

Effect of Added $\text{Cu}(\text{OTf})_2$ on the $\text{Cu}(\text{OTf})_2(\text{Py})_4$ -Mediated Radiofluorination of Benzoyl and Phthaloylglycinates

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ABSTRACT

$\text{Cu}(\text{OTf})_2(\text{Py})_4$ mediated radiofluorination of the boronate esters of ethyl benzoyl and phthaloylglycinates (11 and 16) using 10 mol% of the copper complex following the literature procedure did not provide the fluorinated products. However, the addition of $\text{Cu}(\text{OTf})_2$ resulted in the radio-fluorination of the boronate esters 11 and 16 to obtain ethyl 4- ^{18}F fluorobenzoyl glycinate, 17, (48%) and ethyl 3- ^{18}F phthaloylglycinate (41%) respectively.

1. INTRODUCTION

Positron Emission Tomography (PET) and its related hybrid technologies such as PET/CT and PET/MR are non-invasive imaging modalities that provide *in vivo* physicochemical, pharmaco-kinetic information, measurement and quantification of biochemical processes [1-4]. The unique sensitivities of these techniques allow the detection of cellular changes during disease progression. PET imaging provides quantitative bio-distribution data of molecular probes. Positron annihilation by electron releases two antiparallel γ -photons that are detected simultaneously by γ -cameras and used to construct the PET images. Currently PET is used clinically to detect cancers [5, 6], cardiovascular diseases, and neurological disorders [7]. Also PET has become an important tool in drug discovery and development [8]. Of several short lived β^+ -emitting (positron) nuclides available, the most attractive is fluorine-18 because of its low energy, moderate half-life (109.6 min), and its easy availability in “no-carrier-added” form. During the past decade, various transition-metal-mediated [9-12] (Ag, Pd, Ni, Cu) fluorination methods have been transferred to radiochemistry. Among these, Cu-promoted [13-16] fluorination methods are the most versatile (Cu is less toxic compared to Pd and Ni) for preparing ^{18}F -fluorinated aromatics and hetero aromatics (Figure 1).

2. MATERIALS AND METHODS

All reagents and solvents were purchased from Acros or Aldrich and were used as received.

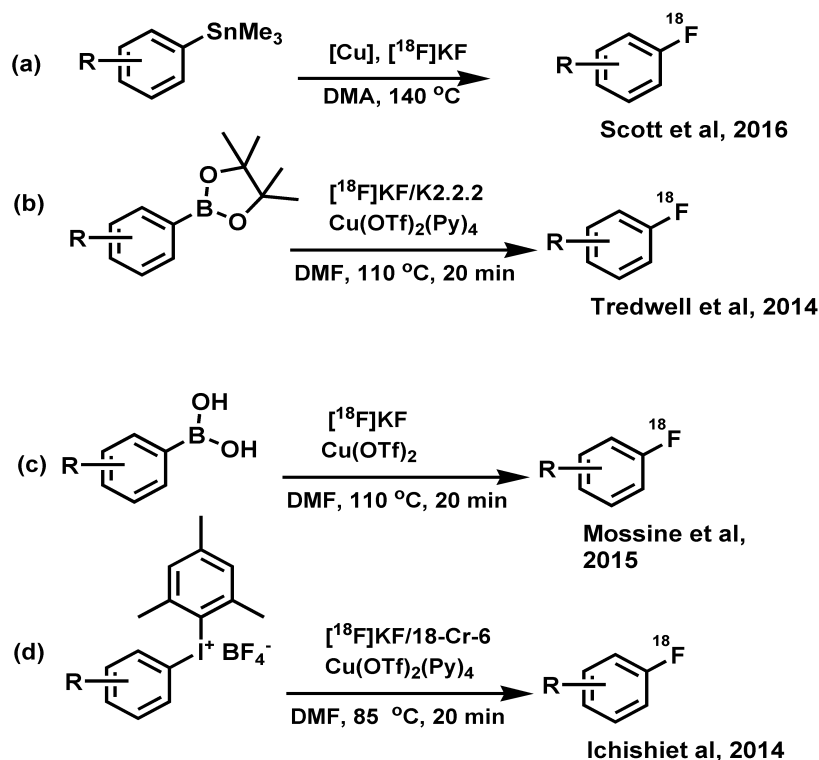


Figure 1. Copper catalyzed radio-fluorinations of arenes.

Flash column chromatography was performed using silica gel (60 A, 230 - 400 mesh, Sorbent Technologies, USA) (Still, 1975). Analytical thin-layer chromatography (TLC) was performed using 250 μm silica plates (Analtech, Inc., Newark, DE) with a visualization by UV (254 nm) or phosphomolebdic acid spray. ^1H and ^{13}C -nuclear magnetic resonance spectra (NMR) were recorded at 300 or 125 MHz, respectively. Chemical shifts for ^1H -NMR and ^{13}C -NMR spectra were referenced to the residual protons of the deuterated solvents or to TMS. High resolution mass spectrometry was performed using a JEOL AccuTOF™ DART Mass Spectrometer. No-carrier-added $[^{18}\text{F}]\text{F}^-$, produced from recycled $[^{18}\text{O}]$ water, was obtained from PetNet (Knoxville, TN). Thin-layer chromatography visualization was performed with radiation detectors using a BioScan AR-2500 radio-TLC reader and Win Scan 1.3 software. Radio-TLC plates were developed using EtOAc/hexane (1/9). F-18 labelling was performed using Advion NanoTek Microfluidic Synthesis System controlled by NanoTek LF 1.4 Software.

