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[^{18}F]Fluorophenyl-L-Amino Acids by Isotopic Exchange on Carbonyl-activated Precursors

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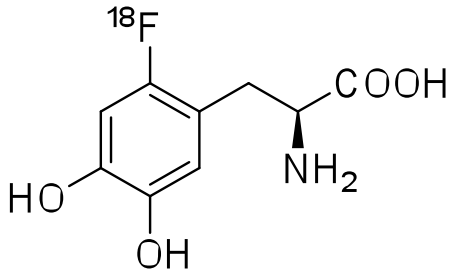
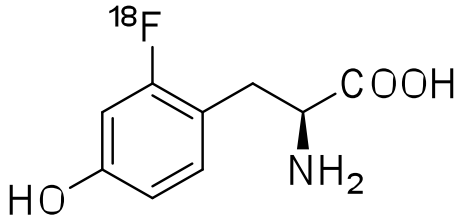
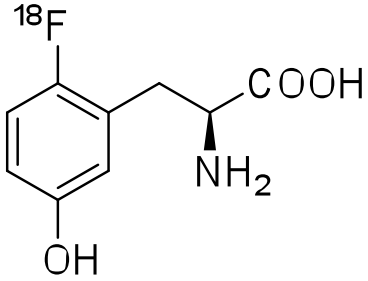
[^{18}F]Fluorophenyl-L-amino acid analogues



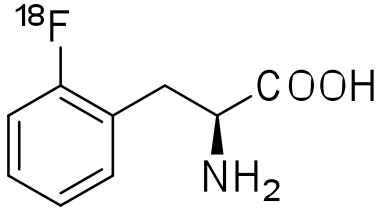
6-[^{18}F]Fluoro-L-DOPA
Garnett, *et al*., Nature 1983, 305, 137.



2-[^{18}F]Fluoro-L-tyrosine
Coenen, H.H. *et al*., J. Nucl. Med. 1989, 30, 1367.

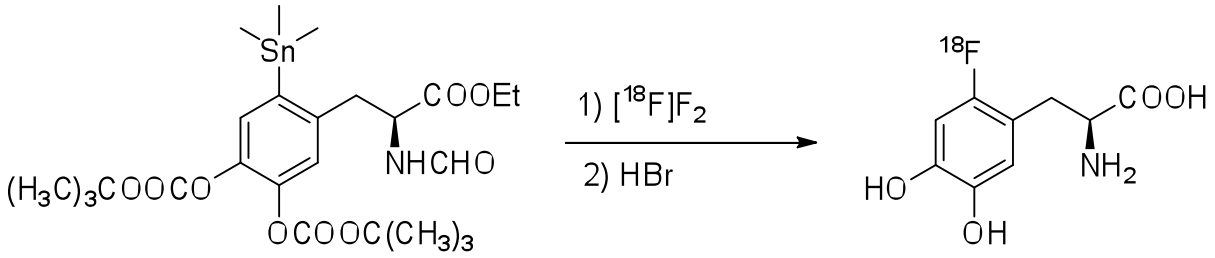


6-[^{18}F]Fluoro-L-*m*-tyrosine
DeJesus, O. T. *et al*., J. Label. Compds. Radiopharm. 1989, 26, 133.

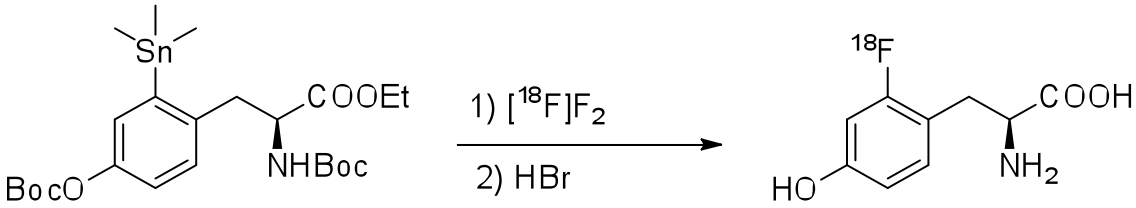


2-[^{18}F]Fluoro-L-phenylalanine
Ito, H.*et al*., J. Nucl. Med. 1995, 35, 1232.
Coenen, H.H. *et al*., Int. J. Rad. Appt. Instrum. Part A. 1988, 39, 1243

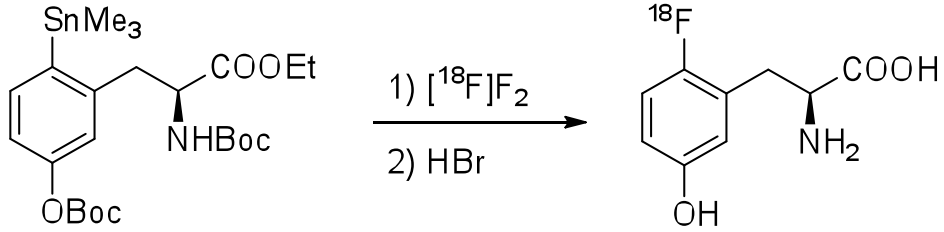
Synthesis of [^{18}F]fluorophenyl-L-amino acids by destannylation reactions



Navamari, M. *et al*., Appl. Radiat. Isot. 1992, *43*, 989.
de Vries, E. F. J. *et al*., Appl. Radiat. Isot. 1999, *51*, 389.

