonen). A µ-Porasil column (10 µm, 6.2 × 300 mm; 'column A') and a C-18 µ-Bondapak column (10 µm, 7.8 × 300 mm; 'column B') were used for preparative conditions. Gas chromatographic analyses were performed on a Delsi instrument equipped with a 4 m column of 5% DC 550 on Chromosorb WAW, a thermal conductivity detector using He as carrier gas (flow rate 2 ml min^{-1}). GLC yields were determined using a calibration curve. Radioactive and mass peaks were measured using a recording integrator. Radiochemical yields were deter-mined with a dose calibrator (Capintec 12 and CRC 15R) and were corrected for decay to the end of bom-bardment (EOB).

Preparation of [^{18}F]potassium fluoride–Kryptofix 222. No-carrier-added aqueous [^{18}F]fluoride was produced by the cyclotron (CGR MeV 325) at the PET centre of Caen (Cyceron) via the ^{18}O[p,n]^{18}F nuclear reaction using a 1 ml enriched water (90–98%) target. The target material was passed through an AG1-X8 (Bio-Rad) anion exchange resin (chloride form, 100–200 mesh) and recovered as [^{18}F]KF by elution with water (1 ml) then aqueous potassium carbonate (0.5 ml, 0.005 g ml^{-1}) into a conical glass reaction vessel. To this solution, potassium carbonate (0.0050 g, 0.036 mmol) and Kryptofix 222 (0.022 g, 0.052 mmol) were added. The water was removed azeotropically with acetonitrile (3 × 0.3 ml) at 110 °C under a stream of nitrogen.

4-[^{18}F]Fluoroiodobenzene (3a).[23] To the dry complex [^{18}F]KF–Kryptofix 222, 4-iodophenyltrimethyl-ammonium triflate (5) (0.092 g, 22 µmol) in DMAc (0.5 ml) was added. The mixture was heated at 145 °C for 15 min (or 50 s in a microwave oven). The reaction was cooled, after which water (2 ml) was added and the reaction mixture passed through a C-18 Sep-Pak. Polar materials were eluted with water (2 ml) and [^{18}F]fluoride 3a with pentane (5 ml). This organic layer was then dried by passage through a neutral alumina Sep-Pak [pre-washed with pentane (5 ml)]. The volatile com-pounds were evaporated off and [^{18}F]fluoride 3a was obtained in 10–12% radiochemical yield in 45 min. 3a was identified by co-elution with an authentic sample both in radioTLC (silica plate, eluent: heptane, R_f= 0.76) and HPLC (column: A, mobile phase heptane, flow: 2 ml min^{-1}; t_R = 5 min.).

2-[^{18}F]Fluoro-5-bromobenzaldehyde (6a). The aldehyde 7 (0.012 g, 52 µmol) in DMSO (1 ml) was added to dry [^{18}F]KF–Kryptofix 222 and the mixture was heated at 150 °C for 20 min in a sealed vial and then cooled. Water was added (2 ml) and the solution passed through a C-18 Sep-Pak. The cartridge was rinsed with water (2 ml) and the title compound 6a was eluted with pentane (10 ml) and dried (MgSO$_4$–K$_2$CO$_3$ column). Yield 60–80%, 50 min from [^{18}F]KF, R_f=0.85 (heptane–AcOEt: 1:1).

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4-[¹⁸F]Fluorobromobenzene (**4a**). A mixture of the [¹⁸F]fluoride (**6a**) and 1,4-dioxane (1 ml) was purged with nitrogen and tris(triphenylphosphine)rhodium chloride (0.012 g, 13 μmol) was added. The reaction was then heated at 150 °C for 15 min. After being cooled, the crude mixture was passed through a silica gel column, prewashed with pentane (2 ml) and the title compound **4a** was eluted with pentane (5 ml). HPLC: column A, heptane–AcOEt 97:3, flow rate 1.5 ml min⁻¹, t_R = 10 min. Yield: 40–66% (45 min from **6a**). R_f = 0.70 (heptane).

