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Nucleophilic Fluorination and Radiofluorination via Aziridinium Intermediates: N-Substituent Influence, Unexpected Regioselectivity, and Differences between Fluorine-19 and Fluorine-18

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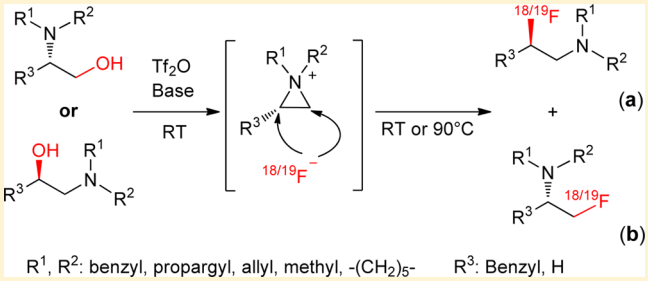
Supporting Information

ABSTRACT: The efficient dehydrofluorination and radiofluorination of *N*,*N*-disubstituted-*β*-aminoalcohols through an anchimeric-assisted mechanism was developed. An investigation into the influence of N-substituents on the ring opening of the aziridinium intermediate indicated differences in the isomeric ratio and the yields of fluorinated products obtained from *N*,*N*-disubstituted-phenylalaninol. This influence was substantial for ^{18}F-radiofluorination, with yields varying from 0 to 71% at room temperature (RT). Although no significant effects were observed in the fluorine-19 chemistry when the reaction was heated to 90 °C, considerable changes appeared during radiofluorination. In the latter case, the radiochemical yields increased, and degradation of the 2-fluoro-propan-1-amine isomer (**b**) occurred, leading to a regiospecific reaction in the radiolabeling of [^{18}F]-fluorodeprenyl. This method involving nucleophilic radiofluorination at RT was successfully applied to the radiolabeling of [^{18}F]-2-fluoroethylamines in which the influence of the N-substituent was also observed.



INTRODUCTION

Positron emission tomography (PET) is a powerful *in vivo* imaging technique used for diagnostic and prognostic purposes and therapy monitoring and as a research tool in various clinical fields.[1−3] Fluorine-18 remains the major positron emitting isotope for the development of radiopharmaceuticals due to its physical properties. The low positron energy emission associated with the decay profile (97% β^+ emission) yields the most favorable properties for PET imaging, which results in accurate absolute quantification and high-resolution images, especially for preclinical dedicated cameras.[4] Its radioactive decay of 109.7 min allows for the distribution of radiopharmaceuticals in nuclear medicine departments, which has resulted in the considerable development of this functional molecular imaging technique. The extensive use of PET has generated a demand for new radiofluorinated tracers, resulting in new challenges for ^{18}F-radiochemistry and leading to the development of new methods.[5]

Important criteria for the radiopharmaceutical production efficiency are a high radiochemical yield (RCY), rapid reaction and processes, simplicity in the automation of the process, and the highest possible specific activity.[6] To satisfy these criteria, radiolabeling should typically occur as late as possible during radiosynthesis to obtain the final radiolabeled compound within a minimum number of steps. Moreover, radiofluorination at RT can be beneficial for the development of radiopharmaceutical kits and the radiolabeling of fragile structures. Radiofluorination typically occurs via nucleophilic substitution because fluoride-18 can be produced in larger quantities than [^{18}F]F_2, which is obtained with a low specific radioactivity.[6] Except for enzymatic fluorination, only a few examples of nucleophilic radiofluorination at RT have been reported.[7−11] Therefore, aliphatic nucleophilic incorporation of fluoride-18 is typically performed at elevated temperatures using sulfonates or halides as leaving groups.[12] When an *O*- or *N*-2-[^{18}F]-fluoroethyl moiety could not be directly labeled from the corresponding precursor, [^{18}F]-fluoroethylhalides or sulfonates have been extensively used, resulting in multistep radiolabeling.[13] This approach requires the preparation of a ^{18}F-fluoroethylating agent and involves its eventual purification followed by an alkylation reaction. Only a few *β*-[^{18}F]-fluoroamines have been labeled using aziridine ring opening but in low radiochemical yields.[14,15] More recent studies obtained superior yields using aziridine activated by *N*-benzoyl, *N*-benzyloxycarbonyl,[16,17] or *N*-phenylsulfonyl substituents.[18,19] The ring opening of aziridine leads to a secondary or primary amine and requires a high temperature for radiofluorination to occur, except for the case of phenylsulfonamides, in which a temperature of 50 °C is sufficient to achieve radiolabeling.[19]

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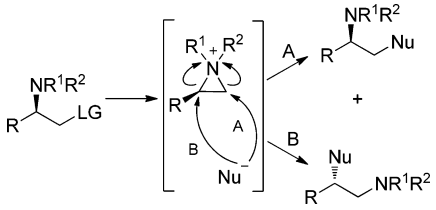
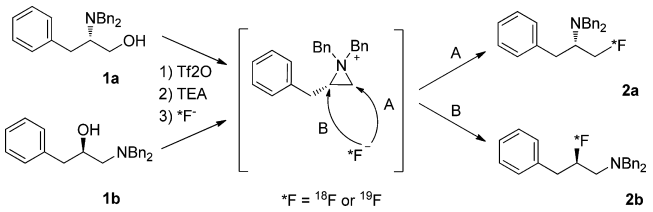
Recently, we reported a new labeling method for β-[^{18}F]-fluoroamines through the S_N2 ring opening of aziridinium by [^{18}F]-fluoride (Scheme 1) developed on a model compound

Scheme 1. Substitution Reaction via an Aziridinium Intermediate



(i.e., *N*,*N*-dibenzylphenylalaninol (**1a**)).[20] The anchimeric-assisted mechanism involving aziridinium ring formation yielded two fluoroamine isomers **2a** and **2b** (Scheme 2).[21,22]

Scheme 2. Fluorination of 1a and 1b



The reaction performed with isomeric alcohol precursor **1b** afforded the same mixture of isomers **2** as that obtained starting from **1a** with similar yields, reinforcing the presence of an aziridinium intermediate. Radiolabeling at RT led to [^{18}F]**2a** and [^{18}F]**2b** in 56−58% radiochemical yield (RCY) from [^{18}F]-fluoride incorporation as a K[^{18}F]F/$K_{2.2.2}$ complex or as [^{18}F]TBAF ([^{18}F]-tetrabutylammonium fluoride). Nucleophilic S_N2 radiofluorination with the formation of a carbon−fluorine bond at RT in one step can be considered significant progress in the development of radiopharmaceuticals.

In this study, we report the examination of the influence of N-substituents on the reactivity and selectivity of the anchimeric-assisted radiofluorination of phenylalaninols, the differences observed between radioactive and nonradioactive fluorination, and the unexpected regioselectivity observed during some radiofluorinations.

RESULTS AND DISCUSSION

To study and compare the influence of the amine substituents on the reactivity of aziridinium, different analogues of *N*,*N*-dibenzylphenylalaninol (**1a**) (Scheme 3) were prepared by N-alkylation from phenylalaninol **3a**. *N*,*N*-diallyl (**4**) and *N*,*N*-dipropargylphenylalaninol (**5a**) were prepared by reaction with allyl and propargyl bromide, respectively. An Eschweiler−Clarke reaction using the noncomplete dialkylation reaction intermediate (**6a**) afforded precursor **7a**[20] for the radiolabeling of [^{18}F]-fluorodeprenyl (**8a**), which is a radiopharmaceutical used to image monoamine oxidase B (MAO-B).[23] Starting from **3a** or *N*-monobenzylphenylalaninol **9a**, the same methylating method yielded **10** and **11**, respectively. Piperidinyl derivative **12** was obtained by the reaction of **3a** with diiodopentane under reflux.

The conditions previously described for the fluorination of **1a** in 64% yield were directly applied to the substrates without any optimization (Table 1). Briefly, the hydroxyl substrate was reacted at RT for 1 h with triflic anhydride (1.1 equiv), and then, diisopropylethylamine (DIPEA, 1.2 equiv) was added followed by the addition of 2 equiv of TBAF in solution in THF for 2 h. At RT, fluorination of **5a** (Table 1, entry 7) was as efficient as that observed for **1a**, and the reaction yield was higher (77%) with diallyl-substituted compound **4** (Table 1, entry 3). The piperidinyl derivative afforded a slightly lower yield (Table 1, entry 5) compared with **1a**. The presence of one methyl substituent rather than a second benzyl or propargyl group afforded higher fluorination yields (Table 1, entries 9 and 11), especially for compound **11** compared with **1a** (Table 1, entries 1). Different ratios were also observed in favor of isomer **a** from 34:66 to 48:52 for **5a** and **7a**, respectively, compared with 39:61 for **1a** (Table 1, entries 7, 9, and 1). This result may be due to the stronger electrodonating effect of the methyl substituent, which is reflected by the increased pK_b of **11** (7.9 instead 6.9 for **1a**, calculated using ACD/Laboratories Software V11.02). By heating the reaction to 90 °C, the fluorination yield increased (Table 1, entries 2, 4, and 8) to 88% for **13**. However, this yield decreased slightly for **14** and **8** without affecting the isomer ratio. Except for the piperidine compound, no effect of the temperature on the isomer ratio was observed, demonstrat-