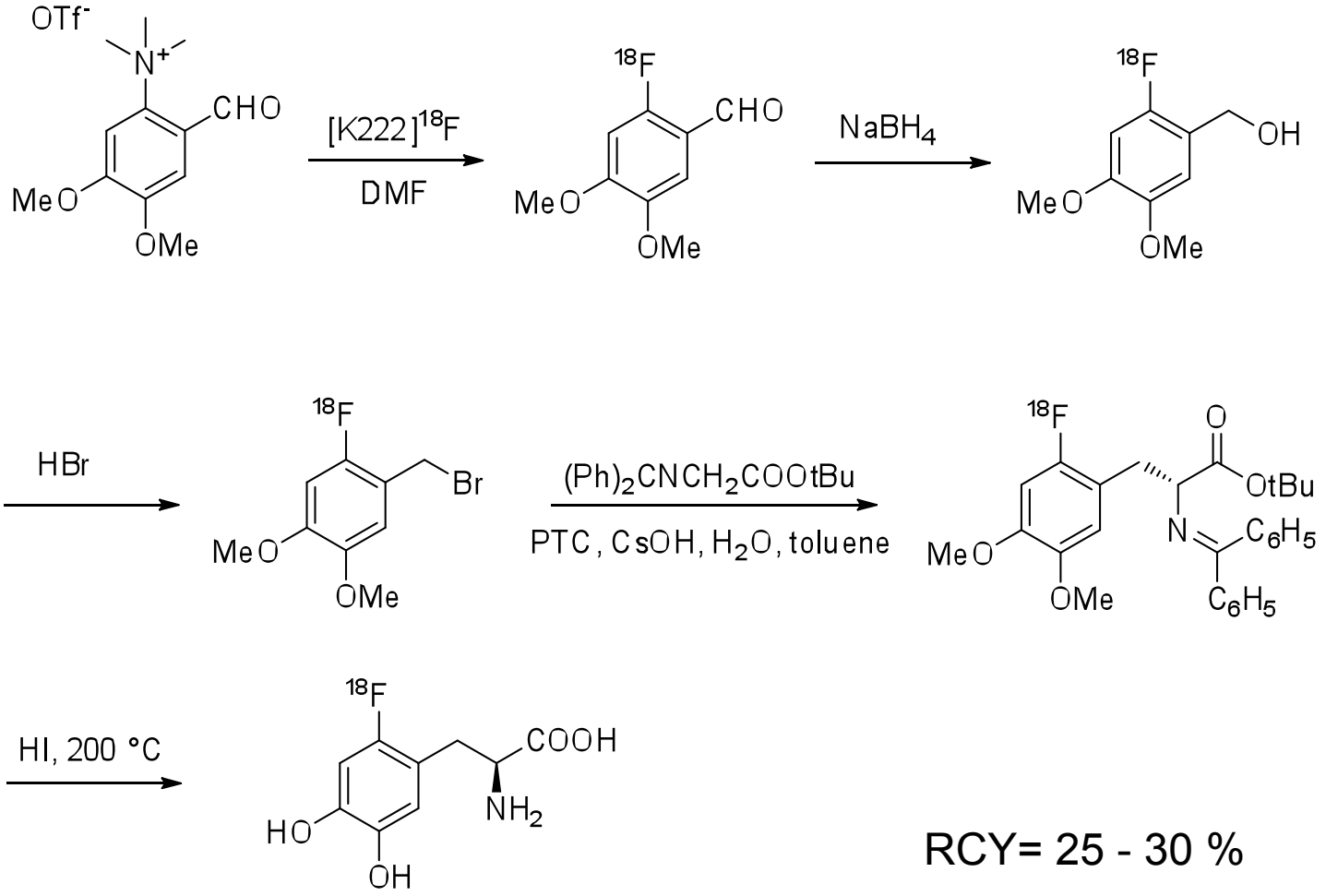


Hess, E. *et al*., Appl. Radiat. Isot. 2002, *57*, 185.



VanBrocklin, H. F. *et al*., Appl. Radiat. Isot. 2004, *61*, 1289.

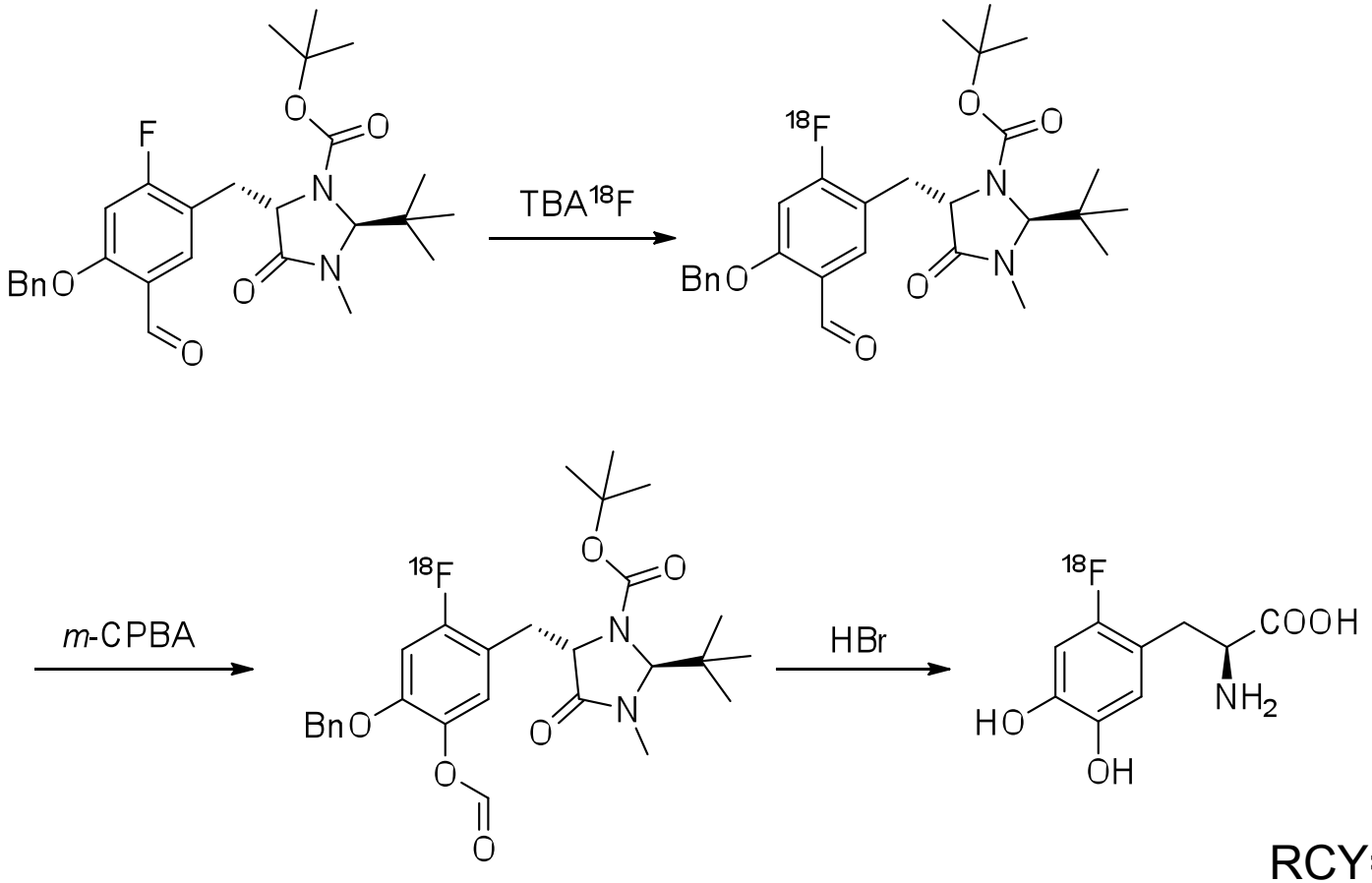
Latest asymetric build-up synthesis of n.c.a. 6-[^{18}F]fluoro-L-DOPA



