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A metal-templated synthesis of precursors for (2*S*)- and (2*R*)-2-(3-[^{18}F]fluoropropyl)tyrosines as potential radiotracers for positron emission tomography

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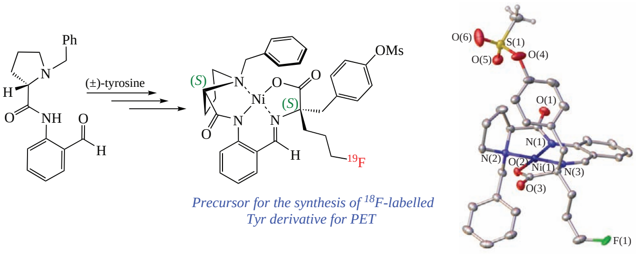
New asymmetric metal-templated synthesis of enantiomers of (2*S*)- and (2*R*)-2-(3-[^{19}F]fluoropropyl)tyrosine precursors were obtained based on a chiral Ni^{II} complex of the Schiff base derived from (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]-benzaldehyde and racemic tyrosine in five steps. The free tyrosine derivatives which can be obtained upon decomplexation seem promising radiotracers for positron emission tomography imaging provided the introduction of ^{18}F isotope.



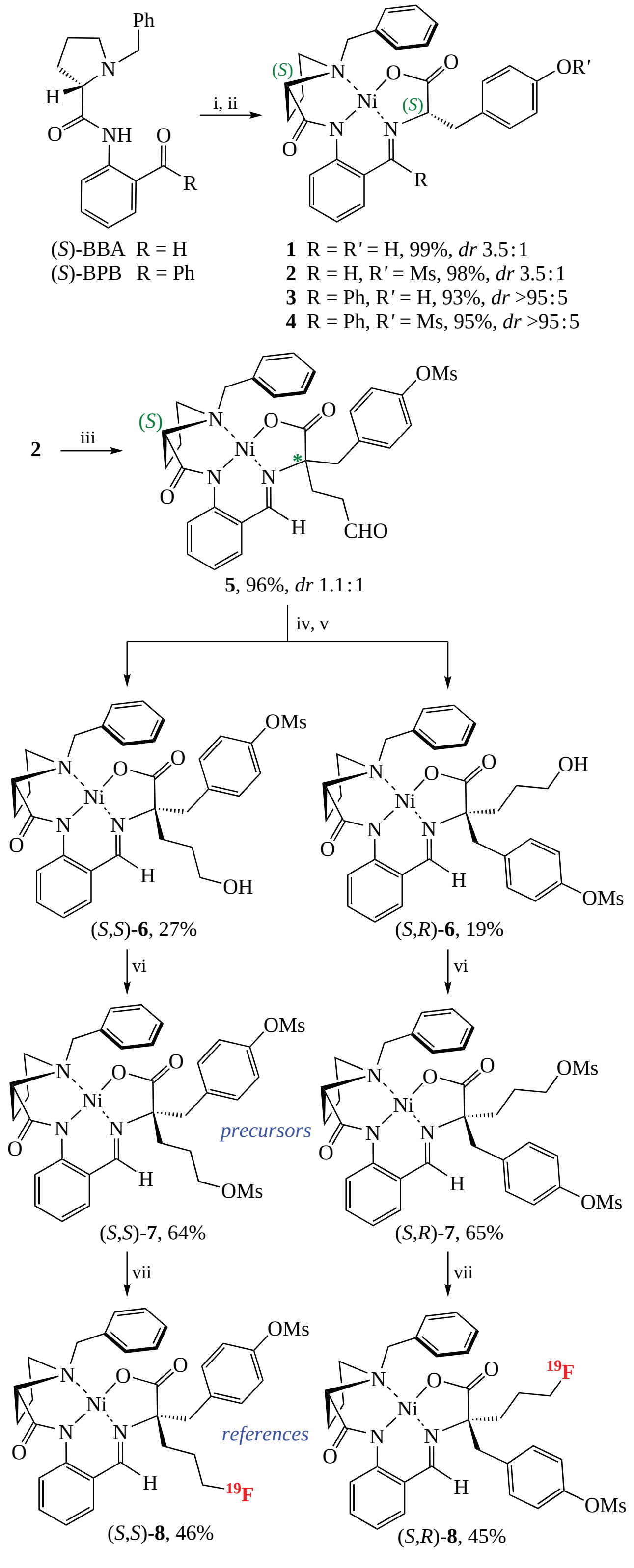
Keywords: ^{18}F-labelled amino acids, tyrosine, asymmetric synthesis, nucleophilic substitution, nickel(II) complexes.

