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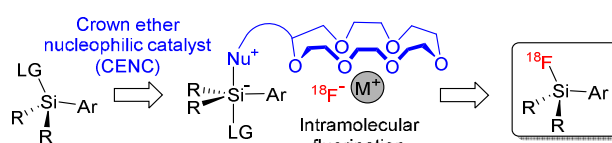
Susovan Jana,^{†§} Mohammed H. Al-hunuti,^{†§} Bo Yeun Yang,[‡] Shuiyu Lu,^{‡*} Victor W. Pike,[‡] and Salvatore D. Lepore^{†*}

[†]Department of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL 33431-0991

[‡]Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-1003

KEYWORDS: phase transfer agent / fluorine-18 / silicon fluorination / PET / crown ether nucleophilic catalyst

ABSTRACT: New bifunctional phase transfer agents were synthesized and investigated for their abilities to promote rapid fluorination at silicon. These agents, dubbed crown ether nucleophilic catalysts (CENCs), are 18-crown-6 derivatives containing a side-arm and a potentially nucleophilic hydroxyl group. These CENCs proved efficacious in the fluorination of hindered silicon substrates, with fluorination yields dependent on the length of linker connecting the metal chelating unit to the hydroxyl group. The efficacy of these CENCs was also demonstrated for rapid radiofluorination under mild conditions for eventual application in molecular imaging with positron emission tomography (PET). The hydrolysis-resistant aryl silicon fragment is promising as a convenient synthon for labeling potential PET radiotracers.



INTRODUCTION

Organosilanes continue to elicit interest as acceptors of positron-emitting fluoride ion ($[^{18}\text{F}]\text{F}^-$) for potential applications in molecular imaging with positron emission tomography (PET).¹ Low molecular weight ^{18}F -labeled organosilanes are now appearing as PET radiotracers, including one example of a radiotracer for imaging 5-HT_{1A} receptors in brain.² Moreover, small $[^{18}\text{F}]$ organofluorosilanes are finding use as synthons for labeling peptides and proteins.³ The silyl fluoride bond (Si-F) in these tracers is often susceptible to hydrolysis *in vivo*. Incorporation of bulky substituents on the silicon can remediate the metabolic instability.⁴ Nonetheless, a sterically hindered silicon center usually reacts slowly with $[^{18}\text{F}]\text{fluoride}$ ion. That is because, in most cases, fluoride ion incorporation is achieved with the help of a bulky ionophoric phase transfer agent (PTA; e.g., 18-crown-6 or kryptofix 2.2.2) to form a “naked” or minimally hydrated $^{18}\text{F}^--\text{K}^+/\text{PTA}$ complex.⁵ Such complexes react relatively slowly with sterically encumbered organosilanes, partly due to a hindered approach of the large ionophore/metal fluoride complex to the silicon center (Strategy A, Scheme 1). This may sometimes become problematic for radiofluorination considering the short half-life of ^{18}F ($t_{1/2} = 109.8$ min).⁶

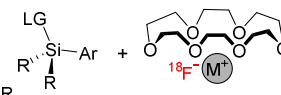
We have previously demonstrated that radiofluorination at aliphatic carbon⁷ and silicon⁸ can be accomplished using metal chelating leaving groups capable of facilitating nucleophilic substitution reactions. We dubbed such groups as “nucleophile assisting leaving groups” (NALGs), arguing that the observed rate enhancements afforded by these nucleofuges are primarily due to stabilizing interactions between substrates and metal-nucleophile pairs to lower transition state energies.⁹ These reactions, especially with crown ether containing leaving groups, were significantly faster than with traditional leaving

groups. This rate enhancement can be rationalized on the basis of the entropic advantage afforded by localizing the fluoride ion nucleophile near to the silicon center. However, this approach suffered problems with solubilizing the $[^{18}\text{F}]\text{fluoride}$ ion due to the high lipophilicity of the silane part of the NALG molecule leading to low overall yields (Strategy B).