4- $[^{18}\text{F}]$ fluoro-1,1'-biphenyl (4): Cyclotron-produced, no carrier added $[^{18}\text{F}]$ fluoride ion (ca. 1.85 GBq) in $[^{18}\text{O}]$ water (225 - 350 μL) was first adsorbed onto anion exchange resin ORTG cartridge within the concentrator module of a NanoTek System and released with a solution of K_2CO_3 (1.8 mg), kryptofix (12.0 mg) in MeCN/ H_2O (9.5:0.5 v/v, 400 μL) into 5 mL v-vial. The solution was dried by three cycles of azeotropic evaporation with MeCN (0.45 mL) at 100°C .

To this anhydrous $^{18}\text{F}^- \text{-K}_{222} \text{-K}^+$ complex was added the boronate ester **3** (16.7 mg, 0.06 mmol), and $\text{Cu}(\text{OTf})_2(\text{Py})_4$ (4.1 mg, 0.006 mmol) and DMF (0.40 mL). The resulting mixture was stirred at 110°C for 20 min. The product was diluted with water (10 mL) and passed through C_{18} Sep-Pak to remove unreacted fluoride and the product was eluted with ethyl acetate (3 mL) to obtain 1.26 GBq of 4- $[^{18}\text{F}]$ fluoro-1, 1'-biphenyl (68% E.O.S). The radio-TLC was performed on silica gel plate using ethyl acetate:hexanes (1:9) as eluent.

Ethyl 4-chlorobenzoylglycinate (10): To a solution of 4-chlorobenzoyl chloride (1.65 g; 10.0 mmol), **8**, triethyl amine (1.50 g; 15.0 mmol) in CH_2Cl_2 at 0°C was added ethyl glycinate hydrochloride (1.68 g; 12.0 mmol), **9**, in small portions over a 10 min. period. The temperature was slowly raised to room temperature and the mixture stirred for 3 hr. The solvent was removed and the residue was treated with an-

hydrous ether (20 mL) and separated triethyl amine hydrochloride was filtered off. The ether layer was thoroughly washed sequentially with water (10 mL), saturated solution of sodium bicarbonate (10 mL), brine (10 mL), and then dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure yielded a colorless solid (2.29; 95%). ^1H NMR CDCl_3 (δ) 1.26 (t, 3H, CH_3), 4.22 (q, 2H, CH_2), 6.65 (bs, 1H, NH), 7.41 (d, $J = 7$ Hz, 2H, Ar- H_2) and 7.69 (d, $J = 7$ Hz, 2H, Ar- H_2).

Ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)benzoylglycinate (11): To a flame-dried nitrogen flushed 25 ml round-bottomed flask were added $\text{Pd}(\text{OAc})_2$ (2.30 mg, 0.01 mmol), Gorlos-Phos- HBF_4 (19.0 mg, 0.04 mmol), KOAc (0.29 g, 3.00 mmol), bis(pinacolato)diboron (0.31 g, 1.20 mmol), ethyl 4-chlorobenzoylglycinate (0.24 g, 1.00 mmol) and dioxane (2 mL). The flask was evacuated and back filled with nitrogen two times. The reaction mixture was heated for 2.0 hr at 90°C and was diluted with ethyl acetate (10 mL) and filtered through a short column of silica gel (eluent: 2×10 mL of ethyl acetate). Evaporation and purification by column chromatography afforded ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl) benzoyl-glycinate (176.0 mg, 53%) as a colorless solid. ^1H NMR CDCl_3 (δ) 1.39 (t, 3H, CH_3), 1.40 (s, 12H, 4 x CH_3), 4.29 (s, 2H, CH_2), 4.38 (q, 2H, CH_2), 6.90 (bs, 1H, NH), 7.82 (d, $J = 8.4$ Hz, 2H, Ar- H_2) and 7.95 (d, $J = 8.4$ Hz, 2H, Ar- H_2). ^{13}C NMR CDCl_3 (δ) 24.9, 41.8, 61.7, 84.9, 124.4, 135.1, 137.3, 166.9 and 170.3. HRMS (ES) calculated for (M + H) $\text{C}_{17}\text{H}_{24}\text{BNO}_5$; 334.18160. Found: 360.18289.