4-[¹⁸F]Fluorobiphenyl (**10a**). 4-[¹⁸F]Fluoroiodobenzene (**3a**) in solvent (1 ml) was purged with nitrogen. The palladium catalyst (0.07–8.86 μmol) was added and the resulting mixture stirred at ambient temperature for 5 min. Phenylmagnesium bromide (**8**) (460–960 μmol; 0.66 M in THF) or tetraphenyltin (**9**) (10 μmol) was then added and the mixture heated for 5 min.

In the experiments using the Grignard reagent **8**, after reaction, hexane (2 ml) was added and the reaction mixture was filtered. The organic layer was analyzed by radioTLC **10a**: R_f = 0.35 (heptane) and HLPC: column A, mobile phase: heptane, t_R = 6 min. Yields: see Table 1; synthesis time: 50 min counted from **3a**.

In the experiments using tetraphenyltin (**9**), the crude mixture was diluted, after reaction, with water (2 ml) and passed through a C-18 Sep-Pak. The cartridge was washed with water (2 ml) and 4-[¹⁸F]fluorobiphenyl (**10a**) was eluted with THF (5 ml). Yields: see Table 1, synthesis time: 35 min counted from **3a**.

4-Fluorostyrene (**13b**). To a solution of **3b** (1 ml) in dry DMF (2 ml), Pd₂(dba)₃ (0.0183 g, 0.020 mmol) and triphenylarsine (0.005 g, 0.26 mmol) were added. The mixture was stirred for 10 min at ambient temperature then heated at 60 °C before adding tributyl(vinyl)stannane (**12**) (0.365 g, 0.336 ml, 1.15 mmol). The mixture was stirred at 60 °C for 16 h and then cooled, and water (50 ml) and light petroleum (20 ml) were added. After phase separation, the organic layer was washed with water (3 × 20 ml), then dried (MgSO₄). The title compound **13b** was formed in 38% yield, determined by GC (column: 200 °C); R_f = 0.8 heptane–ethyl acetate (98:2). **13b** was identified by comparison of its spectral characteristics with those of a commercial sample (Aldrich).

4-[¹⁸F]Fluorostyrene (**13a**) *from 4-[¹⁸F]fluoroiodobenzene* (**3a**). 4-[¹⁸F]Fluoride **3a** in the solvent (1 ml) was transferred to a vessel which had previously been purged with nitrogen gas for 5–10 min. The palladium catalyst (0.28 μmol) was then added, and in some experiments (Table 1) also the ligand (2.24 μmol) and copper(I) iodide (1.12 μmol). After addition of vinylmagnesium bromide (**11**) (0.60–0.96 mmol) or tributyl(vinyl)stannane (**12**) (14 μmol) the mixture was heated for 5–30 min (see Table 1 for the times and temperatures). After being cooled, the crude mixture was diluted with

water (2 ml) and passed through a C-18 Sep-Pak. The Sep-Pak was washed with water (2 ml). 4-[¹⁸F]Fluorostyrene (**13a**) eluted with CH₃CN (5 ml) and was purified on an alumina Sep-Pak. Yields: see Table 1; synthesis time: 45 min from **3a**; R_f = 0.67 (heptane); HPLC: column B mobile phase CH₃CN–H₂O (1:1), flow rate 2.4 ml min⁻¹, t_R = 19 min.