Scheme 1. Strategies for Silicon Radiofluorination

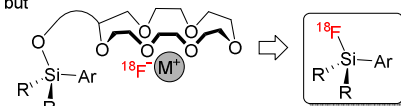
Strategy A: Traditional Practice

- Phase transfer agent to sequester cyclotron-produced $^{18}\text{F}^-$
- Slow intermolecular fluorination with bulky R



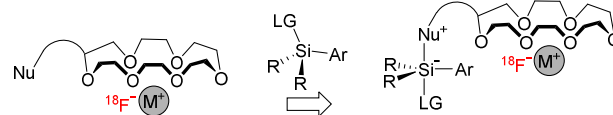
Strategy B: NALG Approach

- Intramolecular fluorination, but
- Poor $^{18}\text{F}^-$ sequestration



Strategy C: CENC Approach in This Work

- Efficient sequestration of $^{18}\text{F}^-$ with metal-CENC complex
- $^{18}\text{F}^-$ is placed in close proximity to Si reaction center with an *in situ* leaving group for intramolecular fluorination



In seeking an improved approach to silicon radiofluorination, we sought to exploit the ability of functionalized crown ethers to sequester metal salts¹⁰ while maintaining the entropic advantage of intramolecular $[^{18}\text{F}]\text{fluoride}$ ion attack on silicon.

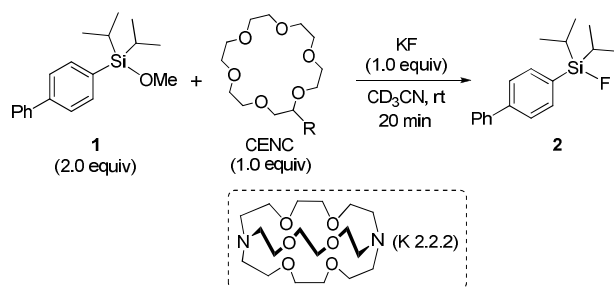
This led us to propose a crown ether carrying a side-arm (lariat) with a terminal nucleophile, i.e. a molecule which we term a “crown ether nucleophilic catalyst” (CENC). Our hypothesis was that a relatively unhindered nucleophile would quickly react with the silicon center bringing with it the crown ether-complexed metal fluoride ion (Strategy C). The fluoride ion might then be delivered intramolecularly to afford the desired silyl fluoride. For this last step, we were inspired by reports from Corriu and coworkers¹¹ that demonstrated highly favorable silicon substitution reactions with pentavalent silicon intermediates analogous to those expected in our CENC approach. To our knowledge, there are no reports of CENCs for silicon substitution reactions, although calix[4]arene-based ether catalysts were reported by the Mandolini group to aid the formation of phosphodiester.¹² In addition, Bakó and coworkers utilized a glucopyranoside-based hydroxyl-containing crown ether to mediate Michael reactions¹³ and Darzens condensations.^{10b,13d} In our work, we aimed to demonstrate that CENCs, based on an 18-crown-6 (18-C-6) scaffold, enhance the fluorination of organosilanes with both KF and cyclotron-produced ¹⁸F-fluoride ion under mild conditions.

RESULTS AND DISCUSSION

CENC design and fluorination with KF

In deciding on a nucleophilic unit for our CENC design, we reasoned that silicon has a high bonding affinity for oxygen. Thus, we began our studies with a commercially available 18-crown-6 lariat alcohol (**4**). In the presence of this simple CENC, substrate **1** (synthesized from a corresponding silane) was converted into silyl fluoride **2** at room temperature over 20 minutes in 49% yield based on KF as limiting reagent. A lower conversion (30%) was observed with 18-C-6 (**3**); the commonly used PTA, kryptofix 2.2.2 (K 2.2.2), led to an 18% conversion under identical conditions (Scheme 2). It appears that the hydroxyl group in **4** enhances the fluorination. In accord, when the terminal hydroxyl group was replaced with a methoxy group, the resulting **5** proved ineffective in the fluorination of **1**, even after 30 minutes (Table 1). Although it is uncertain why **5** reacts much more slowly than **4** or even 18-crown-6 (**3**), these results support the notion that the oxygen of the hydroxyl group in CENC **4** accelerates the fluorination reaction by acting as a nucleophile and/or as a hydrogen bond donor.

Table 1. Hydroxyl Group of CENC Improves Silicon Fluorination of 1



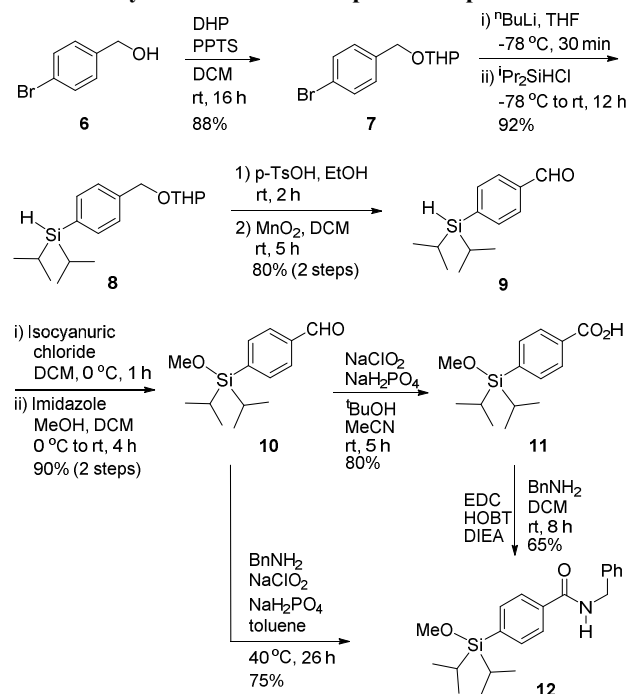
entry	PTA/CENC	R	conv to 2 (%)
1	3 (18-C-6)	H	30