RCY= 25 - 30 %

Lemaire C. *et al., Eur.* J. Org. Chem. 2004, 2899.

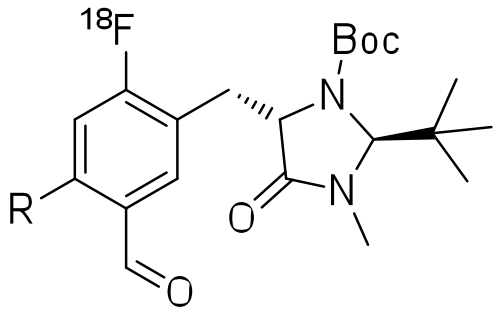
Nucleophilic synthesis of c.a. 6-[^{18}F]fluoro-L-DOPA by isotopic exchange



RCY= 22 %
e.e.= >96 %

Wagner F. M. *et al.*, J. Nucl. Med. 2009, *50*, 1724.

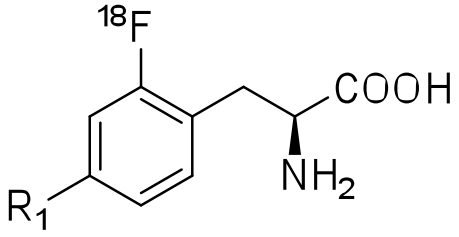
General synthetic concept for nucleophilic synthesis of aromatic [^{18}F]fluoroamino acids by isotopic exchange