Ethyl 4- ^{18}F fluorobenzoylglycinate (17): The details of the NanoTek Microfluidic Synthesis System have been described previously [21]. Cyclotron-produced, no carrier added [^{18}F]fluoride ion (ca. 1.85 GBq) in [^{18}O] water (225 - 350 μL) was first adsorbed onto anion exchange resin ORTG cartridge within the concentrator module of a NanoTek System and released with a solution of K_2CO_3 (1.8 mg), kryptofix (12.0 mg) in MeCN/ H_2O (9.5:0.5 v/v, 400 μL) into 5 mL.

v-vial. The solution was dried by three cycles of azeotropic evaporation with MeCN (0.45 mL) at 110°C . To this anhydrous $^{18}\text{F}^- - \text{K}_{222} - \text{K}^+$ complex was added the boronate ester **11** (20.0 mg, 0.06 mmol), $\text{Cu}(\text{OTf})_2$ (21.0 mg, 0.06 mmol) and $\text{Cu}(\text{OTf})_2(\text{Py})_4$ (4.1 mg, 0.006 mmol) and DMF (1.0 mL). The resulting mixture was stirred at 110°C for 20 min. The product was diluted with water (10 mL) and passed through C_{18} Sep-Pak to remove unreacted fluoride and the product was eluted with ethyl acetate (3 mL) to obtain 0.89 GBq of ethyl 4- ^{18}F fluorobenzoyl glycinate (48% E.O.S). The radio-TLC was performed on silica gel plate using ethyl acetate:hexanes (1:9) as eluent.

4-Chlorophthalimide (13): A mixture of 5-chlorophthalic acid monosodium salt (1.99 g, 10.0 mmol) and ammonium carbonate (1.38 g, 14.3 mmol) was fused at 300°C by pushing the sublimed material back into the flask intermittently. The molten product was quickly poured into an evaporating dish. The brownish solid was pulverized into a fine dust to obtain 4-chlorophthalimide, **13** (1.71 g, 95%). ^1H NMR CDCl_3 (δ) 7.65 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.69 (d, $J = 7.8$ Hz, 1H, Ar-H) and 7.71 (s, 1H, Ar-H), ^{13}C NMR CDCl_3 (δ) 123.4, 124.6, 130.1, 133.9, 134.9, 141.6, 165.4, 166.3.

4-Chlorophthaloylglycinate (15): A mixture of 5-chlorophthalimide, **13**, (348.2 mg, 1.93 mmol), ethyl bromoacetate (379.3 mg, 2.02 mmol), cesium carbonate (658.4 mg, 2.03 mmol) in anhydrous dimethyl formamide (5 mL) was stirred at room temperature for 2.5 h. the reaction mixture was poured into ice cold water and extracted with ether (2×25 mL). The combined ether extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. Removal of the solvent provided a gummy material which was purified by using silica gel column chromatography (eluent: ethyl acetate:petroleum ether = 1:4) to obtain **15** as a colorless solid (448.0 mg, 87%). ^1H NMR CDCl_3 (δ) 1.28 (t, 3H, CH_3), 4.23 (q, 2H, OCH_2), 4.42 (s, 2H, NCH_2), 7.69 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.81 (d, $J = 8.4$ Hz, 1H, Ar-H) and 7.85 (s, 1H, Ar-H) ^{13}C NMR CDCl_3 (δ) 15.8, 39.7, 62.4, 123.8, 124.9, 130.1, 134.1, 134.9, 141.6, 165.8, 166.1 and 167.2.

Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)phthaloylglycinate (16): To a flame-dried and nitrogen filled 25 ml round-bottomed flask were added $\text{Pd}(\text{OAc})_2$ (2.3 mg, 0.01 mmol), Gorlos-Phos- HBF_4 (19.0 mg, 0.04 mmol), KOAc (294.4 mg, 3.0 mmol), bis(pinacolato)diboron (305.9, 1.2 mmol), ethyl 3-chlorophthaloylglycinate (266.5, 1.0 mmol) and dioxane (2 mL). The flask was evacuated and back filled twice with nitrogen. The reaction mixture was heated for 2.0 hr at 90°C . The reaction was diluted with ethyl acetate (10 mL) and filtered through a short column of silica gel (eluent: 2×10 mL of ethyl acetate). Evaporation of the solvent and purification by column chromatography (eluent: ethyl acetate:petroleum

ether = 25:75) afforded ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)phthaloylglycinate (287.5 mg, 81% ph, 2H, OCH₂), 4.41 (s, 2H, NCH₂), 7.81 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.22 (d, *J* = 8.4 Hz, 1H, Ar-H) and 8.39 (s, 1H, Ar-H). ¹³C NMR CDCl₃ 14.1, 24.8, 38.9, 61.8, 122.6, 129.6, 131.0, 134.0, 140.5, 167.1, 167.3 and 167.5. HRMS (ES) calculated for (M + H) C₁₈H₂₂BNO₆; 360.16217. Found: 360.16138.

Ethyl 3-[¹⁸F]phthaloylglycinate (18): Cyclotron-produced, no carrier added [¹⁸F]fluoride ion (50 mCi) in [¹⁸O] water (225 - 350 μL) was first adsorbed onto anion exchange resin ORTG cartridge with in the concentrator module of a NanoTek System and released with a solution of K₂CO₃ (1.8 mg), kryptofix (12.0 mg) in MeCN/H₂O (9.5:0.5 v/v, 400 μL) into 5 mL v-vial. The solution was dried by three cycles of azeotropic evaporation with MeCN (0.45 mL) at 100 °C.