2	4	CH ₂ OH	49
3	5	CH ₂ OMe	0*
4	K 2.2.2	-	18

*Reaction time was 30 min.

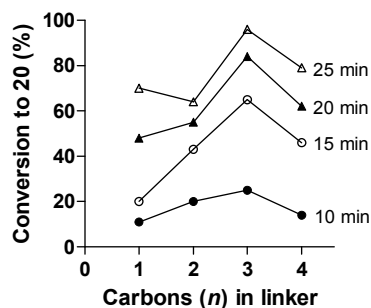
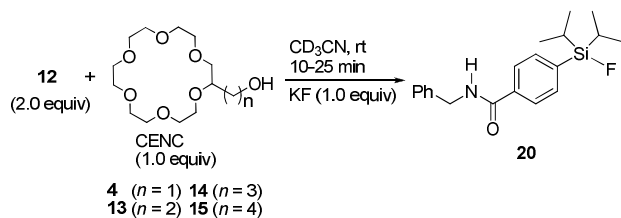
We expect that one of the principal applications of a CENC approach to fluorination could be to radiolabel peptides. To this end, we prepared a small silyl-containing fragment (**11**) that can be easily appended to a peptide via an amide coupling reaction (Scheme 2). Using this approach, we prepared compound **12** as a representative substrate.

Scheme 2. Synthesis of Model Peptide Compound 12



To explore the role of the length of the CENC side-arm, we prepared a series of derivatives of 18-C-6 (**13–19**) using our previously reported procedure.¹⁴ In our initial series of experiments, lariat alcohols containing hydrocarbon side-arms varying from one to four methylene units (**4**, **13–15**) were used as CENCs to fluorinate substrate **12**. To represent more closely the stoichiometry typically used in radiofluorination, substrate **12** was used in a two-fold ratio to the preformed CENC/KF (1:1) complex. In this series, the yields of silicon fluorination varied as a function of hydrocarbon spacer chain length. For all reaction times examined in this hydrocarbon linker series, the optimal length was three methylene units (as in **14**), which gave almost quantitative yield after 25 min (Fig. 1).

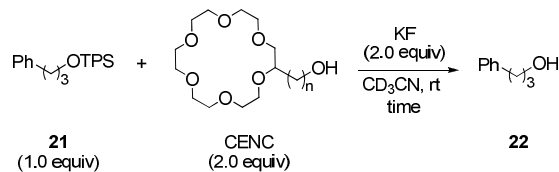
Figure 1. Effect of Hydrocarbon Spacer of CENCs on Silicon Fluorination Conversion



Data are means \pm SD for 3 measurements.

We next sought to ascertain if this trend for CENC side-arm length extended to other substrates and conditions. To this end, desilylation experiments were performed with *tert*-butyldiphenylsilyl (TPS) protected substrate **21** to form alcohol **22**. In this series of experiments, preformed CENC/KF complexes were used in a two-fold molar ratio to substrate. Again, CENC **14** (1-hydroxypropyl side-arm) proved most effective (shortest time) in this desilylation reaction presumably by more rapidly fluorinating the TPS group (Table 2).

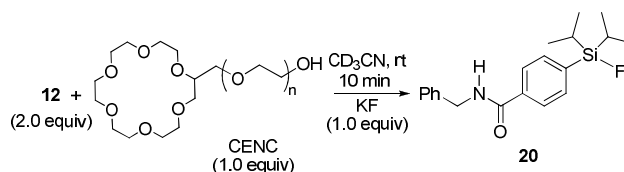
Table 2. Effect of Hydrocarbon Spacer Length in CENCs on the Rate of TPS Deprotection



entry	PTA/CENC	n	time for complete conversion to 22 (h)
1	3 (18-C-6)	-	38
2	4	1	31
3	13	2	24
4	14	3	15
5	15	4	33

Other CENCs containing an alcoholic side-arm were also prepared and examined. The fluorination of **12** using CENCs containing ethylene glycol side-arms led to substantially enhanced conversions in only 10 min (Table 3). These studies revealed that CENCs with side-arms of one (**16**) or three ethylene glycol units (**18**) performed virtually equally well. To our surprise, a side-arm comprised of two ethylene glycol units (**17**) gave a much inferior result. Nevertheless, these studies revealed substantial improvement over the performance of traditional PTAs, such as 18-C-6 and K 2.2.2.