R = OBn

R = H

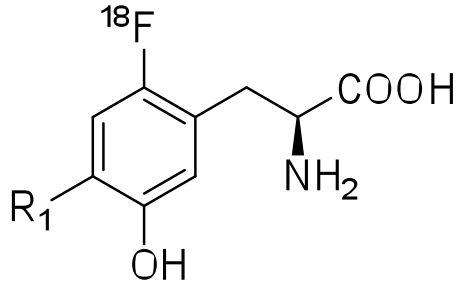
Decarbonylation



R_1 = OH, 2-[^{18}F]fluoro-L-tyrosine

R_1 = H, 2-[^{18}F]fluoro-L-phenylalanine

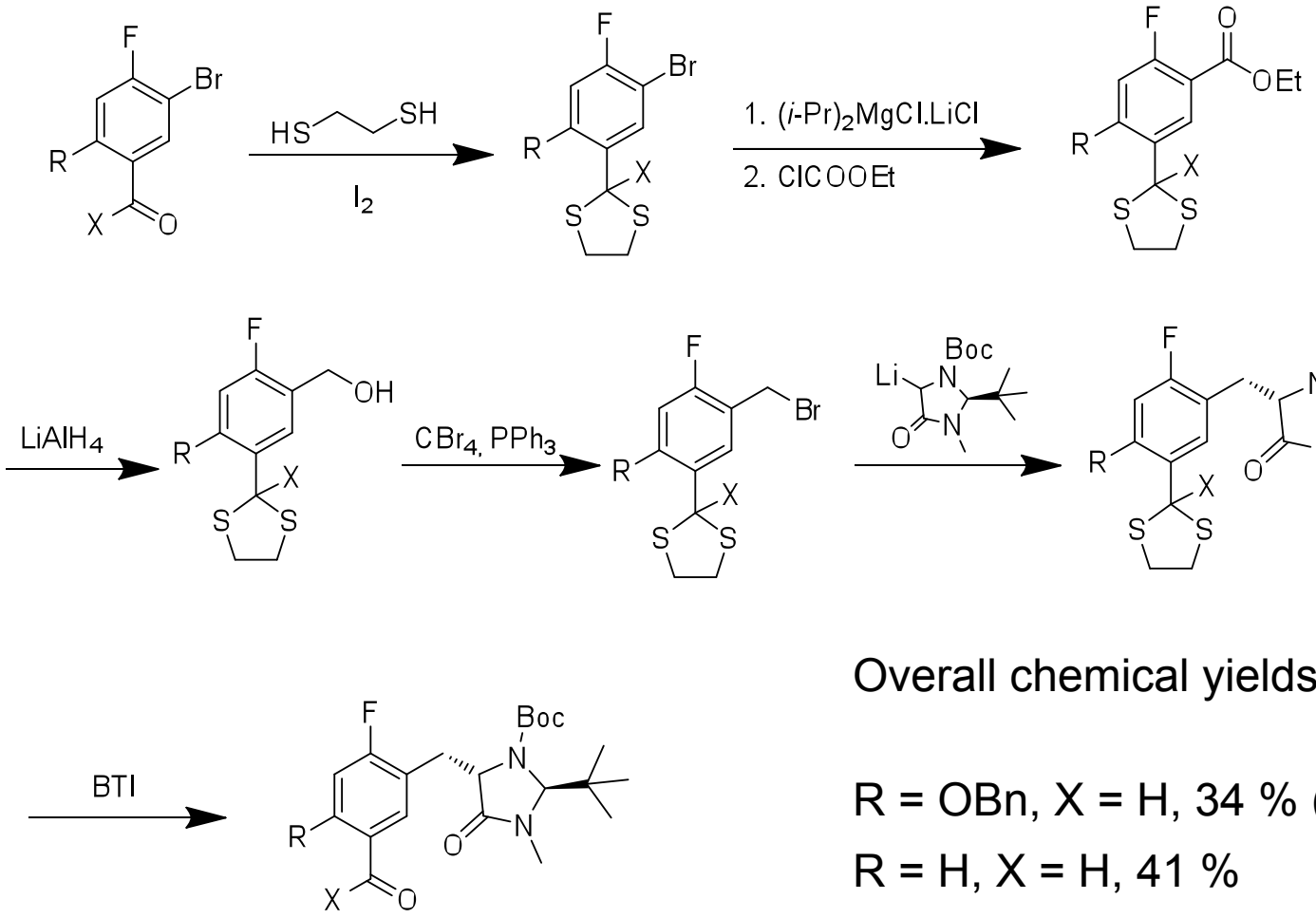
Oxidation



R_1 = OH, 6-[^{18}F]fluoro-L-DOPA

R_1 = H, 6-[^{18}F]fluoro-L-*m*-tyrosine

Synthesis of corresponding precursors



Overall chemical yields

R = OBn, X = H, 34 % (19 %)

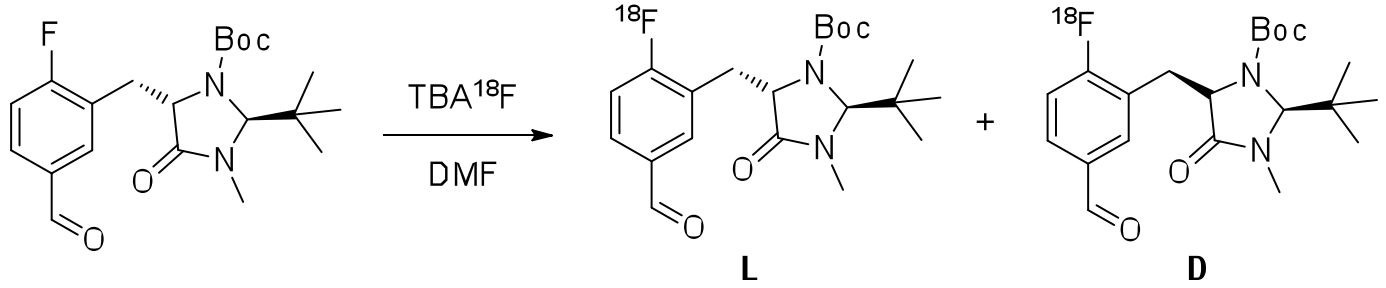
R = H, X = H, 41 %

R = H, X = CH_3, 48 %

Castillo Meleán, J. *et al*., Tetrahedron, 2010, *66*, 9996.

Radiofluorination of 2-[^{18}F]fluoro-L-phenyl-alanine and 2-[^{18}F]fluoro-L-tyrosine precursors

^{19}F/^{18}F isotopic exchange reaction under conventional heating[a,b]