2-Nitro-5-vinylbenzaldehyde (**15**). The stannane **12** (1.41 g, 1.3 ml, 4.4 mmol) was added to a mixture of 5-bromo-2-nitrobenzaldehyde (**7**) (0.924 g, 4 mmol), triphenylarsine (0.195 g, 0.64 mmol), dry DMF (5 ml), Pd₂(dba)₃ (0.072 g, 0.08 mmol) and copper(I) iodide (0.061 g, 0.23 mmol) at 60 °C. After 24 h at this temperature the mixture was cooled, and pyridine (2.2 ml, 27 mmol) followed by pyridinium fluoride (2.5 ml, 1.4 M solution in THF, 3.5 mmol) were added and allowed to react at ambient temperature for 20 h. A precipitate was formed. After filtration, the filtrate was diluted with diethyl ether (100 ml), and washed successively with aqueous ammonia (20%, 2 × 20 ml), HCl (10%, 2 × 50 ml), water (2 × 50 ml) and sodium hydrogencarbonate. The dried solution (MgSO₄) was evaporated and the title compound **15** was purified by flash chromatography on silica eluting with heptane–ethyl acetate (98:2). Yield 0.346 g (49%) of an oily substance. The spectral data are identical with those previously reported.⁵⁵

2-Fluoro-5-vinylbenzaldehyde (**14b**). Triphenylarsine (0.195 g, 0.64 mmol) in DMF (2.5 ml) then Pd₂(dba)₃ (0.073 g, 0.08 mmol) in DMF (4 ml) and copper(I) iodide (0.061 g, 0.32 mmol) were successively added to a solution of 5-bromo-2-fluorobenzaldehyde (**6b**) (0.812 g, 4.00 mmol) in DMF (5 ml). The mixture was stirred and heated to 60 °C before tributyl(vinyl)stannane (1.3 ml, 4.4 mmol) was added. After 24 h at 60 °C the reaction was cooled, and pyridine (2.2 ml, 27 mmol) and pyridinium fluoride in THF (1.4 M, 2.5 ml, 3.5 mmol) were added. The precipitate was filtered off and the filtrate diluted with ether (100 ml). Aqueous ammonia (20%, 2 × 20 ml) was added and after phase separation the organic layer was washed with water, HCl (10%, 2 × 50 ml), water and brine. The dried solution (MgSO₄) was evaporated and the residue was purified on silica gel. The title compound **14b** was eluted with heptane–ethyl acetate (98:2). Yield: 0.211 g (35%) of an oily substance, R_f = 0.6 heptane–ethyl acetate (9:1). ¹H NMR (CDCl₃): δ 7.14 (1 H, d, *J* 15.9 Hz), 7.40 (2 H, m), 7.61 (2 H, m), 7.7 (1 H, m), 10.2 (1 H, s, CHO). ¹³C NMR (CDCl₃): δ 125.6, 126.8, 129.1, 130.5, 135.0, 139.9, 143.3, 163.5 (d, *C* 2, ¹J_{C-F} 258 Hz), 189.7 (CHO).¹⁹F NMR (CDCl₃): δ −122.3. IR (KBr): 3096 (w) 2976 (m) 2870 (m) 1702 (s) 1602 (s) 1474 (s) 1392 (s) cm⁻¹.

2-[¹⁸F]Fluoro-5-vinylbenzaldehyde (**14a**). To the dry complex [¹⁸F]KF–Kryptofix 222, 2-nitro-5-vinylbenzaldehyde (11 mg, 62 μmol) in DMSO (1 ml) was added. The

mixture was stirred at 150 °C for 15 min and then cooled. Water was added (2 ml) and the crude product was passed through a C-18 Sep-Pak cartridge. Polar materials were eluted with water (2 ml) then the title compound **14a** with pentane (5 ml). Yield $27 \pm 3\%$. $R_f = 0.78$ (heptane–ethyl acetate 1 : 1).

4-[^{18}F]Fluorostyrene (**13a**) *from 2-[^{18}F]fluoro-5-vinylbenzaldehyde* (**14a**). A mixture of the aldehyde **14a**, and benzonitrile (1 ml) was purged with nitrogen. Tris(triphenylphosphine)rhodium chloride (0.012 g, 13 µmol) was added and the mixture was heated in a microwave oven for 2 min. After being cooled, the crude mixture was passed through a silica gel column, prewashed with pentane (2 ml), and the title compound **13a** was eluted with pentane (5 ml). Yield $52 \pm 13\%$ from **14a**.