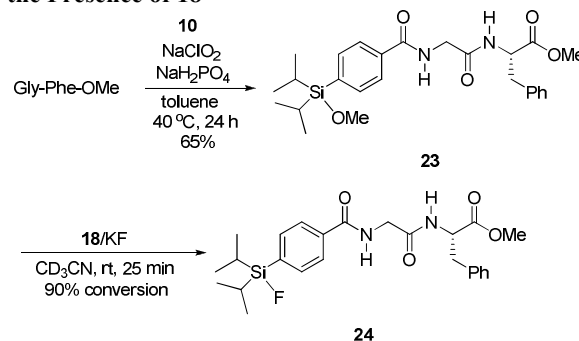
Table 3. Effect of Ethylene Glycol Side-arms of CENCs on Silicon Fluorination Conversion



entry	CENC	n	conv to 20 (%)
1	16	1	88
2	17	2	52
3	18	3	90
4	19	-	27
5	3 (18-C-6)	-	12
6	K 2.2.2	-	17

It was of interest to test the performance of **18** towards a peptidic substrate. Dipeptide **23** was prepared from aldehyde **10** under oxidative amidation conditions. Using CENC **18** with **23** the fluorosilyl dipeptidic product **24** was obtained in 90% yield without epimerization in just 25 min at room temperature (Scheme 3).

Scheme 3. Fluorination of Silicon on a Dipeptide Substrate in the Presence of 18



Radiofluorination reactions

A major drawback of our previously reported NALG approach (Strategy B Scheme 1) was the poor ability of the NALG to solubilize no-carrier-added (NCA) [^{18}F]potassium fluoride into an organic solvent for subsequent reaction. Therefore, it was of primary interest to test the ability of CENCs to perform such sequestration. Table 4 compares the abilities of CENCs **4** and **19** with those of 18-C-6 (**3**) and K 2.2.2 to sequester dried NCA [^{18}F]potassium fluoride into acetonitrile. CENC **19** showed excellent sequestration ability.

Table 4. Sequestration efficiencies of NALG, PTA or CENCs to sequester dry [^{18}F]potassium fluoride into dry acetonitrile for subsequent reaction

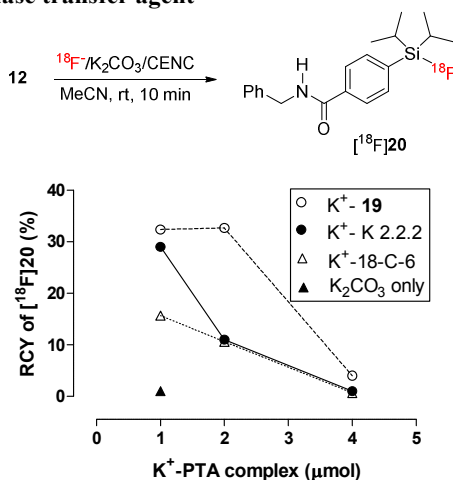
NALG/PTA/CENC	Sequestration
---------------	---------------

	(%)
NALGs	<4 [†]
3 (18-C-6)	21±28
4	70±6
19	93±3
K 2.2.2	91±2

[†] From reference 8

We proceeded to compare the CENC **19** with K 2.2.2 and 18-C-6 as a PTA for the radiofluorination of **12** (2 mg in 450 μ L of MeCN). Control reactions using K₂CO₃ in the absence of a PTA gave < 1% yield. Reactions using varying molecular ratios of K₂CO₃ to PTA afforded [¹⁸F]**20** as the only product. Notably, yields of [¹⁸F]**20** depended on the amount of K₂CO₃/PTA (as K⁺-PTA complex in μ mol) (Fig. 2). A lower amount of K⁺-PTA in the reaction (1.0 μ mol) seemed beneficial, whereas excess base inhibited the reaction. CENC **19** performed slightly better than K 2.2.2 and much better than 18-C-6 as PTA.