In 1927, Otto Warburg discovered that malignant tumors have an increased rate of glucose consumption.[1] In 1977, the Sokoloff group proposed measuring the metabolic rate of glucose in the brain of rats using deoxyglucose labelled with a radioactive carbon isotope [^{11}C],[2,3] which was later replaced with the radioactive ^{18}F isotope labelled fluorodeoxyglucose, which is now the most commonly used radiotracer for positron emission tomography (PET) imaging in cancer diagnosis.[4] However, glucose is also taken up by macrophages, which are produced in areas of inflammation, leading to false positive results in PET scans. The use of labelled amino acids (AAs) may be the solution to this problem,[5–10] but their introduction into PET practice has been hindered by the complexity of obtaining fluorine-18 labelled analogues.[8–10] The choice of this isotope is obvious, as radiotracers with short-lived isotopes ($T_{1/2} < 30$ min) are not commercially available, but must be produced in a radiochemical laboratory using a PET cyclotron.

In 2008, a novel method was developed for the synthesis of a potent radiotracer based on AA, (*S*)-*O*-(2′-[^{18}F]fluoroethyl)-tyrosine (^{18}F-FET).[11] Since then, ^{18}F-FET has become widely used in PET imaging worldwide, but its production requires expensive precursors and identification standards, the synthesis of which are protected by patents. At the moment, there are several challenges with the synthesis of radiotracer precursors. Firstly, the range of available radiotracers is limited, and new types must be developed.[5–10] Secondly, we need a way to obtain enantiomerically pure ^{19}F-containing (*S*)-amino acids as standard compounds for PET.[11] Thirdly, there is an issue with purifying the desired products when using tetraalkylammonium fluorides[12] and other catalysts to replace good leaving groups with fluorine.[13] Fourthly, there is also a concern about dehydrofluorination of the target products as the fluoride anion is a strong base and can cause epimerization of the AA fragment when precursors with α-positioned hydrogen atoms are used.[14]

We and others have recently developed methods for the synthesis of fluorine-containing AAs, potential radiotracers, starting from the chiral Belokon's[15] Ni^{II} complexes of glycine and dehydroalanine.[11,16–21] These methods use nucleophilic fluorination, which has helped to solve some problems associated with introducing the fluorine-18 isotope into the molecules. This has allowed us to develop an effective method for producing [^{19}F]-containing AAs, which can be used as standards or references for PET. The use of this metal-templated strategy has several advantages, including high reproducibility and robustness. The chiral auxiliary provides asymmetric induction and the Ni ion helps to organize the proper geometry of the molecule, simultaneously acting as a protective group for the *N*- and *O*-termini of the AA and increasing the acidity of the α-protons in the AA residue.[15]