N-(2-Propynyl)piperidine (**17**). Piperidine (17.03 g, 19.8 ml, 200 mmol), and 3-bromo-1-propyne (24 g, 18 ml, 200 mmol) in dry triethylamine (61.1 ml, 440 mmol) were stirred at room temperature for 20 h. After addition of diethyl ether (70 ml), the reaction mixture was acidified (HCl 10%, 50 ml). After phase separation, the aqueous layer was made basic (NaOH 2 M, 30 ml) and extracted with diethyl ether (3 × 50 ml). The organic layer was dried (MgSO$_4$) and distillation gave the title compound **17**.[56] Yield 11.4 g (46%), b.p. 55 °C/2 mbar; oily substance. $R_f = 0.4$ pentane–diethyl ether (3:2).^{1}H NMR (CDCl$_3$): δ 1.29–1.35 (2 H, m, H-4), 1.45–1.54 (4 H, m, H-3, H-5), 2.12 (1 H, t, J 2.5 Hz, HC≡), 2.36–2.4 (4 H, m, H-2, H-6), 3.16 (2 H, d, J 2.5 Hz, H$_2$CC≡). IR (NaCl): 3300 (m), 2936 (s), 2754 (w), 1110 (s) cm^{-1}. MS [m/z (% rel. int.)] 123 (28, M) 122 (81) 94 (26) 81 (45) 55 (37) 39 (100). Mol. wt., obs. 123.1046. Calc. for C$_8$H$_{13}$N: 123.1048.

N-[3-(Tributylstannyl)-2-propenyl]piperidine (**16**). *Method A.* Tributylstannane (1.2 ml, 1.29 g, 4.4 mmol) was added to a mixture of N-(2-propynyl)piperidine (0.23 g, 1.86 mmol), toluene (10 ml) and AIBN [2,2′-azo(2-methylpropionitrile)] (0.064 g, 0.39 mmol). The mixture was heated at 110 °C for 4 h and cooled. The volatile compounds were evaporated off and analysis of the residue by ^{1}H NMR spectroscopy showed the formation of a mixture of the isomers **16E**, **16Z** and **16R** (ratio 71:14:13). This mixture (yield 31%) was purified by flash chromatrography on silica gel eluting with light petroleum–ethyl acetate (1: 4). The isomer **16R** and **16Z**, eluted in the two first fractions, could not be obtained pure. The title compound **16E** was obtained in the third fraction. **16E**: Yield 0.12 g (15%) of an oily product, $R_f = 0.45$ light petroleum–ether (1:4). ^{1}H NMR (CDCl$_3$): δ 0.77–0.87 (11 H, m), 1.18–1.54 (22 H, m), 2.3 (4 H, m, CH$_2$), 2.94 (2 H, m), 6.00 and 6.02 (2 H, CH=CH, J_{AB} 18.5 Hz). ^{13}C NMR (CDCl$_3$): δ 9.5 (3 CH$_3$), 13.6 (3 CH$_2$), 24.4, 26.0, 27.3, 29.3, 54.5 (2 C, NCH$_2$CH$_2$), 66.4 (NCH$_2$CH=), 131.7 (CH=CH), 145.7 (CH=CH). ^{119}Sn NMR [(CH$_3$)$_4$Sn]: δ −50.15. MS [m/z

(% rel. int.)]: 415 (0.6, M) 414 (0.8) 358 (76, [$M − C_4H_9$]), 302 (3, [$M − 2 \times C_4H_9$]) 244 (5, [$M − 3 \times C_4H_9$]) 177 (16) 124 (57, [$M − C_{12}H_{27}$Sn]) 98 (100). Mol. wt., obs. 415.2273. Calc. for C$_{20}$H$_{41}$NSn: 415.2261.