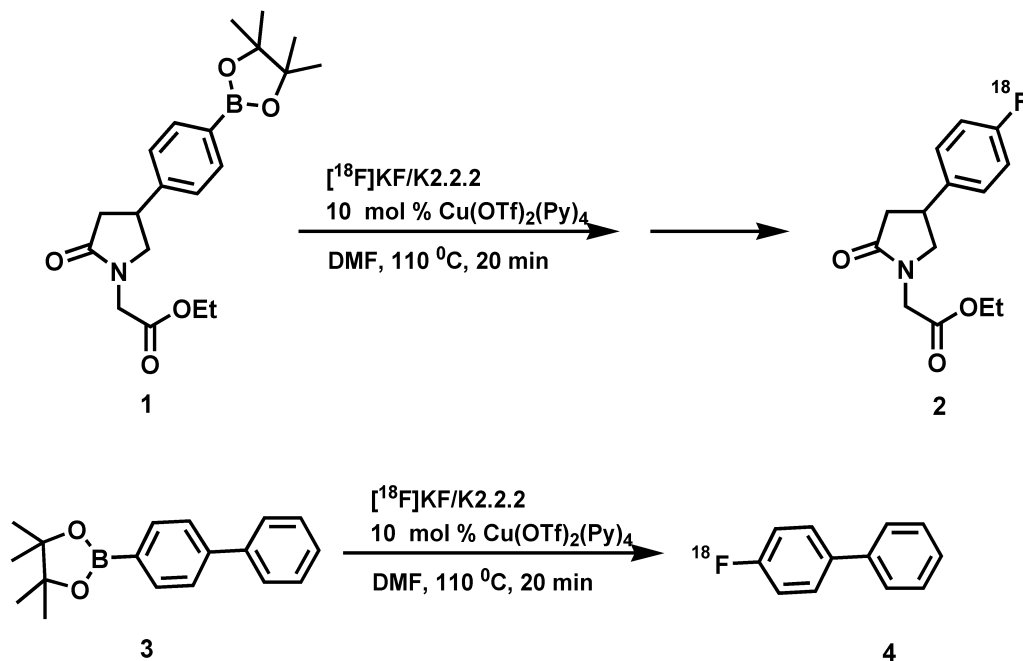
To this anhydrous ¹⁸F⁻-K₂₂₂-K⁺ complex was added the boronate ester **16** (21.5 mg, 0.06 mmol), Cu(OTf)₂ (21.0 mg, 0.06 mmol) and Cu(OTf)₂(Py)₄ (4.1 mg, 0.006 mmol) and DMF (1.0 mL). The resulting mixture was stirred at 110 °C for 20 min. The product was diluted with water (10 mL) and passed through C₁₈ Sep-Pak to remove unreacted fluoride and the product was eluted with ethyl acetate (3 mL) to obtain 0.76 GBq of Ethyl 4-[¹⁸F]fluorophthaloylglycinate (41% E.O.S). The radio-TLC was performed on silica gel plate using ethyl acetate:hexanes (1:9) as eluent.

3. CHEMISTRY AND RESULTS

Several attempts to radiofluorinate boronate ester **1** to obtain 4-(4-[¹⁸F]fluorophenyl)piracetam (**2**), a potential PET brain imaging agent [17, 18], using Tredwell's procedure [15] with 10 mol% of copper complex Cu(OTf)₂(Py)₄ failed in our hands. However, previously reported 4-[¹⁸F]fluoro-1,1'-biphenyl (**4**) was successfully prepared from 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**) in 68% (reported: 74%) radiochemical yield [Scheme 1].

The boronate ester **1** has a structural motif similar to glycinate (>NCH₂COOR). It is known in the literature [19] that both ethyl benzoylglycinate and ethyl phthaloylglycinate readily form complexes **5** and **6** respectively with transition metals such as Fe, Co, Ni, and Cu as shown in Figure 2.

Similarly boronate ester **1** can form the glycinate complex **7** by replacing two pyridines of the pyridine copper complex Cu(OTf)₂(Py)₄. As the pyridine copper complex is consumed to form glycinate complex **7**, there is no copper available to mediate the fluorodeboronation resulting in no product formation.



Scheme 1. Attempted radio-fluorination of piracetam analogue.

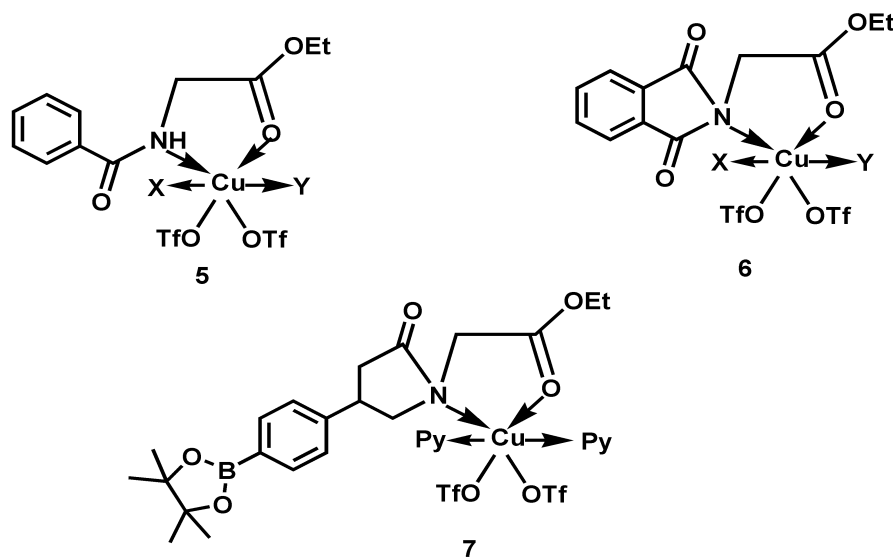


Figure 2. Copper complexes of compounds with glycinate motif.