Scheme 3. Synthesis of *N*,*N*-Disubstituted Phenylalaninol Substrates

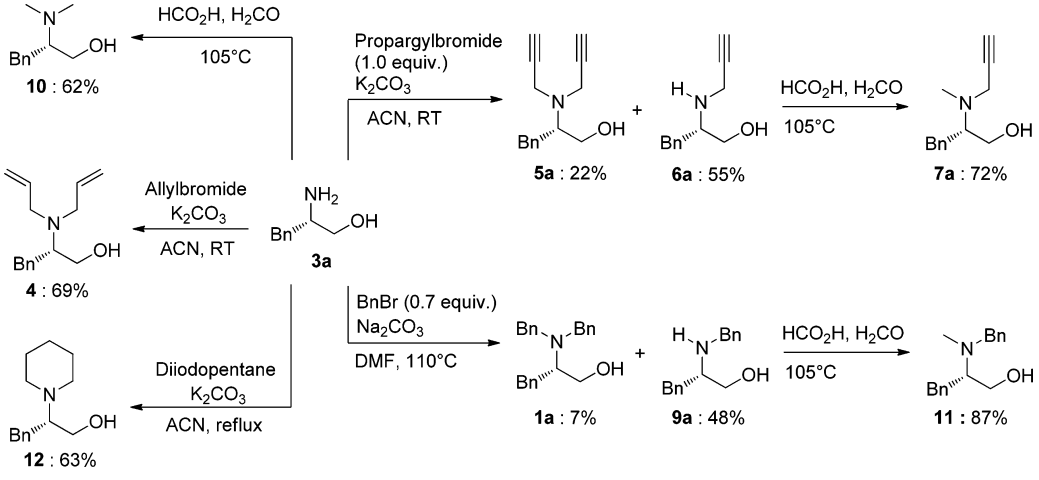


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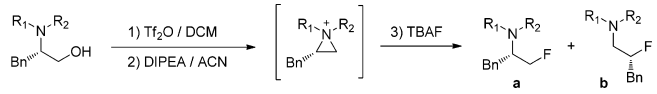
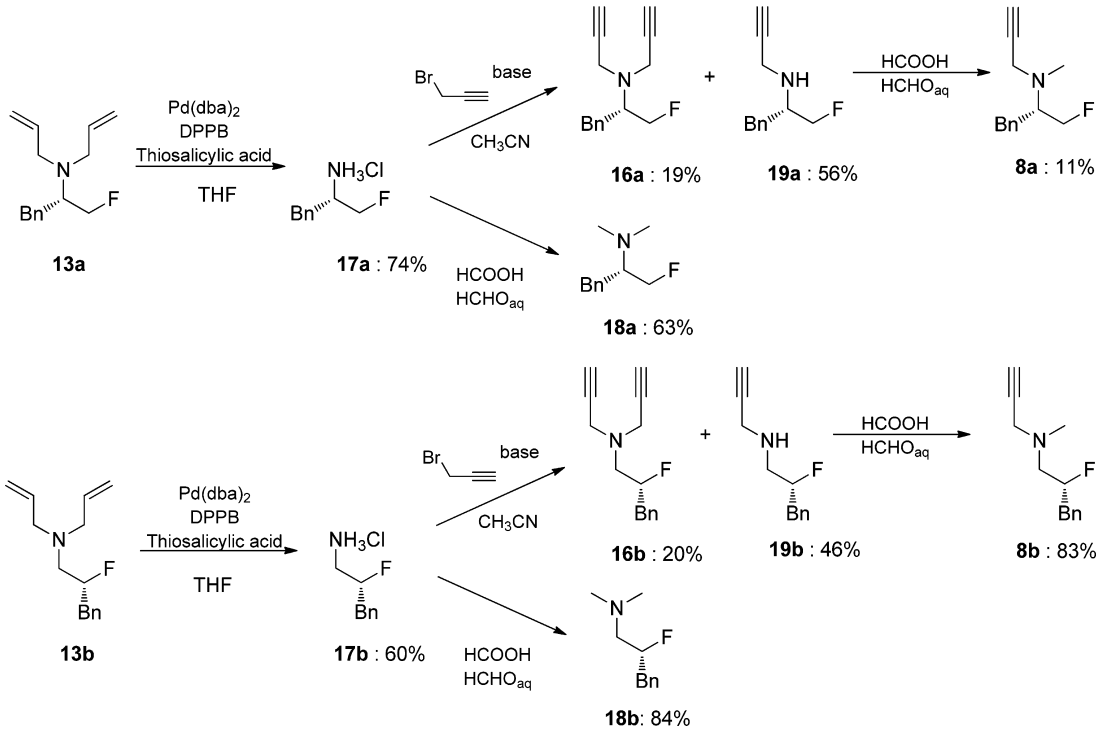
Table 1. Fluorination of Phenylalaninols[a]



entry	substrate	R_1	R_2	reaction temperature (°C)	product	isolated yield (%)	ratio **a:b**
1	**1a**	Bn	Bn	RT	**2**	64	39:61
2	**1a**	Bn	Bn	90	**2**	79	37:63
3	**4**	allyl	allyl	RT	**13**	77	40:60
4	**4**	allyl	allyl	90	**13**	88	38:62
5	**12**	piperidinyl		RT	**15**	45	47:53
6	**12**	piperidinyl		90	**15**	45	31:69
7	**5a**	propargyl	propargyl	RT	**16**	61	34:66
8	**5a**	propargyl	propargyl	90	**16**	72	34:66
9	**7a**	propargyl	Me	RT	**8**	69	48:52
10	**7a**	propargyl	Me	90	**8**	58	48:52
11	**11**	Bn	Me	RT	**14**	80	47:53
12	**11**	Bn	Me	90	**14**	74	46:54

[a]Substrate (0.8 mmol), Tf_2O (1.1 equiv), DIPEA (1.2 equiv), 1 h at RT then TBAF (2 equiv), 2 h.

Scheme 4. Synthesis of Isolated Fluorinated Standards



ing the kinetic fluorination of aziridinium. For piperidine **15**, the yield remained stable, and the ratio progressed in favor of thermodynamic isomer **b** (53 to 69%), which may be due to the rigidity of the piperidine ring.

The influence of the N-substituents on aziridinium ring opening by nucleophiles has rarely been studied. Cossy observed a slight steric effect from benzylic N-substituents (i.e., benzyl, trityl, *p*-methoxybenzyl, and benzhydryl) for the ring extensions of pyrrolidines to piperidines.[24,25] A reactivity comparison between *N*-benzyl- and *N*-allyl-substituted phenylalaninols[26] was studied in the presence of different nucleophiles, and better yields were observed for allylic substituents compared with benzylic substituents on the amine, with a slight effect on the reaction selectivity, which is consistent with our observations using fluorine (Table 1, entries 1 and 3). In contrast, Sharpless and collaborators did not observe any effects from the N-substituents (i.e., morpholine, 1-phenylpiperazine, diallyl and dibenzyl amines) of 2-chlorophenylalanine esters during the nucleophilic opening of the aziridinium ring.[27] Thermodynamic effects could not be retained in the regioselectivity with fluorine because fluorine is not a good leaving group.

Because the **16a**/**16b** and **8a**/**8b** mixtures were not separable by silica gel chromatography, we prepared pure and isolated products using a different approach to obtain standard compounds for establishing the identity of the radiolabeled products by coelution using HPLC. After removal of the *N*-allyl substituents of **13a** and **13b**, amines **17a** and **17b** were isolated and subjected to alkylations (Scheme 4).

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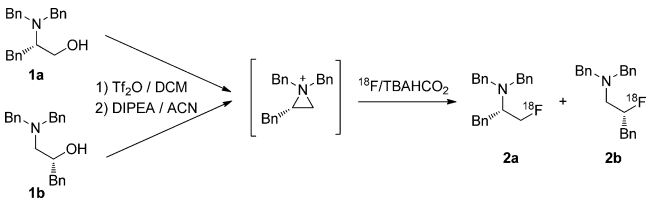
The preparation of the aziridinium intermediate and radiofluorination was performed according to the conditions previously described.[20] Briefly, the hydroxyl precursor was stirred in the presence of triflic anhydride in dichloromethane (DCM) for 1 h to yield the aziridinium intermediate. Then, this aziridinium-containing solution was added to dry [^{18}F]-fluoride which was cooled to RT after azeotropic evaporation with acetonitrile at 90 °C. To investigate the influence of the [^{18}F]-fluoride source, we performed the radiofluorination of **2** using isomers **1a** and **1b** with either the [^{18}F]KF/$K_{2.2.2}$ complex or [^{18}F]TBAF at RT and 90 °C in acetonitrile (Table 2).

Table 2. Radiofluorination Starting from Isomers 1a and 1b



entry	substrate[a]	^{18}F$^-$-source[b]	reaction temperature (°C)	RCY [^{18}F] **2a** + [^{18}F] **2b** (%)[c]	ratio[d] [^{18}F]**2a**:[^{18}F]**2b**
1	**1a**	[^{18}F]KF	RT	58 ± 3	33:67
2	**1a**	[^{18}F]KF	90	83 ± 1	33:67
3	**1b**	[^{18}F]KF	RT	46 ± 9	32:68
4	**1b**	[^{18}F]KF	90	73 ± 4	35:65
5	**1a**	[^{18}F]TBAF	RT	56 ± 6	34:66
6	**1a**	[^{18}F]TBAF	90	66 ± 4	35:65
7	**1b**	[^{18}F]TBAF	RT	40 ± 1	34:66
8	**1b**	[^{18}F]TBAF	90	72 ± 3	34:64

[a]Substrate (33 μmol). [b][^{18}F]KF:[^{18}F]-fluoride/K_2CO_3 (15 μmol)/K_{222} (18 μmol); [^{18}F]TBAF:[^{18}F]-fluoride/$TBAHCO_3$ (23 μmol). [c]^{18}F-RCY established by radio-TLC (n = 3). [d]Established by radio-HPLC.

Starting from each hydroxyl isomer (**1a** and **1b**), we obtained an identical mixture of both isomers ([^{18}F]**2a** and [^{18}F]**2b**, respectively). This result confirmed the exclusive anchimeric-assisted mechanism leading to the formation of the identical aziridinium intermediate. If another mechanism was involved (e.g., direct S_N2 on the triflate leaving group or S_N1), then the corresponding isomer [^{18}F]**2a** or [^{18}F]**2b** starting from **1a** or **1b**, respectively, would be favored. The radiofluorination of **1a** and **1b** resulted in comparable yields and ratios, despite the [^{18}F]-fluoride source, reaction temperature, or hydroxyl isomer precursor. Heating of the reaction led to an increase in the radiofluorination yield by approximately 25% (Table 2, entries 1 vs 2 and 7 vs 8) and reached 83% [^{18}F]-fluoride incorporation (Table 2, entry 2).

Substituent effects on radiofluorination were investigated (Table 3). In contrast to ^{19}F-fluorination at RT (Table 1), radiolabeling starting from *N*,*N*-dipropargylamine **5a** afforded a higher yield (Table 3, entry 11) than *N*,*N*-dibenzylamine **1a** (Table 3, entry 1), whereas *N*,*N*-diallylamine yielded only 17% radiofluorination yield (Table 3, entry 3). Piperidine **12** did not react at RT (Table 3, entry 26), whereas the nonradioactive fluorination of **12** yielded 45% product (Table 1, entry 5). When one methyl substituent was present on the amine, the RCY decreased compared with that of the disubstituted corresponding analogue (Table 3, entries 1 vs 23 and 11 vs 17). For the *N*,*N*-dipropargyl and *N*,*N*-methylpropargyl amines (**5a** and **7a**, respectively), the radiofluorination yield decreased from 67 to 19%. Dimethylamine **10** did not react under any of these conditions. It is important to note the absence of the [^{18}F]-fluoride source effect using [^{18}F]TBAF or the [^{18}F]KF/$K_{2.2.2}$ complex.