Herein, we describe a convenient and practically useful synthesis of enantoimerically pure (2*S*)- and (2*R*)-2-(3-[^{19}F]-fluoropropyl)-containing Tyr precursors based on a metal-templated protocol using a chiral Ni^{II} complex **1** prepared from the Schiff base derived from (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]-benzaldehyde (BBA)[22] and racemic Tyr (Scheme 1). The investigations were started with synthesizing chiral Ni^{II} complexes **1** and **3** using a literature procedure.[11,23] The reaction of the Belokon's chiral auxiliary (*S*)-BBA[22] with racemic Tyr and $Ni(NO_3)_2 \cdot 6H_2O$ in the presence of MeONa yielded the desired Ni^{II} complex **1** as a 3.5 : 1 diastereomer mixture in a yield of 99%. Complex **1** was isolated by simple filtration and used without further purification in subsequent steps (see Scheme 1). As expected, complexation with more bulky (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]benzophenone ligand (*S*)-BPB[24] provided complex **3** with high diastereoselectivity (*dr* > 95 : 5) and in high yield (93%).[11] Next, the hydroxy group of Tyr appendage in both complexes **1** and **3** was successfully protected with a mesyl group to afford complexes **2** and **4** with 98 and 95% yields, respectively.



Scheme 1 *Reagents and conditions*: i, (*S*)-BBA or (*S*)-BPB, Ni(NO$_3$)$_2$·6H$_2$O, *rac*-Tyr, MeONa, MeOH, 45 °C, 1 h; ii, MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 → 20 °C, 8 h; iii, CH$_2$=CHCHO, Et$_3$N, MeOH, room temperature, 24 h; iv, NaBH$_4$, EtOH, 30 min, room temperature; v, chromatography on SiO$_2$, eluent: CHCl$_3$/acetone (1:1); vi, MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 → 20 °C, 15 min; vii, KF, 1 M Bu$_4$NF/THF, MeCN, 80 °C, 5 h.

Further, the Michael addition of complex **4** to acrolein was attempted. However, the reaction failed, most likely due to steric hindrance. In contrast, the reaction between complex **2** and acrolein gave the Michael addition product **5** as a mixture of diastereomers (*dr* 1.1:1) in a nearly quantitative yield (96%). This mixture was then treated with sodium borohydride in absolute ethanol (see Scheme 1). The resulting diastereomeric mixture was easily separated by preparative TLC on silica gel, giving (*S*,*S*)-**6** and (*S*,*R*)-**6** in 27 and 19% yields, respectively. Low yields in this step could be attributed to the possibility of reduction of the imine bond in the complex. In the next step, the hydroxy group in complexes **6** was mesylated resulting in compounds (*S*,*S*)-**7** and (*S*,*R*)-**7** (64 and 65% yields, respectively), which may serve as target PET precursors for ^{18}F labelling.[11,16,18] To demonstrate the possibility of nucleophilic substitution of the Ms group with a fluorine-19 atom in the aliphatic fragment, complexes **7** were treated with anhydrous KF in the presence of 1 M Bu$_4$NF in acetonitrile at 80 °C. The fluorinated complexes (*S*,*S*)-**8** and (*S*,*R*)-**8**, which can be used as standard compounds for PET, were isolated with yields of 46 and 45%, respectively. Importantly, the structures and absolute configurations of complexes (*S*,*S*)-**6** and (*S*,*S*)-**8** were unambiguously determined by single crystal XRD analysis (Figure 1).†

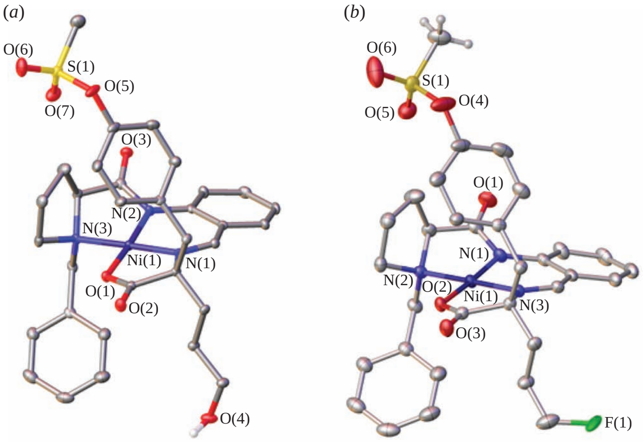


Figure 1 Structures of Ni^{II} (*a*) complex (*S*,*S*)-**6** and (*b*) complex (*S*,*S*)-**8** determined by single crystal XRD analysis. Hydrogen atoms, except for those in the OH group, are omitted, and other atoms are shown as thermal ellipsoids at the 50% probability level. Only heteroatoms are labelled.