L **D**

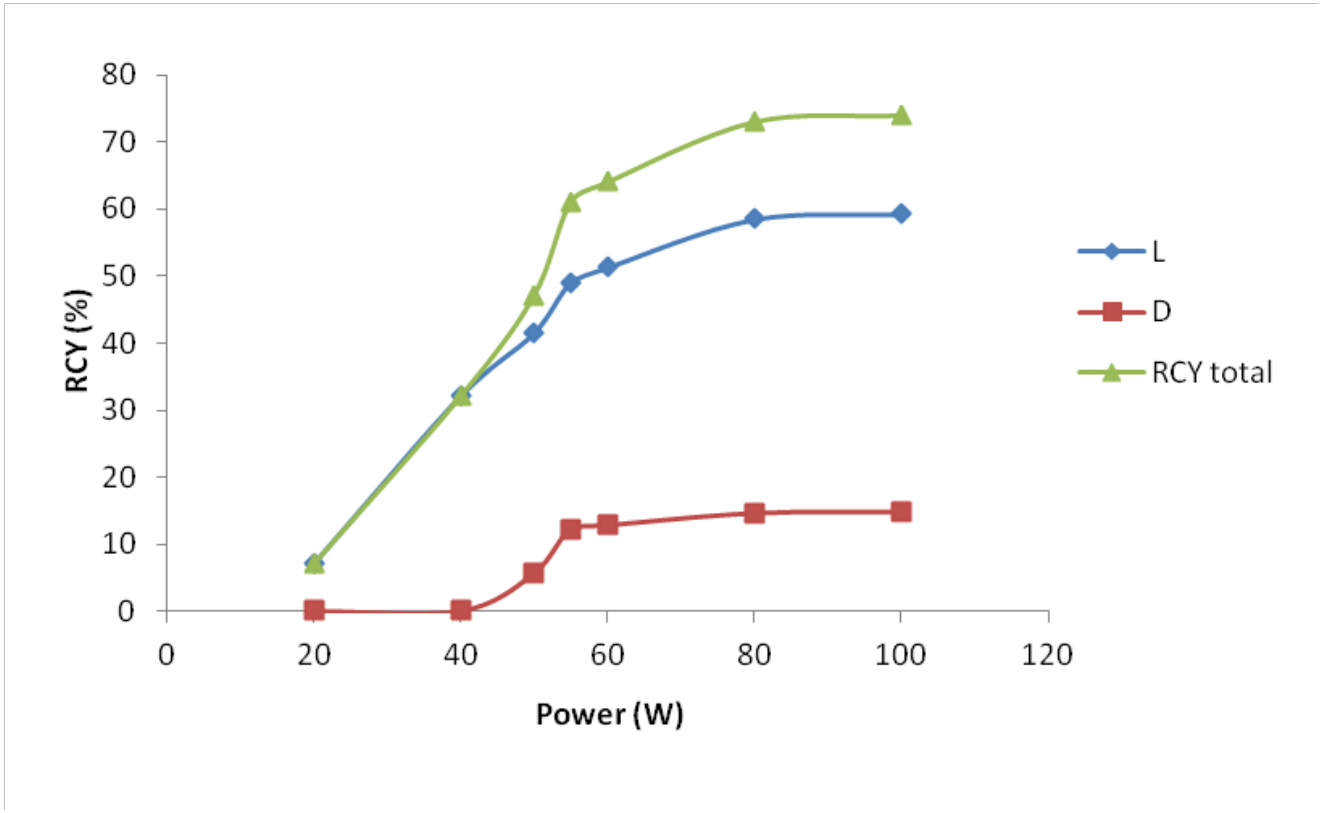
		10 min		20 min	
PTC[c] [µmol]	**Temp. (°C)**	**L (%)**	**D (%)**	**L (%)**	**D (%)**
$TBAHCO_3$ [2.3]	130	28	0	39	0
$TBAHCO_3$ [5.2]	130	51	6	57	7
$TBAHCO_3$ [8.5]	130	60	10	59	14
$TBAHCO_3$ [17.0]	130	61	17	52	30
$TBAHCO_3$ [5.2]	150	26	24	-	-
$[K222]_2CO_3$ [13.0]	130	26	40	14	50

[a]SD = ±5%. [b]1 mL DMF, 15 µmol prec. [c]PTC = phase transfer catalyst

Castillo Meleán, J. *et al.*, Org. Biomol. Chem. 2011, 9, 765.

Radiofluorination of 2-[^{18}F]fluoro-L-phenyl-alanine and 2-[^{18}F]fluoro-L-tyrosine precursors

^{19}F/^{18}F isotopic exchange reaction under microwave heating

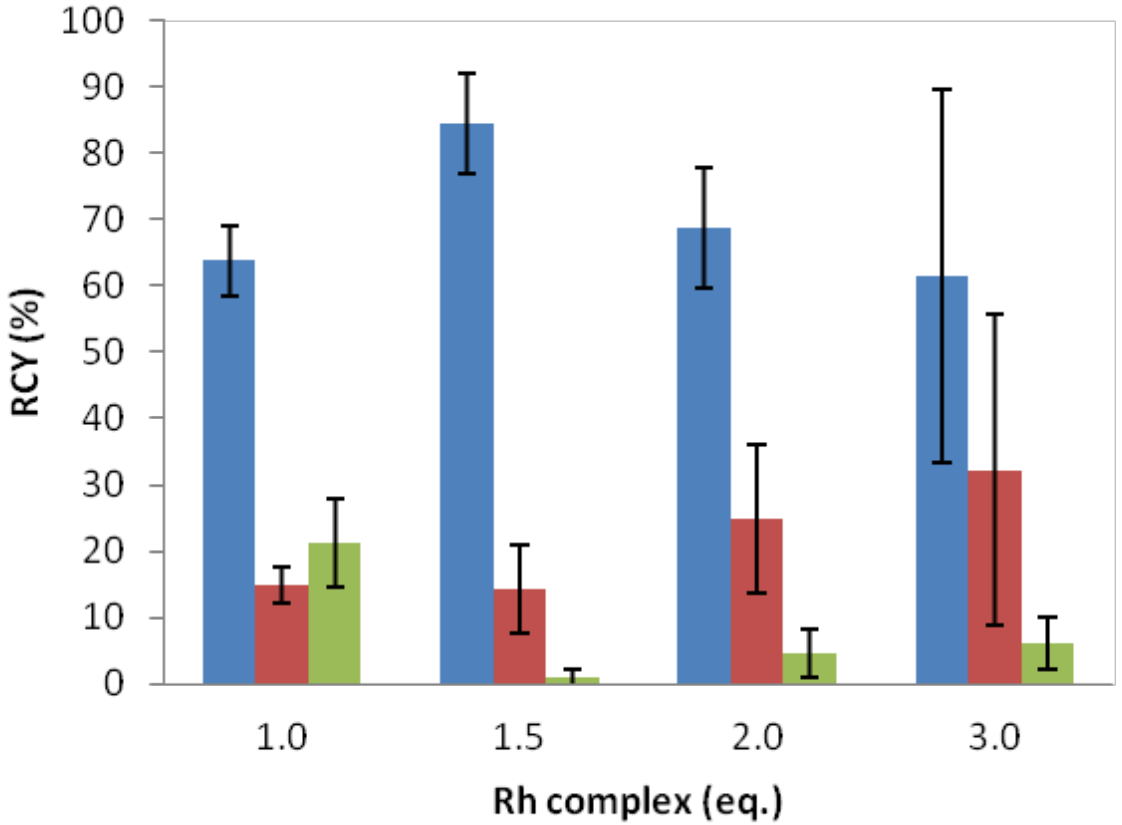


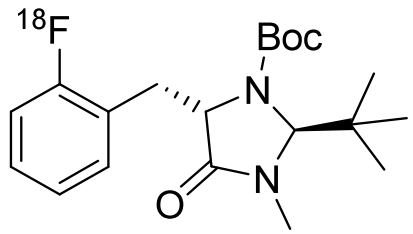
15 µmol precursor, $TBAHCO_3$ 5.1 µmol, 1 mL DMF, 1 min

Castillo Meleán, J. *et al.*, Org. Biomol. Chem. 2011, 9, 765.