The order of reactivity at RT was as follows: *N*,*N*-dipropargylamine > *N*,*N*-methylpropargylamine = *N*,*N*-dibenzylamine ≫ *N*,*N*-diallylamine > *N*,*N*-methylbenzylamine ≫ piperidine > *N*,*N*-dimethylamine. This order is in good agreement with the electronic effect of the substituents on the electronic density of the nitrogen, which could be represented by the respective pK_b values (calculated using ACD/Laboratories Software V11.02) of precursors **5a**, **7a**, **1a**, **4**, **11**, **12**, and **10**, which are 4.29, 6.58, 6.98, 7.14, 7.93, 8.96, and 8.88, respectively. It is important to note that these results are different from those obtained by fluorination with nonradioactive [^{19}F]-fluorine (Table 1) in which the methyl substituent had a positive effect.

To confirm the anchimeric-assisted mechanism, the reaction was performed starting from isomers of **5** and **7**. Compounds **5b** and **7b** were prepared following Scheme 5. Radiofluorinations starting from **5b** and **7b** led to identical results for **5a** and **7a** with [^{18}F]TBAF and the [^{18}F]KF/$K_{2.2.2}$ complex, with similar yields and isomer ratios (Table 3, entries 3 vs 5, 7 vs 9, 11 vs 13, and 17 vs 19).

At RT, the **a**:**b** isomeric ratios were identical for [^{18}F]**2**, [^{18}F]**13**, [^{18}F]**16**, and [^{18}F]**15** (i.e., approximately 35:65). For [^{18}F]**8** and [^{18}F]**15**, the **a**:**b** ratios (55:45 and 37:63, respectively) were slightly different from those observed in Table 1 (48:52 and 47:53, respectively). The ratios obtained for [^{18}F]**2**, [^{18}F]**13**, [^{18}F]**16** and [^{18}F]**14** were the same as those measured for nonradioactive fluorinations (Table 1).

At 90 °C, an increase in the yield was observed for all compounds, except for amines containing a propargyl group, [^{18}F]**16** and [^{18}F]**8**. For piperidine [^{18}F]**15**, the radiofluorination yield substantially increased to 44%, and only traces were observed at RT (Table 3, entries 25 and 26). For *N*,*N*-dimethylamine **10**, small quantities were obtained (up to 12%) at 90 °C, whereas no reaction was detected at RT. Starting from *N*,*N*-dipropargylamine **5a** or isomer **5b**, the RCY of [^{18}F]-fluoride remained stable or exhibited a slight decrease (Table 3, entries 11 to 16). For *N*,*N*-methylpropargylamine **7a** and isomer **7b** (Table 3, entries 17 to 22), radiofluorination decreased from 41% to 17% (Table 3, entries 19 and 20).

Except for [^{18}F]**2**, the isomer ratio varied when the reaction was heated to 90 °C. When the yield increased, the ratio changed in favor of isomer **a** from 35:65 to 43:57 for [^{18}F]**13** and from 37:63 to 49:51 for [^{18}F]**15**. For *N*,*N*-methylbenzylamine, the [^{18}F]**14a**:[^{18}F]**14b** ratio increased to 79:21 compared with 48:52 at RT. When the RCYs decreased at 90 °C, substantial changes in the isomer ratio were observed. For example, the [^{18}F]**8a** isomer represented 55% of the products at RT but more than 95% at 90 °C (Table 3, entries 17, 19, 21 vs 18, 20, 21). This unexpected phenomenon occurred independently of the [^{18}F]-fluoride source. The same results were obtained with isomers **7a** and **7b**, and a direct S_N2 mechanism via a triflate intermediate corresponding to isomer **a** can be dismissed. The influence of the temperature on the radiofluorination yield was studied using three compounds (i.e., [^{18}F]**2**, [^{18}F]**16**, and [^{18}F]**8**) (Figure 1). An increase in the yield was observed for [^{18}F]**2**, even at 90 °C for both isomers. For compound [^{18}F]**16**, the yield reached a plateau at RT for isomer [^{18}F]**16a**, whereas the yield of isomer [^{18}F]**16b**

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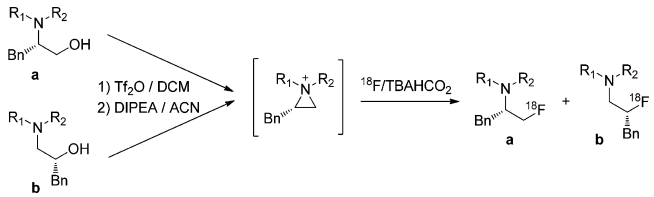
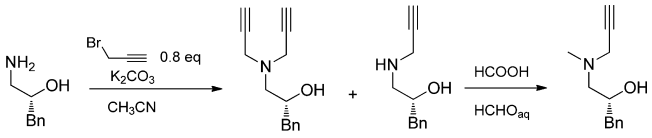
Table 3. Radiofluorination of Phenylpropanol and Phenylalaninol Isomers



entry	substrate[a]	R_1	R_2	^{18}F-product	^{18}F$^-$-source[b]	reaction temperature (°C)	RCY (%)[c] [^{18}F]**a**+**b**	ratio[d] [^{18}F]**a**:**b**
1	**1a**	Bn	Bn	**2**	[^{18}F]TBAF	RT	56 ± 6	34:66
2	**1a**	Bn	Bn	**2**	[^{18}F]TBAF	90	66 ± 4	35:65
3	**4**	allyl	allyl	**13**	[^{18}F]TBAF	RT	17 ± 6	36:64
4	**4**	allyl	allyl	**13**	[^{18}F]TBAF	90	36 ± 3	44:56
5	**4**	allyl	allyl	**13**	[^{18}F]KF	RT	10 ± 2	35:65
6	**4**	allyl	allyl	**13**	[^{18}F]KF	90	36 ± 5	42:58
7	**10**	Me	Me	**18**	[^{18}F]TBAF	RT	0	–
8	**10**	Me	Me	**18**	[^{18}F]TBAF	90	12 ± 1	100:0
9	**10**	Me	Me	**18**	[^{18}F]KF	RT	0	–
10	**10**	Me	Me	**18**	[^{18}F]KF	90	6 ± 3	100:0
11	**5a**	propargyl	propargyl	**16**	[^{18}F]TBAF	RT	67 ± 5	38:62
12	**5a**	propargyl	propargyl	**16**	[^{18}F]TBAF	90	59 ± 5	44:56
13	**5a**	propargyl	propargyl	**16**	[^{18}F]KF	RT	60 ± 6	39:61
14	**5a**	propargyl	propargyl	**16**	[^{18}F]KF	90	60 ± 4	47:53
15	**5b**	propargyl	propargyl	**16**	[^{18}F]TBAF	RT	71 ± 2	33:67
16	**5b**	propargyl	propargyl	**16**	[^{18}F]TBAF	90	57 ± 7	41:59
17	**7a**	propargyl	Me	**8**	[^{18}F]TBAF	RT	31 ± 6	55:45
18	**7a**	propargyl	Me	**8**	[^{18}F]TBAF	90	19 ± 2	100:0
19	**7a**	propargyl	Me	**8**	[^{18}F]KF	RT	41 ± 4	60:40
20	**7a**	propargyl	Me	**8**	[^{18}F]KF	90	17 ± 5	96:4
21	**7b**	propargyl	Me	**8**	[^{18}F]TBAF	RT	40 ± 3	55:45
22	**7b**	propargyl	Me	**8**	[^{18}F]TBAF	90	21 ± 3	95:5
23	**11**	Bn	Me	**14**	[^{18}F]TBAF	RT	10 ± 1	48:52
24	**11**	Bn	Me	**14**	[^{18}F]TBAF	90	21 ± 2	79:21
25	**12**	piperidinyl		**15**	[^{18}F]TBAF	RT	1 ± 1	37:63
26	**12**	piperidinyl		**15**	[^{18}F]TBAF	90	44 ± 5	49:51

[a]Substrate (33 μmol). [b][^{18}F]KF:[^{18}F]-fluoride/K_2CO_3 (15 μmol)/K_{222} (18 μmol); [^{18}F]TBAF:[^{18}F]-fluoride/$TBAHCO_3$ (23 μmol). [c]RCY established by radio-TLC (n = 3). [d]Established by radio-HPLC.

Scheme 5. Synthesis of Phenylpropanol Precursors



decreased with heating. The same phenomenon was observed with [^{18}F]**8**.

To confirm the hypothesis that the **b** isomer was degraded, we performed radiofluorination of [^{18}F]**8** at RT and measured the yield and isomer ratio at different times. After 10 min at RT, the [^{18}F]**8a**:[^{18}F]**8b** isomer ratio was 43:57, which remained stable after 30 min at RT. However, the radioactive yield continued to increase (Figure 2, red curves). When the reaction mixture was heated to 90 °C after 10 min at RT (Figure 2, blue curves), a rapid degradation of isomer [^{18}F]**8b** (Figure 2, dashed blue curve) was observed until it completely disappeared. Simultaneously, the [^{18}F]**8a** isomer continued to form more rapidly than at RT (Figure 2, dotted blue curve). The degradation was not due to the heat itself. When the reaction mixture was quenched with methanol after 10 min at RT, heating at 90 °C for an additional 20 min did not result in degradation of the [^{18}F]**8b** isomer. Therefore, the degradation of [^{18}F]**8b** was due to a secondary reaction in the reaction mixture during heating. The difference in the stability of the fluorinated products from fluorine-19 chemistry and radiochemistry should be due to the difference in the concentration. The radioactive [^{18}F]-fluoride and [^{18}F]-product are present in the reaction mixture in trace amounts (<0.1 μmol), but the precursor (33 μmol) and reactants ($TBAHCO_3$, 22 μmol) are present in large excess. These differences in the reaction conditions may explain the instability observed in the radiochemistry. Due to these highly diluted conditions, some phenomena can be observed in the radiochemistry but not in the fluorine-19 chemistry. Therefore, the stable or decreased RCYs observed at 90 °C were not due to a difference in reactivity but to the rapid degradation of the **b** isomer in the reaction mixture, modifying the measured isomer ratio. If the isomer ratio changes were due to degradation at 90 °C, then the order of the effect of the amine substituent on the stability of the product would be as follows: *N*,*N*-dimethylamine = *N*,*N*-methylpropargylamine > *N*,*N*-methylbenzylamine ≫ piperidine = *N*,*N*-dipropargylamine = *N*,*N*-diallylamine ≫ *N*,*N*-dibenzylamine.