Table 1. Radiofluorination of **11** and **16** (0.06 mmol) with 10 mol% of $\text{Cu}(\text{OTf})_2(\text{Py})_4$ and the effect of variable amounts of $\text{Cu}(\text{OTf})_2$ on radiochemical yields. ^a: reaction conditions using the procedure reported in the literature [15]. The yields were obtained by radio-TLC using Bioscan. The identity of products was determined by comparing with the R_f values of the standards.

No	$\text{Cu}(\text{OTf})_2$ mol%	Solvent	Compound 17 % RCY	Compound 18 % RCY
1 ^a	0	0.4 ml	0.0	0.0
2	50	0.4 ml	2.5	2.0
3	100	0.4 ml	2.5	3.0
4	0	1.0 ml	0.0	0.0
5	10	1.0 ml	12.0	11.5
6	25	1.0 ml	15.0	12.8
7	50	1.0 ml	21.0	25.0
8	75	1.0 ml	28.0	30.5
9	100	1.0 ml	48.0	41.0

In order to further test this observation, we attempted to fluorinate easily accessible benzoylglycinate and phthaloylglycinate boronate esters **11** and **16** using 10 mol% of $\text{Cu}(\text{OTf})_2(\text{Py})_4$. As expected, both the reactions failed. However by adding $\text{Cu}(\text{OTf})_2$ to the reaction mixture, we observed product formation. This prompted us to systematically study the effect of added $\text{Cu}(\text{OTf})_2$; the results are presented in **Table 1** and **Figure 3**. The preparation of requisite boronate esters **11** and **16** is described in **Scheme 2**. The condensation of 4-chlorobenzoyl chloride, **8**, with ethyl glycinate hydrochloride, **9**, in the presence of triethyl amine at room temperature provided ethyl 4-chlorobenzoylglycinate, **10**, in quantitative yield. 4-Chlorophthalimide, **13**, was obtained in 91% yield by fusing 4-chlorophthalic acid, **12**, with $(\text{NH}_4)_2\text{CO}_3$ at 300 °C. *N*-Alkylation of phthalimide **13** with ethyl 2-bromoacetate, **14**, in the presence of CsCO_3 and DMF as solvent at room temperature gave ethyl 4-chlorodphthaloylglycinate, **15**, in 87% yield. Palladium catalyzed borolation of aryl chlorides is assisted by various phosphine ligands such as LB-Phos (dicyclohexyl-2,4,6-trimethylphenylphosphine.HBF₄), Zheda-Phos (dicyclohexyl-2-[*N*-methyl-*N*'-phenylaminophenyl]