Decarbonylation reaction

Decarbonylation under conventional heating





product

by-product

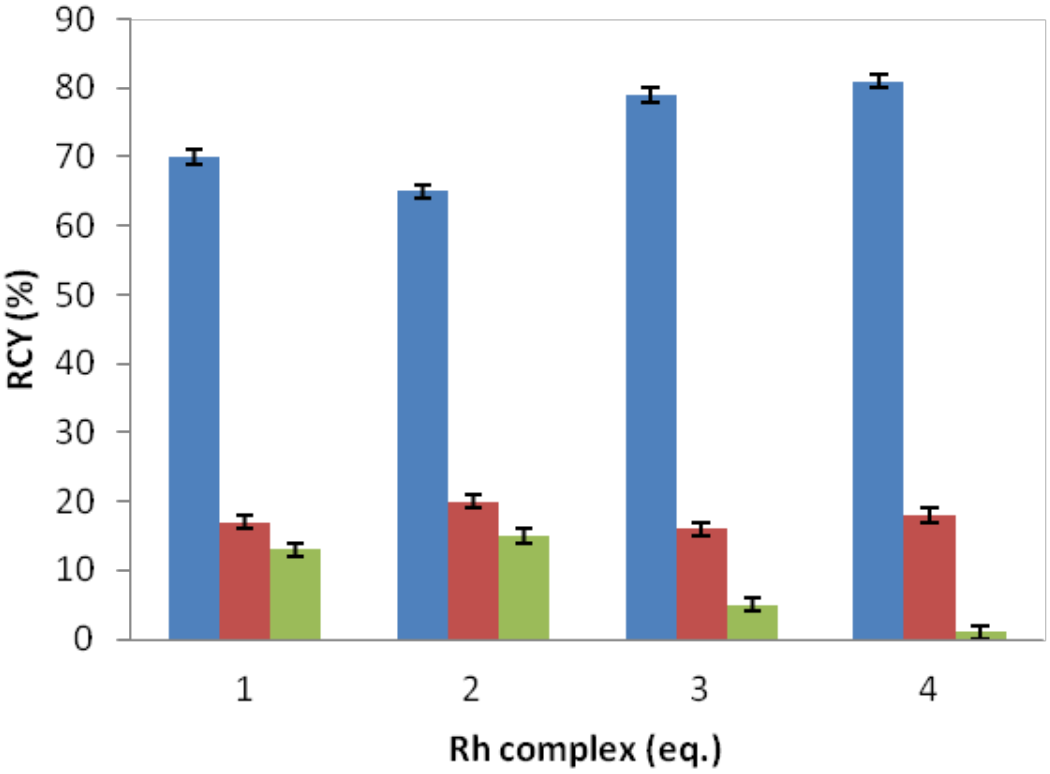
start. mat.

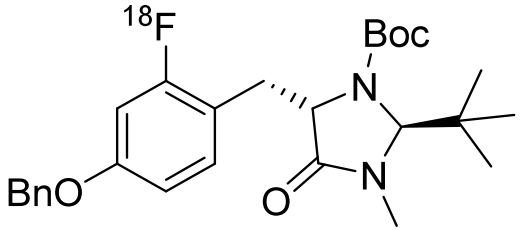
1 mL dioxane, 150 °C, 20 min.

Castillo Meleán, J. *et al.*, Org. Biomol. Chem. 2011, 9, 765.

Decarbonylation reaction

Decarbonylation under microwave heating





product
by-product
start. mat.

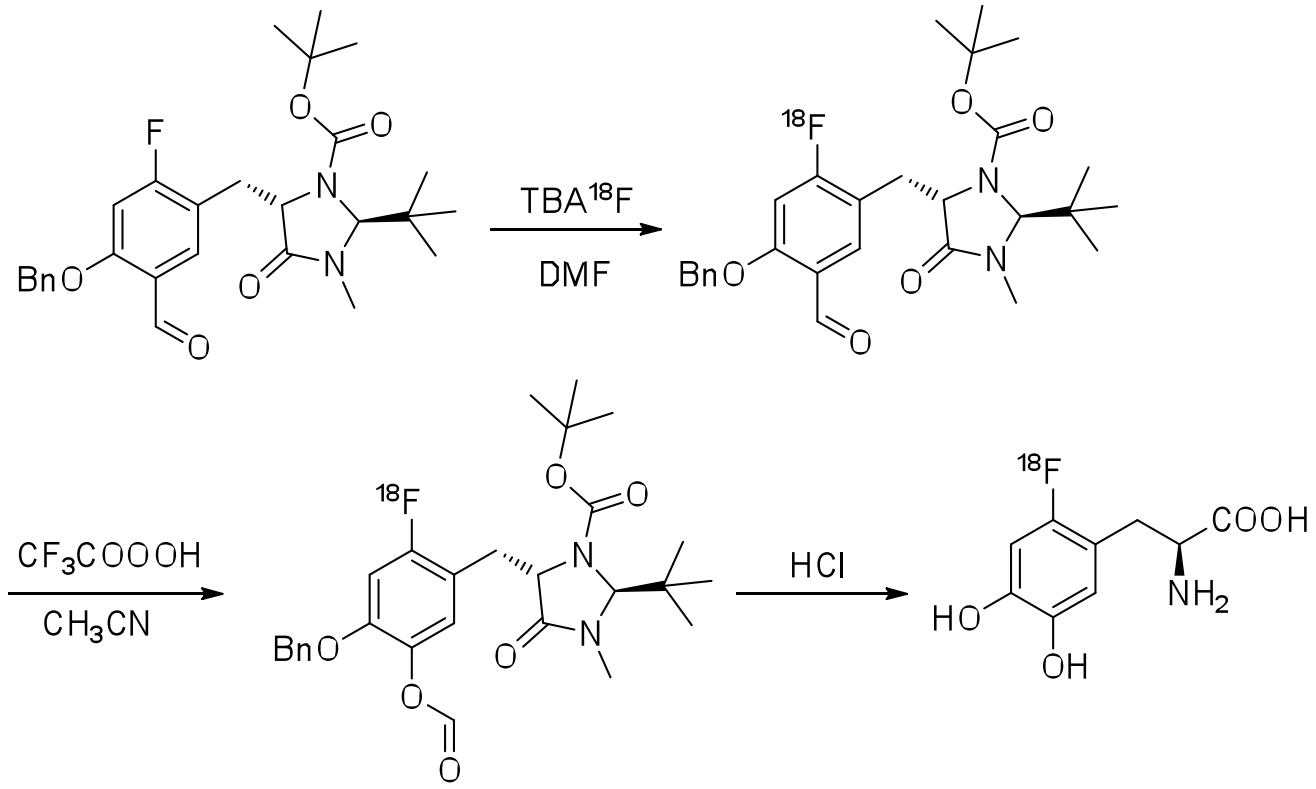
1 mL benzonitrile, 100 W, 50 s.