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† *Crystal data for* (*S*,*S*)-**6**. Red crystals of (*S*,*S*)-**6** (C$_{32}$H$_{35}$N$_3$NiO$_7$S, *M* = 664.40) are orthorhombic, space group *P*2$_1$2$_1$2$_1$, at 120 K, *a* = 10.3241(8), *b* = 12.6869(9) and *c* = 23.0256(16) Å, *V* = 3015.9(4) Å^3, *Z* = 4, d_{calc} = 1.463 g cm^{-3}, μ(MoKα) = 7.66 cm^{-1}, *F*(000) = 1392. Intensities of 24286 reflections were measured with a Bruker APEX2 CCD diffractometer [λ(MoK$_\alpha$) = 0.71073 Å, ω-scans, 2θ < 58°], and 8014 independent reflections were used in further refinement. The refinement converged to wR_2 = 0.0829 and GOF = 0.974 for all the independent reflections [R_1 = 0.0450 was calculated against *F* for 6263 observed reflections with $I > 2\sigma(I)$].

Crystal data for (*S*,*S*)-**8**. Red crystals of (*S*,*S*)-**8** (C$_{32}$H$_{34}$FN$_3$NiO$_6$S, *M* = 666.39) are orthorhombic, space group *P*2$_1$2$_1$2$_1$, at 120 K, *a* = 10.3000(8), *b* = 12.5677(9) and *c* = 23.1153(17) Å, *V* = 2992.2(4) Å^3, *Z* = 4, d_{calc} = 1.479 g cm^{-3}, μ(MoKα) = 7.75 cm^{-1}, *F*(000) = 1392. Intensities of 60964 reflections were measured with a Bruker APEX2 CCD diffractometer [λ(MoK$_\alpha$) = 0.71073 Å, ω-scans, 2θ < 58°], and 7945 independent reflections were used in further refinement. The refinement converged to wR_2 = 0.0818 and GOF = 1.041 for all the independent reflections [R_1 = 0.0367 was calculated against *F* for 7945 observed reflections with $I > 2\sigma(I)$]. Using Olex2,[25] the structure was solved with the ShelXT[26] structure solution program using Intrinsic Phasing and refined with the XL refinement package[27] using Least-Squares minimisation. Hydrogen atom of the OH group was located from difference electron density maps, positions of other hydrogen atoms were calculated, and they all were refined in the isotropic approximation within the riding model.

CCDC 2314694 and 2321327 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

The introduction of the [^{18}F]-isotope followed by the decomposition of the target complexes and the isolation of the isotopically labelled AAs can be carried out using methods similar to those described by the Krasikova and Belokon groups.[11,16,18]

In conclusion, we have developed a novel metal-templated protocol for the synthesis of enantiomerically pure fluorine-18-labelled Tyr precursors with a quaternary α-carbon atom. The (2*S*)- and (2*R*)-2-(3-[^{19}F]fluoropropyl)-Tyr derivatives were synthesized using a chiral Ni$^{\mathrm{II}}$ complex **1** in five steps: (1) the hydroxy group in the Tyr substrate was protected with the Ms group; (2) the Michael addition reaction with acrolein was performed; (3) the aldehyde group was reduced to an alcohol; (4) subsequently, the mesylation was repeated; (5) finally, the OMs group at the aliphatic part was replaced with a ^{19}F atom using anhydrous KF. Eventually, the ^{18}F isotope can be introduced into the Ni$^{\mathrm{II}}$ complexes using the developed protocol and the desired ^{18}F-labelled AAs can be isolated on demand for use as novel PET radiotracers.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.008.

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