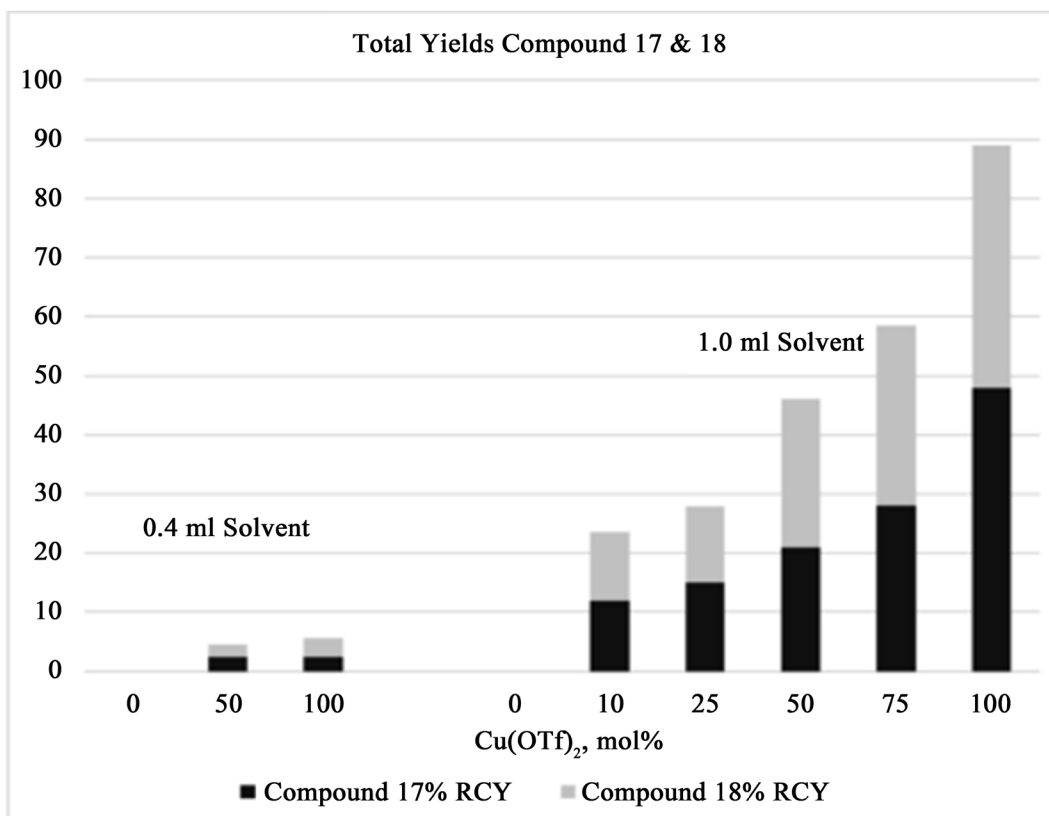
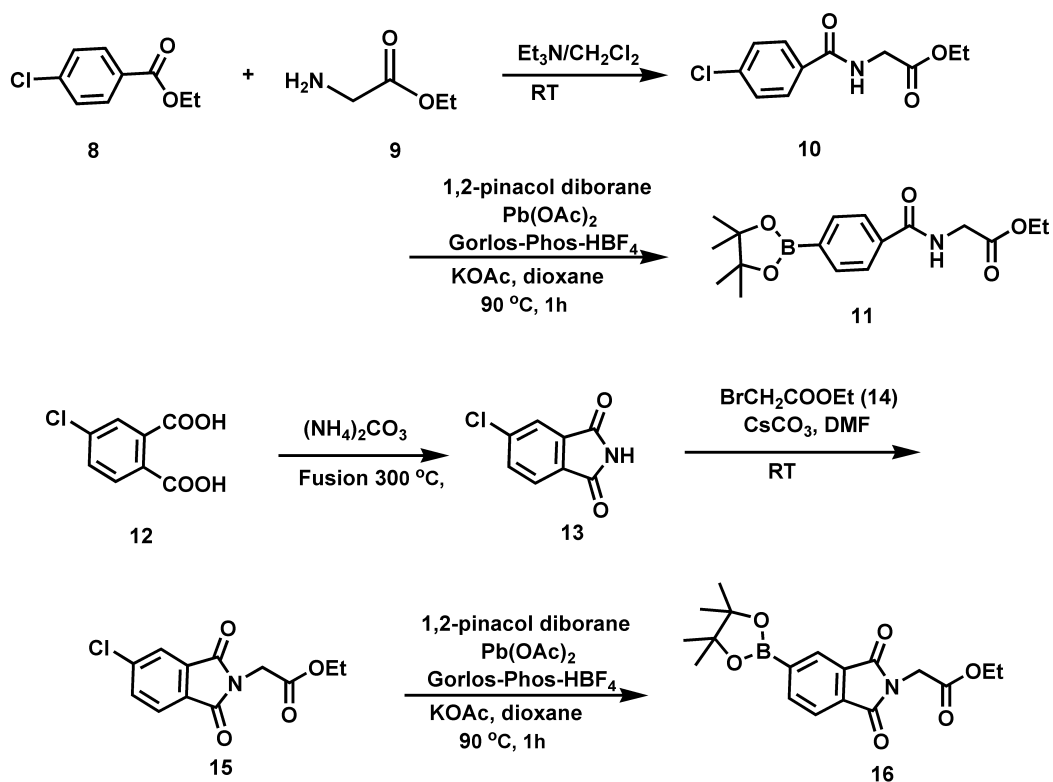
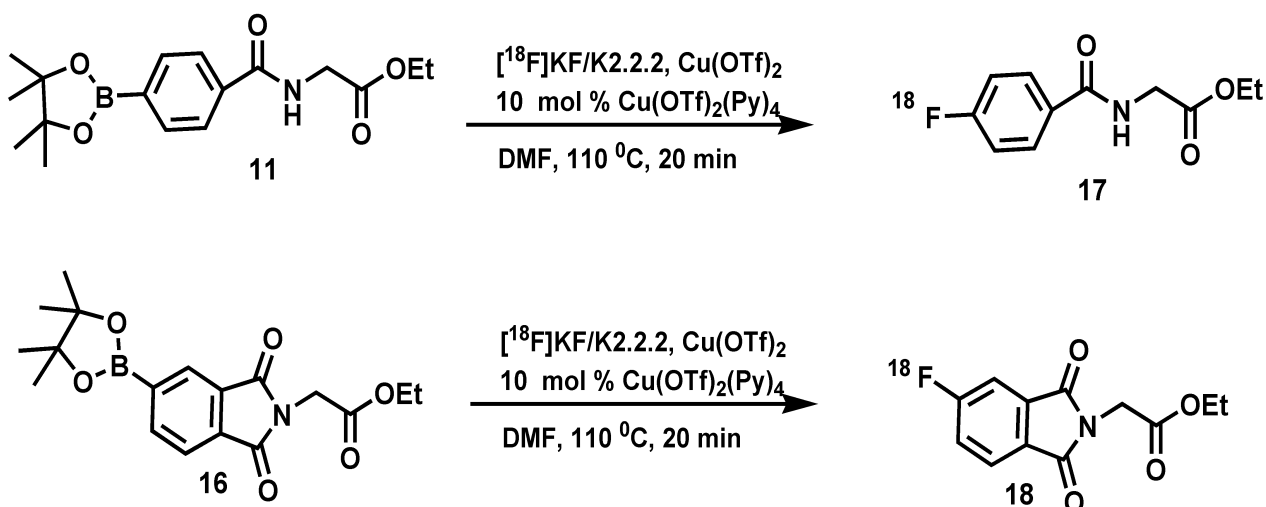