Castillo Meleán, J. *et al.*, Org. Biomol. Chem. 2011, 9, 765.

Summary of radiosynthesis of 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine

- Hydrolysis of the decarbonylated compounds was performed using concentrated HCl and yielded quantitatively the hydrolyzed products.
- The conventional heated reactions yielded 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine in 43% and 49%.
- 34% and 43% RCYs were obtained when microwave heating was applied (38 min reaction time were saved using microwave heating).
- The *e.e.* achieved for 2-[^{18}F]fluoro-L-phenylalanine was 88% while an *e.e* of 92% was obtained in the case of 2-[^{18}F]fluoro-L-tyrosine.

Radiosynthesis of 6-[^{18}F]fluoro-L-DOPA

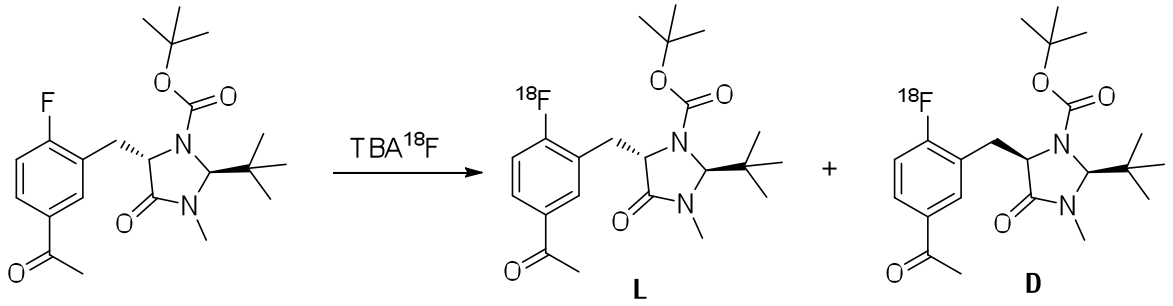


RCY = 40 %
e.e.= 92 %

- Control and identification of side products.
- Optimized BV-oxidation: reduction of reaction time and less toxic solvent.
- Optimized hydrolysis reaction producing quantitative yield.

Radiofluorination of 6-[^{18}F]fluoro-L-*m*-tyrosine precursor

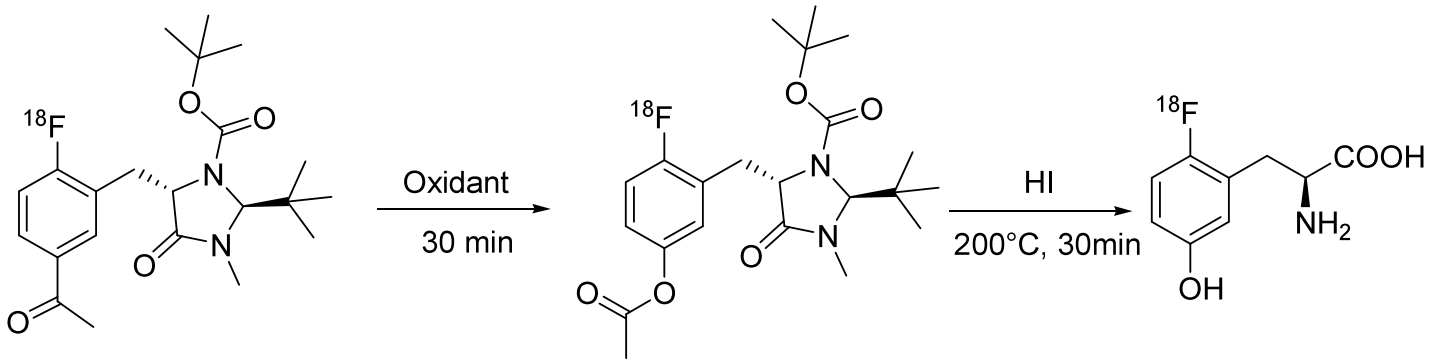
Influence of temperature, time and kind of anion activation on the RCY of the isotopic exchange reaction[a,b]



Solvent	PTC[c] [µmol]		Temp. °C	10 min		20 min	
				L (%)	D (%)	L (%)	D (%)
DMF	$TBAHCO_3$	[7.7]	130	0	0	0	0
DMF	$TBAHCO_3$	[7.7]	150	0	0	0	0
DMSO	$TBAHCO_3$	[7.7]	130	5	0	7	0
DMSO	$TBAHCO_3$	[7.7]	160	16	0	18	0
DMSO	$TBAHCO_3$	[7.7]	180	15	2	16	3
DMSO	$TBAHCO_3$	[10.3]	160	14	6	16	7
DMSO	$TBAHCO_3$	[13.0]	160	21	12	20	13
DMSO	$[K222]CO_3$	[13.0]	160	4	27	5	40

[a]SD = ±3%. [b]1 mL solvent, 15 µmol precursor, conventional heating. [c]PTC = phase transfer catalyst.