N,*N*-Methylpropargylphenylalaninol (**7a**) (Scheme 4) corresponds to the precursor of [^{18}F]-fluorodeprenyl ([^{18}F]**8a**),

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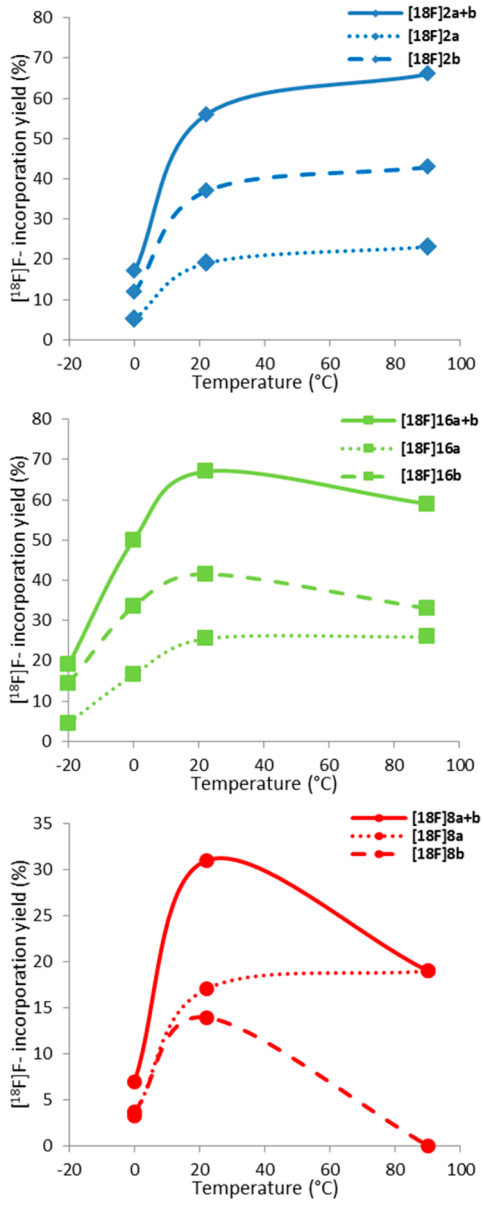

Figure 1. Effects of temperature on the radiofluorination with [^{18}F]TBAF of [^{18}F]**2**, [^{18}F]**16**, and [^{18}F]**8**.

which is a radiopharmaceutical used to image monoamine oxidase B (MAO-B).[23,28] The [^{18}F]-fluoride RCY was 23% for the labeling of this radiotracer, and the isomer ratio was inverted in favor of 1-[^{18}F]-fluoropropyl isomer ([^{18}F]**8a**), which resulted in the selective production of [^{18}F]-fluorodeprenyl. [^{18}F]-Fluorodeprenyl was previously prepared by heating a mixture of two chloride isomers in the presence of [^{18}F]-fluoride, resulting in 50% RCY.[25] However, the ^{18}F-isomer ratio was not specified. In this case, no evidence of aziridinium ring opening by [^{18}F]-fluoride was observed because the competitive S_N2 mechanism would occur at the temperature used in the reaction (120 °C).

To apply our method to a larger number of radiopharmaceuticals, the radiofluorination of 2-[^{18}F]-fluoroethylamines was investigated (Scheme 6). Because the aziridinium ring is symmetrical in these cases, the ring opening yielded only one radiofluorinated product. The reaction conditions developed for the radiolabeling of **1a** were applied to the radiofluorination of fluoroethylamines **25**−**30** (Table 4). At RT, the radiofluorination yields of [^{18}F]**25** and [^{18}F]**28** were lower than those for the corresponding phenylalaninol analogues (23−26% for [^{18}F]**25** compared with 58 and 46% for [^{18}F]**2**, no reaction was observed for [^{18}F]**28**, and 10% was obtained for [^{18}F]**14**). The effect of the benzylic substituent on the aziridinium ring appears to be important for the reactivity of aziridinium. At 90 °C, the radiofluorination yield increased for [^{18}F]**25** (Table 4, entries 2, 4, and 1, 3), whereas no [^{18}F]**28** was obtained from precursor **24**. For analogues [^{18}F]**27** and [^{18}F]**22**, heating did not affect the incorporation of [^{18}F]-fluoride, regardless of the [^{18}F]-fluoride source. These radiochemical yields can be compared with the yields from the classical two-step radiosynthesis, which involves the preparation of 2-[^{18}F]-fluoroethylsulfonate or a halide followed by N-alkylation, leading to the *N*-[^{18}F]-fluoroethylamine product with poor radiochemical yields.[12] The method was applied to the radiolabeling of a radiopharmaceutical used to image dopamine transporters in the brain (i.e., [^{18}F]-FECNT).[29,30] The current radiosyntheses involve the alkylation of a nortropane precursor by different [^{18}F]-fluoroethylsulfonates or bromide in overall radiochemical yields of 16.5% to 40% (decay corrected at the end of bombardment).[31−33] Recently, radiosyntheses in one step from a mesylate precursor were reported with similar radiochemical yields of approximately 45%.[34,35] However, the precursor developed for this synthesis is unstable and requires specific conditions for storage. Here, we applied our method starting from stable alcohol **29**, which afforded 12% and 21% of the

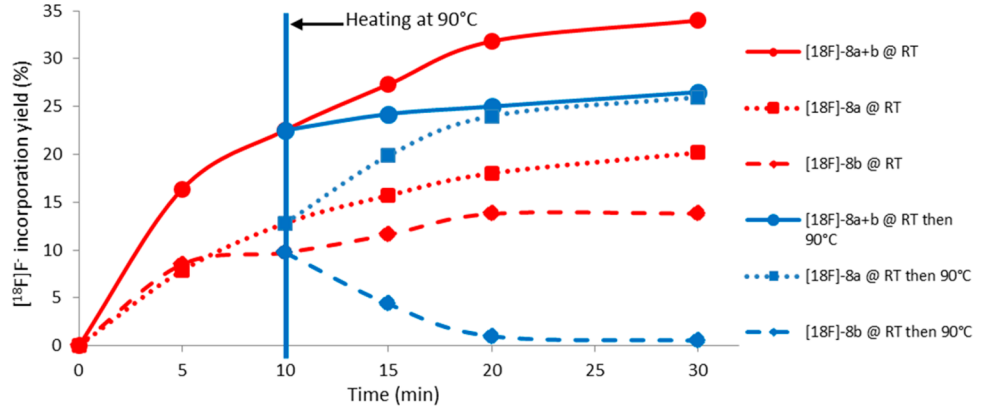

Figure 2. Kinetics and effects of heating during radiofluorination with [^{18}F]TBAF starting from **7a**.

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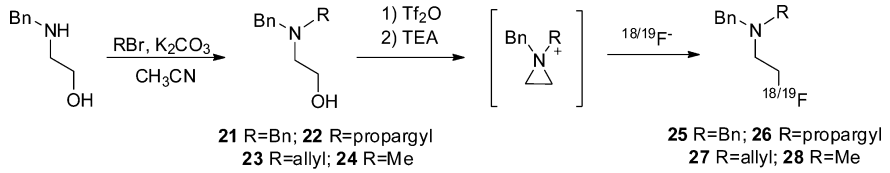
Scheme 6. Radiolabeling of [^{18}F]-Fluoroethylamines



21 R=Bn; **22** R=propargyl
23 R=allyl; **24** R=Me

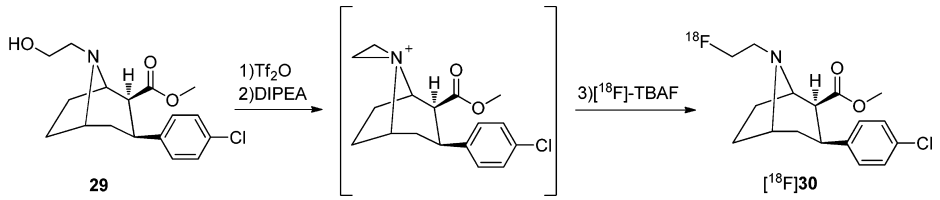
25 R=Bn; **26** R=propargyl
27 R=allyl; **28** R=Me

Table 4. Radiofluorination of Ethylamines

entry	substrate[a]	R	^{18}F-product	^{18}F$^-$-source[b]	reaction temperature (°C)	^{18}F-RCY (%)[c]
1	**21**	benzyl	**25**	[^{18}F]KF	RT	23 ± 2
2	**21**	benzyl	**25**	[^{18}F]KF	90	35 ± 4
3	**21**	benzyl	**25**	[^{18}F]TBAF	RT	26 ± 2
4	**21**	benzyl	**25**	[^{18}F]TBAF	90	48 ± 2
5	**22**	propargyl	**26**	[^{18}F]KF	RT	22 ± 6
6	**22**	propargyl	**26**	[^{18}F]KF	90	29 ± 4
7	**22**	propargyl	**26**	[^{18}F]TBAF	RT	26 ± 4
8	**22**	propargyl	**26**	[^{18}F]TBAF	90	24 ± 2
9	**23**	allyl	**27**	[^{18}F]KF	RT	14 ± 3
10	**23**	allyl	**27**	[^{18}F]KF	90	16 ± 3
11	**23**	allyl	**27**	[^{18}F]TBAF	RT	14 ± 3
12	**23**	allyl	**27**	[^{18}F]TBAF	90	9 ± 2
13	**24**	methyl	**28**	[^{18}F]TBAF	RT	0
14	**24**	methyl	**28**	[^{18}F]TBAF	90	0
15	**29**		**30**	[^{18}F]TBAF	RT	12 ± 1[d]
16	**29**		**30**	[^{18}F]TBAF	90	21 ± 1[d]

[a]Substrate (33 μmol).[20] [b][^{18}F]KF:[^{18}F]-fluoride/K_2CO_3 (15 μmol)/K_{222} (18 μmol); [^{18}F]TBAF:[^{18}F]-fluoride/$TBAHCO_3$ (23 μmol). [c]RCY established by radio-TLC (n = 3). [d]n = 2.

Scheme 7. Radiolabeling of [^{18}F]-FECNT



29 [^{18}F]**30**

desired product ([^{18}F]-FECNT (**30**)) at RT and 90 °C, respectively, without any optimization of the reaction conditions (Scheme 7) (Table 4, entries 15 and 16).

Although the radiochemical yield remains low compared with the other method, this method offers the advantages of a stable precursor and a one-step reaction, which facilitate radiosynthesis automation. In addition, the instability of the previously reported mesylate precursor may be related to the fact that this anchimeric-assisted reaction occurs over time.

The radiosyntheses with high levels of radioactivity were performed on a commercially available GE TRACERLab FX module to prepare more than 1 GBq of a mixture of [^{18}F]**2a** and [^{18}F]**2b** at RT with a 70:30 ratio within 70 min. The specific radioactivity of [^{18}F]**2b** and [^{18}F]**2a** was similar to typical fluorine-18 specific radioactivities obtained in our lab (i.e., 130−320 GBq/μmol at the end of bombardment).