Figure 3. Influence of excess copper triflate on radiochemical yields.



Scheme 2. Preparation of boronate precursors 11 and 16.



Scheme 3. Radio-fluorination of precursors **11** and **16**.

phosphine.HBF₄) and Gorlos-Phos (dicyclohexyl-2,6-diisopropoxy-phenyl)phosphine.HBF₄) [20]. The best yields of the boronate esters **11** (53%) and **16** (87%) were obtained by using Gorlos-Phos as ligand. No borolation took place with Zheda-Phos as it is a sterically hindered ligand. LB-Phos resulted in yields of **11** and **16** in 40% and 78% respectively. Thus aryl chlorides **10** and **15** were successfully converted to the corresponding boronate esters **11** and **16** using 3 mol% of Pd(OAc)₂, 6 mol% of ligand Gorlos-Phos, 1.2 equivalents of B₂Pin₂ and 3 equivalents of KOAc in dioxane at 90 °C for 2 hr.

The radiofluorination of the boronate esters **11** and **16** was performed with 10 mol% of complex Cu(OTf)₂(Py)₄ (Scheme 3) and the effect of different mol equivalents of Cu(OTf)₂ was studied. The radiolabeling of the boronate esters was carried out in the Advion NanoTek Microfluidic Synthesizer. Using the drying macros of NanoTek LF 1.4 software, a complex of kryptofix 222/K₂CO₃/[¹⁸F]fluoride was thoroughly dried and allowed to react with the boronate esters **11** and **16** in the presence of Cu(OTf)₂(Py)₄ and Cu(OTf)₂ in DMF at 110 °C for 20 min to obtain fluorinated compounds **17** and **18** respectively. The yields for the compounds **17** and **18** were maximized using one mole equivalent of Cu(OTf)₂ in 1 mL of DMF as shown in Table 1 and Figure 3.

Following the reaction conditions from the literature [15] using 10 mol% of Cu(OTf)₂(Py)₄ and 0.4 ml of dimethyl formamide, no fluorination products were obtained. Fluorinated products **17** and **18** were prepared using diluted reaction mixture in 1 mL (2.5 times more diluted than literature method)) of dimethyl formamide and varying amounts of copper triflate. The highest radiochemical yields for **17** (48%) and **18** (41%) were obtained with 100 mol% of copper triflate. Radiofluorination of the boronate ester **1** resulted in relatively lower yields (20% ± 5%) of [¹⁸F]fluorophenyl piracetam **2**. Further studies to improve reaction yields are underway.

4. CONCLUSIONS

Ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)benzoylglycinate, **11**, and ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)phthaloylglycinate, **16**, were successfully radiofluorinated to obtain ethyl 4-[¹⁸F]fluorobenzoylglycinate, **17**, and ethyl 3-[¹⁸F]phthaloylglycinate, **18**, respectively by modifying the literature procedure. The effect of varying amounts of Cu(OTf)₂ was systematically studied to improve the radiochemical yields of **17** (48%) and **18** (41%).