Method B. To a stirred mixture of copper(I) cyanide (0.38 g, 4.3 mmol) and dry THF (3 ml) cooled to −78 °C, butyllithium in THF (6 ml, 1.6 M, 9.6 mmol) was added dropwise. After the addition, the cooling bath was removed and the mixture stirred at ambient temperature for 15 min. Tributylstannane (2.3 ml, 2.49 g, 8.57 mmol) was added at −78 °C and the reaction mixture stirred at this temperature for 30 min. N-(2-Propyn-1-yl)piperidine (**17**) (0.38 g, 3 mmol) in THF (1 ml) was then added. After being stirred for 30 min at −78 °C, the reaction mixture was treated with aq. NH$_4$Cl–NH$_4$OH (9:1, 20 ml) and extracted with diethyl ether (3 × 30 ml). The organic layers were combined and dried (MgSO$_4$) and the solvents evaporated off. ^{1}H NMR analysis of the crude product showed the formation of a mixture of the isomers **16E** and **16R** (ratio 91:9). Chromatography on silica gel using ether–light petroleum (1 :4) yielded the pure title compound **16E**. Yield 0.72 g (56%).

Method C. A mixture of the chloro(tributylstannyl)-propenes **18E**, **18Z**, **18R** (ratio 81:9:10; 0.472 g, 1.3 mmol), piperidine (0.254 ml, 0.218 g, 2.6 mmol) and ethanol (3 ml) was heated under reflux for 17 h and then cooled. Diethyl ether (10 ml) was added and the organic phase washed with aqueous sodium hydroxide (2.5 M, 2 × 10 ml). After evaporation of the volatile compounds, the crude product (0.54 g) was purified by chromatography on silica using light petroleum–ethyl acetate (3:1). Only the E isomer was isolated pure. Yield 0.181 g (34%).

1-Piperidin-1-yl-3-(4-fluorophenyl)-2-propenone (**19**). To a solution of 4-fluorocinnamic acid (1.125 g, 6.5 mmol) in dry acetonitrile (10 ml), cooled to 0 °C, triethylamine (0.6 g, 0.91 ml, 6.5 mmol) was added dropwise and the mixture was stirred for 30 min. Ethyl chloroformate (0.70 g, 0.62 ml, 6.5 mmol) was then added, then after 35 min, piperidine (0.56 g, 0.65 ml, 6.5 mmol) in dry acetonitrile (8 ml) was added. The mixture was refluxed for 2 h then cooled to room temperature. The volatile compounds were evaporated off, and water (15 ml) and diethyl ether (20 ml) were added. After extraction with diethyl ether (2 × 20 ml) the organic phase was washed with brine (3 × 20 ml) dried (MgSO$_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography and the title compound **19** was eluted with light petroleum–ethyl acetate (3:1). Yield 1.12 g (74%), m.p. 136 °C (lit.[45] 136–138 °C). $R_f = 0.2$ light petroleum–ethyl acetate (3:1). ^{1}H NMR (CDCl$_3$): δ 1.48–1.61 (6 H, m), 3.54 (4 H, m), 6.76 (1 H, d, J 15.4 Hz, HC=), 6.97 (2 H Ar, t, J 8.6 Hz), 7.43 (2 H Ar, dd, J 8.6, 5.4 Hz), 7.54 (1 H, d, J 15.4 Hz, HC=). ^{13}C NMR

(CDCl$_3$): δ 24.7, 25.7, 26.9, 43.5, 47.1, 115.7, 116.1, 117.6, 129.6, 131.8, 141.0, 163.4 (d, $^1J_{C-F}$ 238 Hz), 165.4. IR (KBr): 2936 (m), 1646 (s), 1596 (s), 1584 (s), 1510 (s), 1454 (s), 1442 (s), 122 (s), 1162 (s), 1018 (s), 992 (s) 832 (s) cm^{-1}. MS [m/z (% rel. int.)] : 233 (100, M) 149 (98) 138 (35) 121 (37) 112 (25) 101 (28) 96 (12) 84 (10). Mol. wt., obs. 233.1215. Calc. for C$_{14}$H$_{16}$FNO: 233.1216

