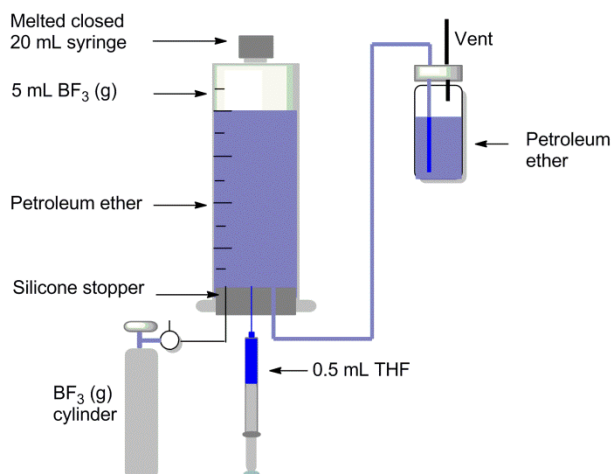


## Radiosynthesis

After irradiation,  $^{18}\text{F}$ -fluoride in  $^{18}\text{O}$ -enriched water was delivered to the hot cell and quantitatively trapped on the QMA cartridge. The QMA cartridge was rinsed with acetone (10 mL) and flushed with nitrogen for 100 s. The freshly prepared  $\text{BF}_3\cdot\text{THF}$  complex solution (5 mL) was passed through an in-house-made Lewatit® MP-64 cartridge and the QMA cartridge as a single bulk passage of solvent lasting ~10 s.  $^{18}\text{F}$ -TFB largely remained on the cartridge while 20-40% of the  $^{18}\text{F}$ -fluoride was released from the QMA cartridge, possibly by formation of  $\text{H}^{18}\text{F}$  under the acidic conditions caused by  $\text{BF}_3$ . The QMA cartridge was rinsed with a solution of 10 mL THF and 13 mL water to remove the impurities from the QMA cartridge. To decrease the residual acetone and THF in the final product, 100 s of nitrogen flush was applied after THF rinsing.  $^{18}\text{F}$ -TFB was eluted from the QMA cartridge with 5 mL sterile saline to the product vial, in which 5 mL sterile saline was added in advance for further dilution of the product. The crude product solution was purified by trapping the unreacted  $^{18}\text{F}$ -fluoride on three alumina-N Light SepPaks. In the HPLC analysis of the final product, a carbonate peak at 3.6 min and an unknown impurity peak at 3.8 min were initially observed. Investigation revealed these to be contaminants present on the stock QMA and alumina cartridges. By pretreating the cartridges with 20 mL 0.9% saline and 20 mL water, the peaks were reduced to a trace amount.

## Preparation of $\text{BF}_3\cdot\text{THF}$ Complex Solution

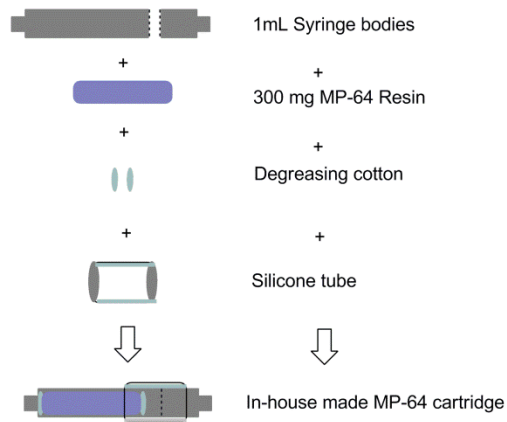
A solution of  $\text{BF}_3\cdot\text{THF}$  complex in petroleum ether was prepared freshly within 30 min of the radiosynthesis of  $^{18}\text{F}$ -TFB (Fig. 1). The luer opening of a 20 mL polypropylene syringe was melted closed. A silicone stopper was placed in the opposite opening. A 20 mL sterile vial with PEEK tubing was connected to the 20 mL syringe as shown in Figure 1. The syringe body was completely filled with petroleum ether and about half of the sterile vial was also filled with petroleum ether (PE).  $\text{BF}_3$  gas (~5 mL) was flowed into the syringe from a  $\text{BF}_3$  cylinder through a PEEK tube, thereby displacing the corresponding petroleum ether to the sterile vial. After removal of the  $\text{BF}_3$  addition tube, 0.5 mL THF was injected through the silicone stopper. The  $\text{BF}_3$  gas was dissolved in the added THF quickly, and petroleum ether was sucked back into the syringe from the auxiliary vial without entry of atmospheric air. The tube was removed and the mixture became a homogenous solution with gentle shaking. The concentration of the  $\text{BF}_3$  in the solution was  $\sim 1.8 \mu\text{mol}/\text{mL}$ .



**SUPPLEMENTAL FIGURE. 1.** Preparation of  $\text{BF}_3\cdot\text{THF}$  complex solution

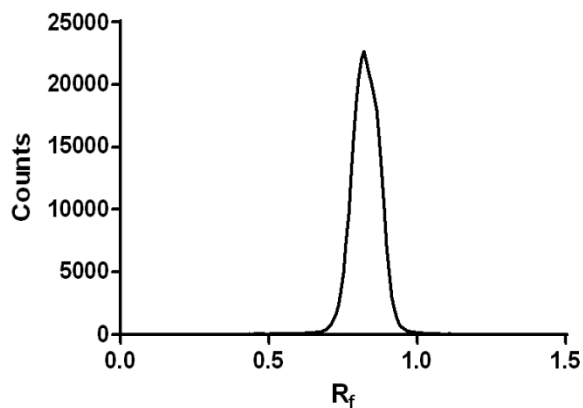
## Preparation of In-house-made Lewatit® MP-64 Cartridge

Lewatit® MP-64 chloride form resin was procured from Sigma Aldrich (St. Louis, Mo) and converted to carbonate form by treatment with 1 M  $K_2CO_3$  solution (10 equivalent), water (100 equivalent, w/w) and tetrahydrofuran (THF) (100 equivalent, w/w) in a column, and then dried on a heating plate at 100 °C overnight. A 1 mL syringe body was filled with 200-400 mg Lewatit® MP-64 carbonate form and stoppered with some degreasing cotton at both sides. The syringe was cut off and jointed with another 1 mL syringe body using a sheath of silicone tubing (Fig. 2).