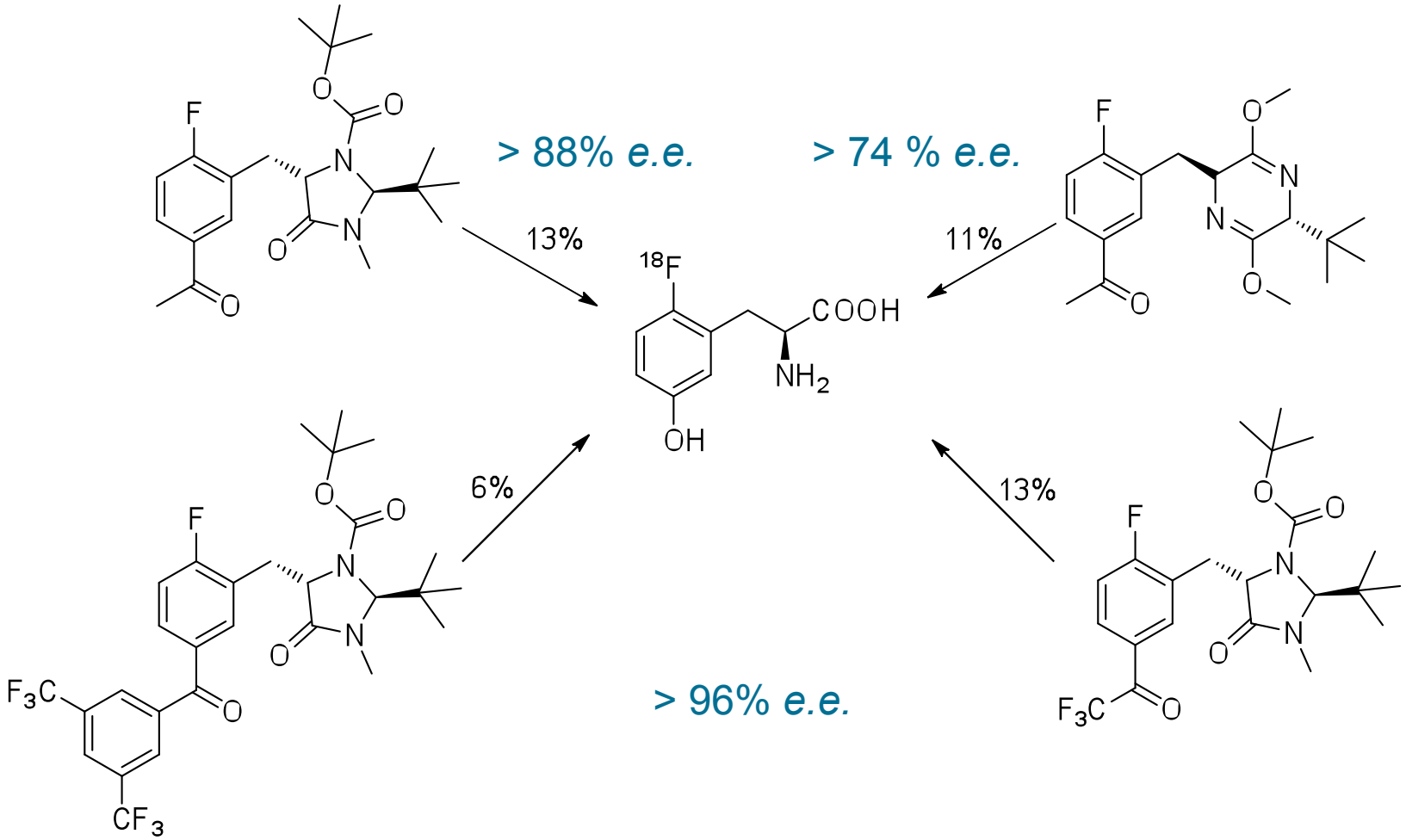
Baeyer-Villiger oxidation and subsequent hydrolysis



Solvent	Oxidant	Temp. (°C)	Yield (%)	enant. purity (%)
CH_3Cl	*m*-CPBA	60	13	>99
CH_3Cl	CH_3COOOH	60	68	97
CH_3Cl	CF_3COOOH^*	60	86	94

*CF_3COOOH was formed *in situ* from sodium percarbonate and trifluoroacetic anhydride.

Comparison of different precursors for isotopic exchange synthesis of 6-[^{18}F]fluoro-*m*-L-tyrosine



Conclusions

- A nucleophilic synthesis of 2-[^{18}F]fluoro-L-phenylalanine and 2-[^{18}F]fluoro-L-tyrosine by isotopic exchange has been developed. The radiosynthetic procedure leads to the amino acids in ca. 40% overall radiochemical yield with high enantiomeric purity of > 93%.
- The nucleophilic radiosynthesis of 6-[^{18}F]fluoro-L-DOPA by isotopic exchange could be optimized providing the tracer with ca. 40% RCY and a high enantiomeric purity of > 96%.
- 6-[^{18}F]Fluoro-L-*m*-tyrosine was only achieved using a phenone derivative precursor in13% overall RCY with an enantiomeric purity of > 93%.
- The specific activity of the tracers prepared here was at least as high as that achieved by electrophilic methods and it will increase further with higher starting activity.