(E)-N-*[3-(4-Fluorophenyl)prop-2-enyl]piperidine* (**2b**). A suspension of LiAlH$_4$ (0.141 g, 3.71 mmol) and AlCl$_3$ (0.165 g, 1.24 mmol) in dry diethyl ether (5 ml) was stirred for 1 h at ambient temperature after which the amide **19** (0.396 g, 1.7 mmol) in dry diethyl ether (25 ml) was added dropwise. The organic layer was washed with water then brine. The dried (MgSO$_4$) solution was evaporated and the residue was purified by chromatography on silica gel using dichloromethane–methanol (9:1). Yield 0.29 g (76%), white solid, m.p. 208 °C. Anal. C$_{14}$H$_{18}$FN: C, H, N. R_f = 0.4 dichloromethane–methanol (9:1).^{1}H NMR (CDCl$_3$): δ 1.52 (2 H, m, CH$_2$), 1.70–1.79 (4 H, m, CH$_2$), 2.64 (4 H, m, CH$_2$), 3.29 (2 H, d, J 6.8 Hz, N-CH$_2$C=), 6.27 (H-2, dt, J 15.9, 6.8 Hz), 6.53 (H-3, d, J 15.9 Hz), 6.98 (2 H Ar, d, J 8.7 Hz), 7.23 (2 H Ar, dt, J 8.7, 5.6 Hz).^{13}C NMR (CDCl$_3$): δ 22.6, 23.5, 53.3, 60.2, 115.6, 116.0, 119.5, 128.6, 128.7, 131.5, 137.1, 163.0 (d, $^1J_{C-F}$ 248.6 Hz). IR: 2934 (m), 1600 (m), 1508 (s), 1456 (m), 1228 (s), 982 (m), 816 (m) cm^{-1}. MS [m/z (% rel. int.)]: 219 (100, M) 201 (10) 135 (25) 110 (29) 83 (11). Mol. wt., obs. 219.1415. Calc. for C$_{14}$H$_{18}$FN: 219.1423

(E)-1-(4-[^{18}F]Fluorophenyl)-3-piperidylpropene (**2a**) from 4-[^{18}F]Fluorobromobenzene (**4a**). 4-[^{18}F]Fluoride **4a** in DMF (0.5 ml), 1,4-dioxane (0.5 ml) and BnPdCl(Ph$_3$P)$_2$ (450 µg, 0.6 µmol) were stirred at ambient temperature for 5 min. The stannyl amine **16E** (0.005 g, 12 µmol) and CuI (230 µg, 1.2 µmol) were added and the resulting mixture was heated at 180 °C for 10 min. After being cooled, the crude product was passed through a silica gel Sep-Pak (pre-washed with dichloromethane). **2a** was eluted with dichloromethane (5 ml) and purified by HPLC: column A, mobile phase CH$_2$Cl$_2$–MeOH (9:1), flow rate 3 ml min^{-1}, t_R = 19 min. Yield 41%, 45 min from **4a** or 24%.

(E)-1-(4-[^{18}F]Fluorophenyl)-3-piperidylpropene (**2a**) from 4-[^{18}F]fluoroiodobenzene (**3a**). To a solution of 4-[^{18}F]fluoride **3a** in the solvent (1 ml), the palladium catalyst (0.65–2.12 µmol) was added. The mixture was stirred for 5 min at ambient temperature before copper(I) iodide (0.91–2.4 µmol, Table 3) was added. Finally, the tin derivative **16E** was added. After being heated for 5–30 min, the crude reaction mixture was passed through a silica Sep-Pak, pre-conditioned with CH$_2$Cl$_2$ (2 ml). The compound eluted with CH$_2$Cl$_2$ (5 ml) was identified by radioTLC: R_f = 0.27 CH$_2$Cl$_2$–MeOH (9:1) and

HPLC: µ-Porasil, eluent: CH$_2$Cl$_2$–MeOH (9:1), 3 ml min^{-1}, t_R = 20 min. Yields: see Table 3.

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