ACKNOWLEDGEMENTS

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REFERENCES

1. Preshlock, S., Tredwell, M. and Gouverneur, V. (2016) ^{18}F -Labeling of Arenes and Heteroarenes for Applications in Positron Emission Tomography. *Chemical Review*, **116**, 719-766. <https://doi.org/10.1021/acs.chemrev.5b00493>
2. Miller, P.W., Long, N.J., Vilar, R. and Gee, A.D. (2008) Synthesis of ^{11}C , ^{18}F , ^{15}O , and ^{13}N Radiolabels for Positron Emission Tomography. *Angewandte Chemie International Edition*, **47**, 8998-9033. <https://doi.org/10.1002/anie.200800222>
3. Campbell, M.G. and Ritter, T. (2015) Modern Carbon-Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chemical Review*, **115**, 612-633. <https://doi.org/10.1021/cr500366b>
4. Brooks, A.F., Topczewsky, J.J., Ichishi, N., Sanford, M.S. and Scott, P.J.H. (2014) Late-Stage ^{18}F Fluorination: New Solutions to Old Problems. *Chemical Science*, **5**, 4545-4553. <https://doi.org/10.1039/C4SC02099E>
5. Schober, H. and Gonen, M. (2007) ^{18}F Radiotracers in PET and Pet/CT: Limitations and Potential. *J. Nucl. Med.*, **48**, 4S-18S.
6. Luthra, S.K. and Robins, E.G. (2012) Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications (Eds: Gouverneur, V.; Muller, K), Imperial College, London.
7. Ametamey, S.M., Honer, M. and Schubiger, P.A. (2008) Molecular Imaging with PET. *Chemical Review*, **108**, 1501-1516. <https://doi.org/10.1021/cr0782426>
8. Miller, P.W., Long, N.J., Vilar, R. and Gee, A.D. (2008) Synthese von ^{11}C - , ^{18}F - , ^{15}O - und ^{13}N -Radiotraceren für die Positronenemissionstomographie. *Angewandte Chemie*, **120**, 9136-9172. <https://doi.org/10.1002/ange.200800222>
9. Teare, H., Robins, E.G., Kirjavainen, A., Fordback, S., Sanford, G., Solin, O., Luthra, S.K. and Gouverneur, V. (2010) Radiosynthesis and Evaluation of ^{18}F Selectfluor Bis(Triflate). *Angewandte Chemie International Edition*, **122**, 6973-6976. <https://doi.org/10.1002/ange.201002310>
10. Stenhagen, I.S.R., Kirjavainen, A., Fordback, S., Robins, E.G., Jorgensen, C.G., Solin, O., Luthra, S.K. and Gouverneur, V. (2013) ^{18}F Fluorination of an Arylboronic Ester Using ^{18}F Selectfluor Bis(Triflate): Application to 6- ^{18}F Fluoro-L-DOPA. *Chemical Communications*, **49**, 1386-1388. <https://doi.org/10.1039/c2cc38646a>
11. Bergman, J., Solin, O. and Luthra, S.K. (1997) Fluorine-18 Labeled Gas for Synthesis of Tracer Molecules. *Nucl. Med. Biol.*, **24**, 677-683.
12. Lee, E., Kamlet, A.S., Powers, D.C., Neuman, G.B., Borsalian, G.B., Furuya, T., Choi, D.C., Hooker, J.M. and Ritter, T. (2011) A Fluoride Derived Electrophilic Late Stage Fluorination. *Science*, **334**, 639-642.
13. Makaravage, K.J., Brooks, A.F., Mossine, A.V., Sanford, M.S. and Scott, P.J.H. (2016) Copper-Mediated Radiofluorination of Arylstannanes with ^{18}F KF. *Org. Lett.*, **18**, 5440-5443.
14. Ichilshi, N., Brooks, A.F., Topczewski, J.J., Rodnick, M.E., Sanford, M.S. and Sanford, P.J. (2014) Copper-Catalyzed ^{18}F Fluorination of (Mesityl) (Aryl) Iodonium Salts. *Org. Lett.*, **16**, 3224-3227.
15. Tredwell, M., Preshlock, S.M., Taylor, N.J., Gruber, S., Huiban, M., Passchier, J., Mercier, J., Agenicot, C. and Gouverneur, V. (2014) A General Copper-Mediated Nucleophilic ^{18}F Fluorinations of Arenes. *ngew. Chem. Int. Ed.*, **53**, 7751-7755; *Angew. Chem.* **2014**, 126, 7585-7589.
16. Mossine, A.V., Brooks, A.F., Makaravage, K.J., Miller, J.M., Ichilshi, N., Sanford, M.S. and Scott, P.J.H. (2015) Synthesis of ^{18}F Arenes via the Copper-Mediated ^{18}F Fluorination of Boronic Acids. *Organic Letters*, **17**, 5780-5783. <https://doi.org/10.1021/acs.orglett.5b02875>
17. Amin, A., Sanad, M. and Abd-Elhaile, S. (2013) Radiochemical and Biological Characterization of Tc-Piracetam for Brain Imaging. *Radiochemistry*, **55**, 624-628.

18. Blevins, D., Akula, M., Kabalka, G. and Osborne, D. (2017) Synthesis of 4-(4-[¹⁸F]Fluorophenyl)piracetam, a Potential PET Agent for Parkinson's Disease. *J. Label. Compds. Radiopharm.*, **60**, S256.
19. El-Asmy, A.A., Hafez, M.A., Saad, E.M. and Taha, F.I. (1994) Electrochemical Synthesis of Benzoylglycine and Ethylphthaloyl-Glycine Complexes of Transition Metal Ions. *Transition Metal Chemistry*, **19**, 603-605. <https://doi.org/10.1007/BF00980412>
20. Li, P., Fu, C. and Ma, S. (2014) Gorlos-Phos for Palladium-Catalyzed Borylation of Aryl Chlorides. *Organic & Biomolecular Chemistry*, **12**, 3604-3610. <https://doi.org/10.1039/c4ob00293h>
21. Chun, J., Lu, S., Lee, Y. and Pike, V. (2010) Fast and High-Yield Microreactor Syntheses of *ortho*-Substituted [¹⁸F]Fluoroarenes from Reactions of [¹⁸F]Fluoride Ion with Diaryliodonium Salts. *The Journal of Organic Chemistry*, **75**, 3332-3338. <https://doi.org/10.1021/jo100361d>