■ CONCLUSION

We developed a nucleophilic radiofluorination method using [^{18}F]-fluoride via an anchimeric-assisted mechanism for the radiolabeling of β-[^{18}F]-fluoroamines. Aziridinium intermediates were obtained from stable phenylalaninol precursors. One-pot ^{19}F-fluorination using TBAF yielded two isomers resulting from aziridinium ring opening. The N-substituents resulted in a variation of the isomer ratios (**a**:**b**) between 31:69 and 48:52, with fluorination yields ranging from 45% to 88%. The reaction temperature did not significantly affect the efficiency or regioselectivity of the fluorination. Radioactive β-[^{18}F]-fluoroamines were obtained in one step by nucleophilic substitution starting from [^{18}F]-fluoride. The [^{18}F]-fluoride forms (i.e., [^{18}F]TBAF or [^{18}F]KF/$K_{2.2.2}$ complex) did not affect the radiochemical yield. We demonstrated the neighboring-group mechanism by performing the radiofluorination starting from both of the phenylalaninol precursors (**a**:**b** isomers of alcohols **1**, **5** and **7**), which led to similar [^{18}F]-fluorine RCYs and an identical **a**:**b** ratio. The N,N-substituents exerted a substantial influence on the radiofluorination. [^{18}F]-Fluoride incorporations varied from no reaction (for *N*,*N*-dimethylamine or piperidine) to 71% yield (for *N*,*N*-dipropargylamine) at RT. The isomer ratio was mostly comparable to the ratios obtained using ^{19}F-fluorine. Heating during radiofluorination substantially improved the radiochemical yield in some cases (from 1% to 44% for piperidine). However, when the radiochemical yield increased slightly or even decreased when heated at 90 °C, we observed a change in the **a**:**b** ratio in favor of 1-fluoro-propan-2-amine isomer **a**. The ratio changes were due to the instability of

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the [^{18}F]**b** isomer in the reaction mixture. The *N*-methyl substituent resulted in a very unstable **b** isomer, leading to selective radiofluorination of the [^{18}F]**a** isomer at 90 °C. This radiolabeling method was extended to *β*-[^{18}F]-fluoroethylamines, which afforded a unique radioactive product in moderate to low yields without any optimization of the reaction conditions. The method was successfully applied to the radiolabeling of two radiopharmaceuticals, [^{18}F]-fluorodeprenyl and [^{18}F]-FECNT. For [^{18}F]-fluorodeprenyl, radiofluorination only yielded the **a** isomer at 90 °C. This new radiofluorination method may be useful for the routine preparation of ^{18}F-radiopharmaceuticals starting from stable precursors in a fewer number of steps. The possibility to perform the nucleophilic radiofluorination at RT also affords new opportunities in the field of PET chemistry.

EXPERIMENTAL SECTION

Materials and Methods. Reagents and solvents used, unless stated otherwise, were of commercially available reagents grade quality and were used without further purification. Thin-layer chromatographies (TLC) were run on precoated aluminum plates of silica gel 60F$_{254}$, and retention factors (R_f) were established using a UV-lamp at 254 nm or visualization with ninhydrin solution. Silica gel flash chromatographies were performed on prepacked columns (20−40 μm). Optical rotations were determined on a polarimeter and are given in cm^3 g^{-1} dm^{-1}, while the concentrations are given in g cm^{-3}. Melting points were determined on a digital melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400 MHz (^{1}H), 100.6 MHz (^{13}C), and 376.5 MHz (^{19}F). Fluorine-19 NMR spectra are coupled to proton. Chemical shifts were reported as parts per million (δ in ppm) using tetramethylsilane (TMS) as internal standard or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Coupling patterns are abbreviated as s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet). IR spectra were recorded on a FT-IR spectrometer and are given in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a Q-TOF spectrometer by electrospray ionization (ESI-TOF). Analytical HPLC was realized with a photodiode arrays detector (198−380 nm) coupled with a NaI probe radioactive detector. Purity was determined by HPLC on an analytical column (Macherey-Nagel, Nucleodur C18 Gravity, 250 × 4.6 mm, 5 μm; flow rate: 1 mL/min; UV-detection λ = 210 nm). The purity of compounds was found to be more than 98%. Radioactivity measurements were carried out with an ionization chamber.

*(S)-2-(N-Benzylamino)-3-phenylpropan-1-ol (**9**) and (S)-2-(N,N-Dibenzylamino)-3-phenylpropan-1-ol (**1a**).* To a solution of **3a** (2.02 g, 13.2 mmol) in DCM (5 mL) at RT was added Na_2CO_3 (0.95 g, 8.9 mmol) followed by benzyl bromide (1.06 mL, 8.9 mmol). The mixture was heated to 110 °C and stirred overnight. After cooled to RT, H_2O (20 mL) was added to the mixture, and aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by chromatography on silica gel (heptane/AcOEt, 90/10 to 40/60) gave compound **9** as a white solid (1.52 g, 48%) and **1a** (306 mg, 7%) as yellow oil. **9**: mp: 67−68 °C (litt. 54−56 °C);[36] $[\alpha]_D^{20}$ −18.3 (*c* 1.00, $CHCl_3$). Characterization data are in accordance to the published data.[36] **1a**: $[\alpha]_D^{20}$ +40 (*c* 1.90, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 10.6 min. Characterization data are in accordance to the published data.[37]

*(S)-2-(N,N-Diallylamino)-3-phenylpropan-1-ol (**4**).* Compound **4** was prepared following the procedure described for the synthesis of **1b** using (*S*)-2-amino-3-phenyl-propan-1-ol (**3a**)[37] (752 mg, 4.98 mmol), K_2CO_3 (1.51 g, 10.93 mmol), and allyl bromide (0.88 mL, 10.17 mmol). Product **4** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 90/10) as an yellow oil (790 mg, 69%). $[\alpha]_D^{20}$ −35.4 (*c* 1.00, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 6.8 min. Characterization data are in accordance to the published data.[38]

*(S)-2-(N-Propargylamino)-3-phenylpropan-1-ol (**6a**) and (S)-2-(N,N-Dipropargylamino)-3-phenylpropan-1-ol (**5a**).* Compound **6a** was prepared following the procedure described for the synthesis of **1b**, starting from (*S*)-2-amino-3-phenyl-propan-1-ol (**3a**)[37] (1.93 g, 12.8 mmol), K_2CO_3 (3.88 g, 10.9 mmol), and a solution of propargyl bromide in toluene (80 wt %, 1.4 mL, 13.0 mmol). After purification by chromatography on silica gel (heptane/AcOEt, 80/20 to 60/40), product **6a** was obtained as a white solid (1.32 g, 55%) and compound **5a** (640 mg, 22%) as an yellow oil. **6a**: mp 71−72 °C; $[\alpha]_D^{20}$ + 9.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.32−7.20 (m, 5H), 3.66 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.6 Hz, 1H), 3.44 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 3.38 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 3.16−3.10 (m, 1H), 2.83−2.73 (m, 2H), 2.20 (t, $^4J_{HH}$ = 2.4 Hz, 1H), 1.97 (bs, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 138.5, 129.6, 128.9, 126.8, 82.2, 71.9, 62.5, 58.9, 38.2, 36.1; IR (ATR) ν_{max}: 3294, 2929, 1494, 1451, 1338, 1053, 743, 699; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{16}NO$ 190.1232; Found 190.1223. **5a** $[\alpha]_D^{20}$ −8.2 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.30−7.16 (m, 5H), 3.65 and 3.60 (ABX system, $^2J_{AB}$ = 17.2 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.4 Hz, 4H), 3.47−3.37 (m, 2H), 3.26−3.18 (m, 2H), 2.72 (bs, 1H), 2.48−2.42 (m, 1H), 2.29 (t, $^4J_{HH}$ = 2.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.1, 129.3, 128.9, 126.7, 80.2, 73.5, 65.0, 60.7, 39.3, 33.5; IR (ATR) ν_{max}: 3288, 2928, 1030, 742, 632; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{15}H_{18}NO$ 228.1388; Found 228.1377; HPLC purity: eluent MeOH/H2O 70/30, t_r = 7.2 min.

*(S)-2-(N,N-Benzylmethylamino)-3-phenylpropan-1-ol (**11**).* Compound **11** was prepared following the procedure described for the synthesis of **10**, starting from **9** (720 mg, 3.0 mmol), formic acid (0.57 mL, 15.1 mmol), and formaldehyde (37% in H_2O) (0.67 mL, 9.4 mmol). Compound **11** was obtained after purification by chromatography on silica gel (AcOEt/Hept, 85/15) as colorless oil (659 mg, 87%). $[\alpha]_D^{20}$ −6.0 (*c* 1.00, $CHCl_3$). Characterization data are in accordance to the published data.[39]

*(S)-3-Phenyl-2-piperidin-1-yl-propan-1-ol (**12**).* To a solution of **3a** (500 mg, 3.3 mmol) in CH_3CN (10 mL) at 0 °C was added K_2CO_3 (1 g, 7.3 mmol) followed by diiodopentane (0.52 mL, 3.5 mmol). The mixture was heated to reflux and stirred overnight. The solvent was evaporated before CH_2Cl_2 (20 mL) and water (20 mL) were added to the residue. The layers were separated, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by chromatography on silica gel (heptane/AcOEt, 65/25) gave compound **12** as a white solid (455 mg, 63%). mp: 50−51 °C; $[\alpha]_D^{20}$ −3.3 (*c* 1.0, $CHCl_3$). Characterization data are in accordance to the published data.[40]

*(S)-2-(N,N-Methylpropargylamino)-3-phenylpropan-1-ol (**7a**).* A mixture of **6a** (200 mg, 1.06 mmol), formic acid (0.2 mL, 5.30 mmol), and formaldehyde (37% in water) (0.12 mL, 1.6 mmol) was stirred at 105 °C overnight. The mixture was cooled to RT and acidified to pH 1 with HCl (2 N). The solvent was evaporated, and CH_2Cl_2 (20 mL) and water (20 mL) were added to the residue. The layers were separated, and the aqueous layer was washed further with water (2 × 20 mL). The combined aqueous layers were brought to pH 8−9 by the addition of aqueous ammonia (28%) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Compound **7a** was obtained after purification by chromatography on silica gel (CH_2Cl_2/MeOH, 99/1) as colorless oil (154 mg, 72%). $[\alpha]_D^{20}$ −20.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.30−7.16 (m, 5H), 3.50−3.32 (m, 4H), 3.11−3.06 (m, 2H), 2.43 (s, 3H), 2.42−2.35 (m, 1H), 2.29 (t, $^4J_{HH}$ = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.3, 129.2, 128.7, 126.4, 80.5, 73.2, 65.5, 60.4, 43.8, 36.1, 32.4; IR (ATR) ν_{max}: 3289, 2935, 2799, 1453, 1030,740, 699; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{13}H_{18}NO$ 204.1388; Found 204.1387; HPLC purity: eluent MeOH/H_2O 65/35, t_r = 8.9 min.