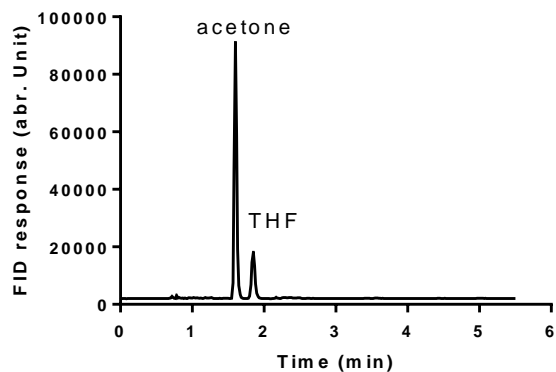
**SUPPLEMENTAL FIGURE. 2.** In-house-made Lewatit® MP-64 cartridge

## Radio-TLC of purified $^{18}F$ -TFB



**SUPPLEMENTAL FIGURE. 3.** Radio-TLC of purified  $^{18}\text{F}$ -TFB ( $R_f = 0.8 - 0.85$ ) with the silica gel stationary phase and methanol mobile phase. If present, unreacted  $^{18}\text{F}$ -fluoride would remain at the origin.

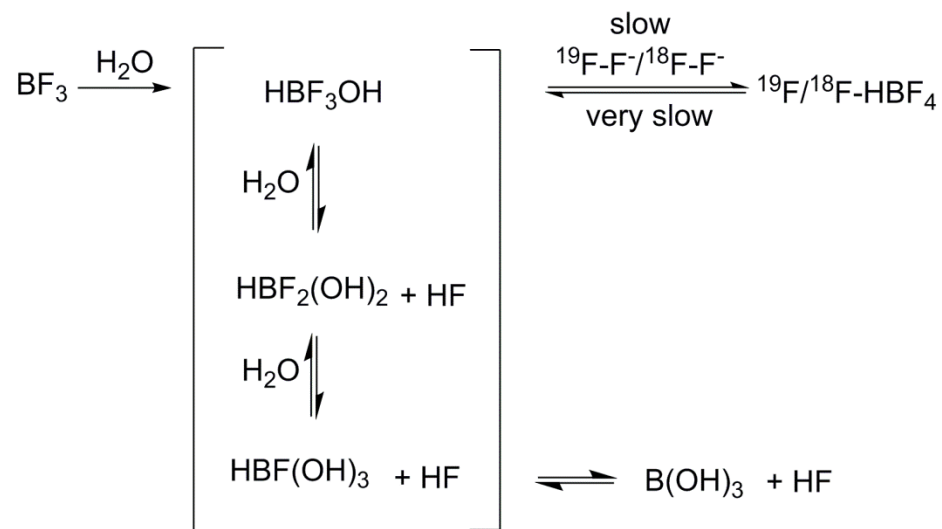
#### GC analysis of residual organic solvents $^{18}\text{F}$ -TFB



**SUPPLEMENTAL FIGURE. 4.** GC analysis of residual organic solvents in the final  $^{18}\text{F}$ -TFB product. No obvious petroleum ether peaks were observed.

## Plausible Reaction Scheme for $^{18}\text{F}$ -TFB

A putative chemical reaction mechanism for synthesis of  $^{18}\text{F}$ -TFB via  $\text{BF}_3$  is shown in scheme 1.  $\text{BF}_3$  hydrates with water quickly to form  $\text{HBF}_3\text{OH}$  (1). Although the  $\text{BF}_3$ -THF complex solution is prepared in near anhydrous conditions, the QMA cartridge is likely containing trace amounts of water after trapping of the  $^{18}\text{F}$ -fluoride and treatment with acetone and nitrogen. Indeed, the  $^{18}\text{F}$ -fluoride itself may be in a hydrated form (2) on the QMA cartridge. Although it is possible that  $\text{BF}_3$  reacts directly with  $^{18}\text{F}$ -fluoride ion,  $\text{HBF}_3\text{OH}$  is the more likely intermediate to react with  $^{18}\text{F}$ -fluoride to make  $^{18}\text{F}$ -TFB. In the presence of water,  $\text{HBF}_3\text{OH}$  may react further to form a series of intermediates, which ends with the release of boric acid and HF (1). The release of  $^{19}\text{F}$ -fluoride from  $\text{BF}_3$  may represent a source of unlabeled fluoride that can decrease the specific activity of the product.



**SUPPLEMENTAL SCHEME 1.** Putative reaction scheme for formation of  $^{19}\text{F}/^{18}\text{F}$ -TFB from  $\text{BF}_3$ .

## References

1. Wamser CA. Equilibria in the system boron trifluoride-water at 25 °C. *J Am Chem Soc.* 1951;73:409-416.
2. Cai L, Lu S, Pike VW. Chemistry with F-18 fluoride ion. *Eur J Org Chem.* 2008:2853-2873.