*(S)-N,N-Dimethyl-2-amino-3-phenylpropan-1-ol (**10**).* A mixture of **3a** (503 mg, 3.3 mmol), formic acid (0.63 mL, 17 mmol), and formaldehyde (37% in water) (0.76 mL, 10 mmol) was stirred at 105

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°C overnight. The mixture was cooled to RT and acidified to pH 1 with HCl (2 N). The solvent was evaporated, and CH_2Cl_2 (20 mL) and water (20 mL) were added to the residue. The layers were separated, and the aqueous layer was washed further with water (2 × 20 mL). The combined aqueous layers were brought to pH 8−9 by the addition of aqueous ammonia (28%) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Compound **10** was obtained after purification by chromatography on silica gel (CH_2Cl_2/MeOH, 98/2) as white solid (372 mg, 62%). mp: 48−50 °C (lit. 49−51 °C);[41] $[\alpha]_D^{20}$ −1.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.28−7.11 (m, 5H), 3.40−3.29 (m, 2H), 3.16 (bs, 1H), 2.92−2.81 (m, 2H), 2.33 (s, 6H), 2.31−2.25 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.6, 129.1, 128.6, 126.3, 67.0, 60.6, 40.31, 40.29, 30.7; IR (ATR) ν_{max}: 3334, 2929, 2859, 2813, 1602, 1103, 1026, 732, 698; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{18}NO$, 180.1388, found 180.1386.

Typical Procedure for Fluorination. To a solution of alcohol (0.6 mmol) in dry CH_2Cl_2 (4.5 mL) in a conic vial under nitrogen atmosphere was added a solution of trifluoromethanesulfonic anhydride (1 M in CH_2Cl_2, 0.66 mL). The solution was stirred at RT for 1 h. *N*,*N*-Diisopropylethylamine (125 μL, 0.72 mmol) was then added and after 1 min stirring, a solution of TBAF (1 M in THF, 1.2 mL) was added. The reaction mixture was stirred further for 2 h at RT and quenched with aqueous NaOH (15%, 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were concentrated under reduced pressure, and the residue was purified by chromatography on silica gel.

*(R)-N,N-Dibenzyl-2-fluoro-3-phenylpropan-1-amine (**2b**) and (S)-N,N-Dibenzyl-1-fluoro-3-phenylpropan-2-amine (**2a**).* Following the typical procedure for fluorination, starting from (*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropan-1-ol **1a**,[42] isomers **2b** (50 mg, 25%) and **2a** (78 mg, 39%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 100/1) as colorless oils. **2b**: $[\alpha]_D^{20}$ −1.9 (*c* 2.48, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 25.5 min. Characterization data are in accordance to the published data.[22] **2a**: $[\alpha]_D^{20}$ −19.9 (*c* 1.36, $CHCl_3$); HPLC purity: eluent MeOH/H_2O 85/15, t_r = 28.7 min. Characterization data are in accordance to the published data.[22]

*(R)-N,N-Diallyl-2-fluoro-3-phenylpropan-1-amine (**13b**) and (S)-N,N-Diallyl-1-fluoro-3-phenylpropan-2-amine (**13a**).* Following the typical procedure for fluorination, starting from **4** (184 mg, 0.8 mmol), isomers **13b** (58 mg, 31%) and **13a** (86 mg, 46%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 98/2) as colorless oils. **13b**: $[\alpha]_D^{20}$ + 0.3 (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.32−7.21 (m, 5H), 5.88−5.78 (m, 2H), 5.16−5.10 (m, 4H), 4.92−4.74 (m, 1H), 3.15 (d, $^3J_{HH}$ = 6.0 Hz, 4H), 2.96−2.88 (m, 2H), 2.73−2.59 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 137.7 (d, $^3J_{CF}$ = 4.2 Hz), 135.8, 129.7, 128.7, 126.9, 118.0, 93.7 (d, $^1J_{CF}$ = 173.1 Hz), 58.0, 56.7 (d, $^2J_{CF}$ = 21.5 Hz), 40.1 (d, $^2J_{CF}$ = 21.2 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −180.2; IR (ATR) ν_{max}: 3077, 3029, 3026, 1643, 1454, 1030, 995, 918, 744, 699; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{21}NF$ 234.1658; Found 234.1653; HPLC purity: eluent MeOH/H_2O 80/20, t_r = 7.7 min. **13a**: $[\alpha]_D^{20}$ −22.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.30−7.17 (m, 5H), 5.82−5.72 (m, 2H), 5.20−5.07 (m, 4H), 4.53−4.32 (m, 2H), 3.30−3.13 (m, 5H), 2.85 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 2.72 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 9.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 140.0, 137.5, 129.6, 128.7, 126.4, 117.0, 83.9 (d, $^1J_{CF}$ = 172.0 Hz), 61.0 (d, $^2J_{CF}$ = 17.5 Hz), 53.9 (d, $^4J_{CF}$ = 1.8 Hz), 33.2; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −226.2; IR (ATR) ν_{max}: 3078, 3027, 3026, 1641, 1455, 991, 918, 742, 699; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{21}NF$ 234.1658; Found 234.1660; HPLC purity: eluent MeOH/H_2O 80/20, t_r = 10.2 min.

*N-Benzyl-N-methyl-(1-benzyl-2-fluoroethyl)amine (**14a**) and N-Benzyl-N-methyl-(2-fluoro-3-phenylpropyl)amine (**14b**).* Following the typical procedure for fluorination, starting from **11** (153 mg, 0.6 mmol), isomers **14a** (58 mg, 38%) and **14b** (65 mg, 42%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 95/5) as colorless oils. **14a**: $[\alpha]_D^{20}$ −38.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.31−7.18 (m, 10H), 4.62−4.40 (m, 2H), 3.74 (s, 2H), 3.14−3.04 (m, 1H), 2.93 (dd, 1H, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 6.0 Hz), 2.78 (dd, 1H, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 8.8 Hz), 2.37 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 140.1, 139.8, 129.6, 128.9, 128.7, 127.2, 126.5, 83.4 (d, $^1J_{CF}$ = 171.1 Hz), 64.3 (d, $^2J_{CF}$ = 17.3 Hz), 59.3 (d, $^4J_{CF}$ = 1.8 Hz), 38.0 (d, $^4J_{CF}$ = 1.6 Hz), 33.1 (d, $^3J_{CF}$ = 6.6 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −225.4; IR (ATR) ν_{max}: 2951, 2792, 1453, 1010, 732, 697; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{21}NF$ 258.1658; Found 258.1662; HPLC purity: eluent MeOH/H_2O 85/15, t_r = 9.5 min. **14b**: $[\alpha]_D^{20}$ + 1.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.20−7.16 (m, 10H), 4.91−4.73 (m, 1H), 3.52 (s, 2H), 2.91 (dd, 2H, $^2J_{HH}$ = 23.2 Hz, $^3J_{HH}$ = 6.4 Hz), 2.67−2.50 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.1, 137.5 (d, $^4J_{CF}$ = 4.3 Hz), 129.7, 129.3, 128.7, 128.6, 127.4, 126.9, 93.5 (d, $^1J_{CF}$ = 171.7 Hz), 63.0 (d, $^4J_{CF}$ = 1.2 Hz), 60.4 (d, $^2J_{CF}$ = 21.5 Hz), 43.4 (d, $^4J_{CF}$ = 1.5 Hz), 40.0 (d, $^2J_{CF}$ = 21.1 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −179.9; IR (ATR) ν_{max}: 2945, 2787, 1453, 1020, 738, 697; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{21}NF$ 258.1658; Found 258.1659; HPLC purity: eluent MeOH/H_2O 85/15, t_r = 7.7 min.

*(S)-1-(1-Benzyl-2-fluoro-ethyl)-piperidine (**15a**) and (R)-1-(2-Fluoro-3-phenyl-propyl)-piperidine (**15b**).* Following the typical procedure for fluorination, starting from **12** (131 mg, 0.6 mmol), isomers **15a** (28 mg, 21%) and **15b** (32 mg, 24%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 85/5) as colorless oils. **15a**: $[\alpha]_D^{20}$ −12.5 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.34−7.21 (m, 5H), 4.61−4.34 (m, 2H), 2.96−2.65 (m, 7H), 1.65−1.57 (m, 4H), 1.52−1.46 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD, TMS) δ 140.1, 129.6, 128.7, 126.4, 82.7 (d, $^1J_{CF}$ = 171.0 Hz), 67.1 (d, $^2J_{CF}$ = 17.3 Hz), 51.1 (d, $^4J_{CF}$ = 1.5 Hz), 32.9 (d, $^3J_{CF}$ = 6.7 Hz), 26.9, 25.0; ^{19}F NMR (376.5 MHz, CD_3OD) δ −224.6; IR (ATR) ν_{max}: 2931, 1467, 1000, 1029, 734, 698; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{21}NF$ 222.1658; Found 222.1664; HPLC Purity: eluent: MeOH/H_2O/TFA 15/85/0.1, t_r = 22.8 min. **15b**: $[\alpha]_D^{20}$ + 0.6 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.34−7.20 (m, 5H), 4.99−4.81 (m, 1H), 3.00−2.93 (m, 2H), 2.64−2.51 (m, 2H), 2.48−2.44 (m, 4H), 1.63- 1.55 (m, 4H), 1.46−1.42 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD, TMS) δ 137.4 (d, $^4J_{CF}$ = 4.5 Hz), 129.7, 128.7, 126.8, 93.0 (d, $^1J_{CF}$ = 171.6 Hz), 62.6 (d, $^2J_{CF}$ = 21.0 Hz), 55.4 (d, $^4J_{CF}$ = 1.2 Hz), 40.3 (d, $^2J_{CF}$ = 21.3 Hz), 26.3, 24.5; ^{19}F NMR (376.5 MHz, CD_3OD) δ −178.2; IR (ATR) ν_{max}: 2931, 1468, 1120, 1029, 777, 698; HRMS HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{21}NF$ 222.1658; Found 222.1665; HPLC Purity: Column: Macherey-Nagel, Nucleodur C18 Polartech, 250 × 4.6 mm, 5 μm; flow rate: 1 mL/min; eluent: MeOH/H_2O/TFA 15/85/0.1, t_r = 20.1 min.

*(S)-1-Fluoro-3-phenylpropan-2-ammonium chloride (**17a**).* A solution of 1,4-bis(diphenylphosphino)butane (110 mg, 0.26 mmol) and tris(dibenzylideneacetone)dipalladium (196 mg, 0.34 mmol) in dry THF (9 mL) was stirred under argon for 15 min at RT. The orange mixture was added to a solution of **13a** (200 mg, 0.86 mmol) and thiosalicylic acid (572 mg, 3.71 mmol) in dry THF (15 mL). The mixture was then stirred under argon at 60 °C for 5 h. After cooling to RT, the reaction was quenched with HCl (1 N, 10 mL), and AcOEt (10 mL) was added to the mixture. The two layers were separated, and the organic layer was extracted with HCl (1 N, 2 × 5 mL). The combined aqueous layers were alkalized with a solution of NaOH (1 N) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and an excess of HCl (1 N in diethyl ether) was added (2 mL, 2 mmol). The solvent was evaporated under reduced pressure, and the residue was washed with Et_2O to give **17a** (120 mg, 74%) as white solid. mp 136−138 °C (litt. 143−144 °C from CH_3CN);[43] $[\alpha]_D^{20}$ −10.2 (*c* 0.76, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.43−7.32 (m, 5H), 4.89 (bs, 3H), 4.72−4.42 (m, 2H), 3.83−3.71 (m, 1H), 3.04 (d, $^3J_{HH}$ = 8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, CD_3OD, TMS) δ 137.1, 131.2, 131.0, 129.5, 83.5 (d, $^1J_{CF}$ = 171.4 Hz), 54.8 (d, $^2J_{CF}$ = 18.4 Hz), 36.3 (d, $^3J_{CF}$ = 5.2 Hz); ^{19}F NMR (376.5 MHz, CD_3OD) δ −234.9; IR (ATR) ν_{max}: 2868, 1492, 1619, 1023, 741, 701; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{13}NF$ 154.1032; Found 154.1028

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*(S)-N,N-Dimethyl-1-fluoro-3-phenylpropan-2-amine (**18a**).* Compound **18a** was prepared following the procedure described for the synthesis of **10**, starting from **17a** (20 mg, 0.1 mmol), formic acid (0.071 mL, 9.5 mmol), and formaldehyde (37% in H_2O) (0.06 mL, 9.0 mmol). **18a** was obtained without further purification as a colorless oil (12 mg, 63%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.36−7.24 (m, 5H), 4.59−4.34 (m, 2H), 2.99−2.88 (m, 2H), 2.75−2.68 (m, 1H), 2.48 (s, 6H); ^{13}C NMR (100.6 MHz, CD_3OD, TMS) δ 139.7, 129.5, 128.9, 126.6, 82.4 (d, $^1J_{CF}$ = 171.0 Hz), 66.2 (d, $^2J_{CF}$ = 17.2 Hz), 42.0 (d, $^4J_{CF}$ = 1.5 Hz), 32.2 (d, $^3J_{CF}$ = 6.8 Hz); ^{19}F NMR (376.5 MHz, CD_3OD) δ −226.0; IR (ATR) ν_{max}: 2935, 2781, 1603, 1454, 1008, 737, 698. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{17}NF$ 182.1345; Found 182.1351.

*(S)-N,N-Dipropargyl-1-fluoro-3-phenylpropan-2-amine (**16a**) and (S)-N,N-Propargyl-1-fluoro-3-phenylpropan-2-amine (**19a**).* Compounds **16a** and **19a** were prepared following the procedure described for the synthesis of **1b**, starting from **17a** (66 mg, 0.35 mmol), NaOH (45 mg, 1.12 mmol), and a solution of propargyl bromide in toluene (80 wt %, 39 μL, 0.36 mmol). Amines **16a** (15 mg, 19%) and **19a** (37 mg, 56%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 80/20) as colorless oils. **16a**: $[\alpha]_D^{20}$ −22.9 (c 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.32−7.20 (m, 5H), 4.66−4.35 (m, 2H), 3.70 (d, $^4J_{HH}$ = 2.4 Hz, 4H), 3.33−3.20 (m, 1H), 3.07−3.03 (m, 1H), 2.83 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 10.0 Hz, 1H), 2.28 (t, $^4J_{HH}$ = 2.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.1, 129.6, 128.9, 126.7, 83.2 (d, $^1J_{CF}$ = 170.6 Hz), 80.4, 73.3, 63.2 (d, $^2J_{CF}$ = 17.9 Hz), 40.3 (d, $^4J_{CF}$ = 2.6 Hz), 33.7 (d, $^3J_{CF}$ = 5.9 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −227.2; IR (ATR) ν_{max}: 3293, 3027, 3026, 1603, 1455, 1125, 999, 918, 742, 700, 638; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}NF$ 230.1345; Found 230.1350; HPLC purity: eluent MeOH/H_2O 70/30, t_r = 11.4 min. **19a**: $[\alpha]_D^{20}$ + 4.5 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.50−4.27 (m, 2H), 3.53 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 3.38−3.30 (m, 1H), 2.81 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 2.24 (t, $^4J_{HH}$ = 2.4 Hz, 1H), 1.54 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 138.0, 129.6, 128.9, 127.0, 84.7 (d, $^1J_{CF}$ = 170.3 Hz), 82.0, 72.0, 57.4 (d, $^2J_{CF}$ = 18.7 Hz), 37.1 (d, $^3J_{CF}$ = 6.1 Hz), 36.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −229.0; IR (ATR) ν_{max}: 3294, 2925, 1454, 1007; 744, 699, 636; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}NF$ 192.1189; Found 192.1192.

*(S)-N,N-Methylpropargyl-1-fluoro-3-phenylpropan-2-amine (**8a**).* Compound **8a** was prepared following the procedure described for the synthesis of **10**, starting from **19a** (30 mg, 0.16 mmol), formic acid (60 μL, 1.59 mmol), and formaldehyde (37% in H_2O) (71 μL, 0.95 mmol). Compound **8a** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 80/20) as colorless oil (3.6 mg, 11%). $[\alpha]_D^{20}$ −24.7 (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.35−7.22 (m, 5H), 4.62−4.33 (m, 2H), 3.55 (s, 2H), 3.16−3.00 (m, 2H), 2.77 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 10.0 Hz, 1H), 2.55 (s, 3H), 2.30 (t, $^4J_{HH}$ = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 139.4, 129.6, 128.9, 126.7, 82.6 (d, $^1J_{CF}$ = 170.9 Hz), 80.5, 73.2, 64.2 (d, $^2J_{CF}$ = 17.5 Hz), 44.3 (d, $^4J_{CF}$ = 2.0 Hz), 38.5 (d, $^4J_{CF}$ = 1.7 Hz), 33.3 (d, $^3J_{CF}$ = 6.2 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −227.5; IR (ATR) ν_{max}: 3295, 2360, 1454, 1016, 740, 700, 648; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}NF$ 206.1345; Found 206.1341; HPLC purity: eluent MeOH/H_2O/TFA 30/70/0.1, t_r = 10.1 min.

*(R)-2-Fluoro-3-phenylpropan-1-ammonium chloride (**17b**).* Following the procedure for the preparation of **17a**, starting from **13b** (286 mg, 1.23 mmol), compound **17b** (140 mg, 60%) was obtained as a white solid. mp: 236−237 °C (lit. 129−132 °C);[44] $[\alpha]_D^{20}$ + 6.3 (c 1.00, MeOH). Characterization data are in accordance to the published data.[44]

*(R)-N,N-Dimethyl-2-fluoro-3-phenylpropan-1-amine (**18b**).* Compound **18b** was prepared following the procedure described for the synthesis of **10**, starting from **17b** (20 mg, 0.1 mmol), formic acid (0.071 mL, 9.5 mmol), and formaldehyde (37% in H_2O) (0.06 mL, 9.0 mmol). Compound **18b** was obtained without further purification as colorless oil (16 mg, 84%). $[\alpha]_D^{20}$ −21.3 (c 0.83, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.37−7.27 (m, 5H), 5.32−5.14 (m, 1H), 3.44−3.33 (m, 3H), 3.05 (dd, 1H, $^2J_{HH}$ = 23.4 Hz, $^3J_{HH}$ = 6.2 Hz), 2.91 (s, 6H); ^{13}C NMR (100.6 MHz, CD_3OD, TMS) δ 135.3, 129.2, 128.3, 126.8, 89.0 (d, $^1J_{CF}$ = 172.3 Hz), 60.1 (d, $^2J_{CF}$ = 19.9 Hz), 42.9, 38.3 (d, $^2J_{CF}$ = 20.2 Hz); ^{19}F NMR (376.5 MHz, CD_3OD) δ −185.9; IR (ATR) ν_{max}: 2952, 2417, 1474, 998, 749, 697; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{17}NF$ 182.1345; Found 182.1351.

*(R)-N,N-Dipropargyl-2-fluoro-3-phenylpropan-1-amine (**16b**) and (R)-N-Propargyl-2-fluoro-3-phenylpropan-1-amine (**19b**).* Compounds **19b** and **16b** were prepared following the procedure described for the synthesis of **1b**, starting from **17b** (61 mg, 0.32 mmol), K_2CO_3 (143 mg, 1.03 mmol) and a solution of propargyl bromide in toluene (80 wt %, 38 μL, 0.35 mmol). **16b** (15 mg, 20%) and **19b** (28 mg, 46%) were obtained after purification by chromatography on silica gel (heptane/AcOEt, 90/10) as colorless oils. **16b**: $[\alpha]_D^{20}$ −0.7 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.34−7.24 (m, 5H), 4.96−4.78 (m, 1H), 3.51 (d, $^4J_{HH}$ = 2.0 Hz, 4H), 3.04−2.91 (m, 2H), 2.83−2.73 (m, 2H), 2.23 (t, $^4J_{HH}$ = 2.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 137.1 (d, $^3J_{CF}$ = 4.9 Hz), 129.7, 128.8, 127.0, 93.8 (d, $^1J_{CF}$ = 173.2 Hz), 79.0, 73.5, 56.1 (d, $^2J_{CF}$ = 21.3 Hz), 43.5 (d, $^4J_{CF}$ = 2.2 Hz), 39.8 (d, $^2J_{CF}$ = 21.3 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −180.1; IR (ATR) ν_{max}: 3292, 3030, 2926, 1444, 1030, 746, 700, 635; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}NF$ 230.1345; Found 230.1350; HPLC purity: eluent MeOH/H_2O 70/30, t_r = 10.3 min. **19b**: $[\alpha]_D^{20}$ −6.7 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 4.93−4.75 (m, 1H), 3.49 and 3.43 (ABX system, $^2J_{AB}$ = 16.8 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.4 Hz, 2H), 3.09−2.79 (m, 4H), 2.22 (t, $^4J_{HH}$ = 2.4 Hz, 1H), 1.55 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 137.0 (d, $^3J_{CF}$ = 5.6 Hz), 129.6, 128.8, 127.0, 94.3 (d, $^1J_{CF}$ = 171.5 Hz), 82.1, 72.0, 52.0 (d, $^2J_{CF}$ = 20.8 Hz), 39.7 (d, $^2J_{CF}$ = 21.3 Hz), 38.6; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −183.7. IR (ATR) ν_{max}: 3293, 2923, 1454, 1109, 1030; 746, 699, 645; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}NF$ 192.1189; Found 192.1198.

*(R)-N,N-Methylpropargyl-2-fluoro-3-phenylpropan-1-amine (**8b**).* Compound **8b** was prepared following the procedure described for the synthesis of **10** starting from **19b** (18 mg, 94 μmol), formic acid (60 μL, 1.59 mmol), and formaldehyde (37% in H_2O) (71 μL, 0.95 mmol). Amine **8b** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 80/20) as colorless oil (16 mg, 83%). $[\alpha]_D^{20}$ −17.3 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.33−7.23 (m, 5H), 4.92−4.73 (m, 1H), 3.43 and 3.38 (ABX system, $^2J_{AB}$ = 17.2 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.4 Hz, 4H), 3.00−2.92 (m, 2H), 2.70−2.57 (m, 2H), 2.37 (s, 3H), 2.21 (t, $^4J_{HH}$ = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 137.3 (d, $^3J_{CF}$ = 4.6 Hz), 129.7, 128.8, 127.0, 93.2 (d, $^1J_{CF}$ = 172.0 Hz), 78.7, 73.6, 58.9 (d, $^2J_{CF}$ = 21.0 Hz), 46.7 (d, $^4J_{CF}$ = 1.7 Hz), 42.8, 40.0 (d, $^2J_{CF}$ = 21.2 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −180.8; IR (ATR) ν_{max}: 3295, 2945, 1454, 1030, 745, 700, 644; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}NF$ 206.1345; Found 206.1342; HPLC purity: eluent MeOH/H_2O/TFA 30/70/0.1, t_r = 11.4 min.

*(R)-1-(N-Propargylamino)-3-phenylpropan-2-ol (**6b**) and (R)-1-(N,N-Dipropargylamino)-3-phenylpropan-2-ol (**5b**).* Compounds **6b** and **5b** were prepared following the procedure described for the synthesis of **1b**, starting from **3b**[20] (704 mg, 4.66 mmol), K_2CO_3 (1.40 g, 10.13 mmol), and a solution of propargyl bromide in toluene (80 wt %, 0.4 mL, 3.71 mmol). Products **6b** (358 mg, 41%) and **5b** (143 mg, 14%) were obtained after purification by chromatography on silica gel (from 90/10 heptane/AcOEt to 100% AcOEt), respectively, as colorless oil and as white solid. **6b**: mp: 62−63 °C; $[\alpha]_D^{20}$ −39.4 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.35−7.23 (m, 5H), 3.96−3.89 (m, 1H), 3.46 (d, $^4J_{HH}$ = 2.4 Hz, 2H), 2.91 (dd, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 3.0 Hz, 1H), 2.80 (d, $^3J_{HH}$ = 6.4 Hz, 2H), 2.62 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 8.8 Hz, 1H), 2.42 (bs, 2H), 2.24 (t, $^4J_{HH}$ = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 138.4, 129.7, 128.9, 126.8, 82.0, 72.0, 71.0, 53.9, 41.9, 38.3; IR (ATR) ν_{max}: 3283, 3150, 1603, 1462, 1441, 1333, 1102, 1077, 1030, 701, 647; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}NO$ 190.1232; Found: 190.1228; **5b**: $[\alpha]_D^{20}$ −39.4 (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.33−7.21 (m, 5H), 3.96−3.90 (m, 1H), 3.48 (d, 4H, $^4J_{HH}$ = 2.4 Hz), 2.97 (bs, 1H), 2.83−2.73 (m, 2H), 2.70 (dd, 1H, $^2J_{HH}$

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= 12.8 Hz, $^3J_{HH}$ = 3.2 Hz), 2.48 (dd, 1H, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 10 Hz), 2.23 (t, 2H, $^4J_{HH}$ = 2.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 138.4, 129.7, 128.7, 126.7, 78.8, 73.6, 68.7, 58.9, 42.9, 41.5; IR (ATR) ν_{max}: 3289, 2921, 1453, 1330, 1075, 748, 700, 633; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO$ 228.1388; Found 228.1396.

*(R)-1-(N,N-Methylpropargylamino)-3-phenylpropan-2-ol (**7b**).* Compound **7b** was prepared following the procedure described for the synthesis of **10**, starting from **6b** (270 mg, 1.43 mmol), formic acid (0.27 mL, 7.16 mmol), and formaldehyde (37% in H_2O) (0.32 mL, 4.27 mmol). Product **7b** was obtained after purification by chromatography on silica gel (heptane/AcOEt, 85/15) as colorless oil (223 mg, 77%). $[\alpha]_D^{20}$ −26.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.32−7.20 (m, 5H), 3.92−3.85 (m, 1H), 3.40 and 3.34 (ABX system, $^2J_{AB}$ = 17.0 Hz, $^4J_{AX}$ = $^4J_{BX}$ = 2.2 Hz, 2H), 3.18 (bs, 1H), 2.79 (dd, $^2J_{H-H}$ = 13.6 Hz, $^3J_{H-H}$ = 7.2 Hz, 1H), 2.71 (dd, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 5.2 Hz, 1H), 2.54−2.50 (m, 1H), 2.38−2.34 (m, 1H), 2.33 (s, 3H), 2.21 (t, $^4J_{H-H}$ = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS) δ 138.3, 129.3, 128.4, 126.3, 78.3, 73.3, 68.1, 61.2, 46.1, 41.5, 41.3; IR (ATR) ν_{max}: 3286, 2845, 2797, 1602, 1330, 1086, 1029, 747, 699; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd For $C_{13}H_{18}NO$ 204.1388; Found: 204.1380.

*2-(N,N-Benzylmethylamino)ethanol (**24**).* Compound **24** was prepared following the procedure described for the synthesis of **10**, starting from 2-benzyloaminoethanol (1.0 g, 6.6 mmol), formic acid (1.25 mL, 33 mmol), and formaldehyde (37% in H_2O) (1.50 mL, 19.8 mmol). Compound **24** was obtained after purification by chromatography on silica gel (DCM/MeOH, 99/1 to 87/2) as colorless oil (555 mg, 61%). Characterization data are in accordance to the published data.[45]

Typical Procedure for Radiofluorination. No-carrier-added aqueous [^{18}F]-fluoride was produced by ^{18}O[p,n]^{18}F nuclear reaction of a target consisting of ^{18}O-enriched water (97%, Eurisotop, France) irradiated with a 18 MeV proton beam. [^{18}F]-fluoride was trapped on a quaternary ammonium solid phase extraction cartridge (QMA Waters preconditioned with K_2CO_3, ABX, Germany) then eluted with tetrabutylammonium carbonate. After three azeotropic evaporations with acetonitrile at 90 °C under nitrogen steam, dry [^{18}F]-fluoride was cooled down to RT. Triflic anhydride (1 M in CH_2Cl_2, 37 μL) was added to a solution of **1** (33 μmol) in CH_2Cl_2 (260 μL). After 1 h of reaction at RT, DIPEA (40 μmol) in CH_3CN (200 μL) was added to the crude and allowed to react for 1 min. Then, the reaction mixture was transferred into the vial containing dry [^{18}F]-fluoride (40 MBq) and tetrabutylammonium carbonate (23 μmol). The solution was stirred at RT for 30 min. An aliquot (0.025 mL) was taken off and diluted in MeOH (0.2 mL). Analyses were performed by radio-TLC to establish the RCY and by radio-HPLC to measure the isomer ratio. Identity of the radiofluorinated compounds was assessed by HPLC coelution with nonradioactive reference ^{19}F-compounds. HPLC chromatograms shown below are the coinjection of the radioactive crude radiofluorination with nonradioactive reference product. Radioactivity detector (NaI probe) is placed in line after the UV detector generating a delay of 0.48 min between both signals.

*Radiosynthesis of [^{18}F]**2a** and [^{18}F]**2b** using a GE TRACERLab FX N Pro module.* A solution of labeling precursor **1a** (11 mg, 33 μmol) and triflic anhydride (37 μL, 37 μmol) in CH_2Cl_2 (0.55 mL) was stirred for 1 h at RT before addition to vial 4. The fluorine-18 produced by the cyclotron was trapped on an ion-exchange resin (QMA light, Waters, ABX), separated from ^{18}O-enriched water, and then eluted with a solution of tetrabutylammonium carbonate (0.1 M in water, 200 μL) and acetonitrile (0.3 mL) (vial 1). The mixture was heated to 95 °C under reduced pressure under a flow of helium. 0.6 mL of acetonitrile (vial 2) was added, and the mixture was further heated at 95 °C under reduced pressure. Then the reactor 1 was cooled down at RT (<28 °C). Precursor solution (vial 4) and a solution of *N*,*N*-diisopropylethylamine (7 μL) in acetonitrile (193 μL) (vial 5) were added to the reactor. The fluorination reaction occurred during 30 min at RT under stirring before MeOH (2 mL) (vial 6) was added to the reactor. Then the reaction mixture was concentrated under vacuum at RT to eliminate CH_2Cl_2. HPLC eluent (2 mL) (vial 3) was added to the reactor to dissolve the reaction mixture for the HPLC injection (column: XTerra C18, 250 × 10 mm, Waters; eluent: MeOH/H_2O 75/25; flow rate: 5 mL/min). The both isomer products [^{18}F]**2a** and [^{18}F]**2b** were collected together (retention time: t_r(**2a**) = 20.5 min; t_r(**2b**) = 22.1 min). The collected fraction containing the two pure radiolabeled isomers was injected in HPLC to determine the ratio between both products, to measure the specific activity, and to assess their identity by coelution with reference compounds (column: Nucleodur C18 Gravity, Macherey-Nagel, 250 × 4.6 mm, 5 μm; eluent: MeOH/H_2O 85/15; flow rate: 1 mL/min; UV detection at λ= 210 nm). The radiosynthesis was performed within 75 min, and the decay corrected radiochemical yields were between 3 and 10%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01714.

Supplementary figures, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra for all new compounds, and HPLC characterization of all the radiolabeled compounds (PDF)

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Notes

The authors declare no competing financial interest.

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