Figure 2. Radiofluorination of 12 Using K 2.2.2, 18-C-6 or 19 as phase transfer agent



The radiofluorination of substrate **12** was screened with various CENCs in optimal ratio to base. We selected the following as standard conditions to evaluate all phase transfer agents in radiofluorination: K₂CO₃/CENC (0.66/1.32 μ mol), substrate (2 mg), solvent (MeCN, 450 μ L), reaction temperature (rt) and reaction time (20 min). Some of these conditions were chosen to closely resemble the conditions used for conversion measurements earlier illustrated in Figure 1 and Table 3. [¹⁸F]**20** was the only product (see Supplemental Fig. S1 for an example of chromatogram). Yields are summarized in Table 5, and are based on isolated product fraction from HPLC.

Table 5. Screening of CENCs or other PTA systems in Radiofluorination of 12 to Afford [¹⁸F]20****

entry	CENC/PTA	Yield of [¹⁸ F] 20 [†] (%)
1	3 (18-C-6)	14±4
2	4	35±2
3	13	30±7

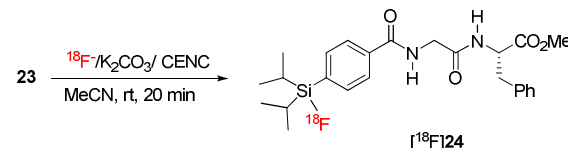
4	14	36±7
5	15	23±8
6	16	29±7
7	17	26±7
8	18	33±8
9	19	38±11
10	3 + MeOH	7±4
11	3 + HO(CH ₂) ₂ OH	12±3
12	K 2.2.2	38±5

[†]Mean \pm SD, ($n = 3$)

Use of CENCs with hydroxyl-terminated side-arms (**4**, **13–19**) clearly improved the yields for silicon radiofluorination over use of the basal unit 18-C-6 (**3**). The top performer, **19** with two $-\text{CH}_2\text{OH}$ side-arm units, rivals the performance of K 2.2.2. By contrast, the simple addition of MeOH (2 eq) or ethylene glycol (1 eq) to 18-C-6 (**3**), to mimic the chemical composition of **19**, had detrimental or no effect respectively, on the radiofluorination yield. CENCs containing a three methylene unit spacer (**14**) or three ethylene glycol unit side-arm (**18**) are the best CENCs in their respective series. These radiochemistry results parallel those from non-radioactive materials conducted at much larger scale and stoichiometry.

It was of interest to compare the performance of CENC **19** with that of 18-C-6 (**3**) for the radiofluorination of the silyl-dipeptidic compound **23** under similar conditions (Table 6). [¹⁸F]**24** was the only product. Remarkably, the use of CENC **19** gave 6-fold greater yield than the use of 18-C-6.

Table 6. Radiofluorination of Dipeptide 24



entry	CENC	Yield of [¹⁸ F] 24 (%)
1	3 (18-C-6)	2±0.3
2	19	12±2

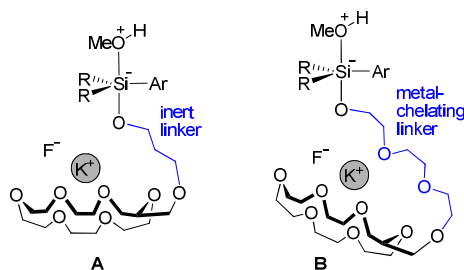
[Mean \pm SD ($n = 3$)]

Mechanistic considerations

Our studies on the mechanism of rate enhancement afforded by our CENCs over 18-C-6 (**3**) are at an early stage. Our current rationale is that the hydroxyl group of the lariat side arm initially attacks the silicon center to give a pentacoordinate intermediate such as **A** or **B** (Fig. 3). Studies by Corriu and coworkers demonstrate that various silicon substitution reactions involving R₃SiX were catalytically accelerated by Lewis bases such as HMPA, carboxylates, and DMSO. These agents led to the formation of a pentacoordinate silicon intermediate, which proved to be reactive towards nucleophiles leading to a hexacoordinate intermediate, which rapidly collapsed to give substitution product.¹¹ Others have shown that pentacoordinate

silicon anions are exceptionally stabilized by an 18-C-6/ K^+ counter ion complex.¹⁵

Figure 3. Possible Rationale for Enhanced Reactivity of CENCs



Based on these precedents, it is possible that an initial hydroxyl group attack is favorable due to a stabilizing interaction of the nearby 18-C-6/ K^+ moiety with the silicon anion center (Fig. 3). In this scenario, one might expect there to be an optimal distance between the hydroxyl group and the crown ether. With a hydrocarbon unit linking the hydroxyl group and macrocyclic ether, the optimal distance appears to be three methylene units. By contrast, an oligoether linker likely participates in chelating interactions with the potassium cation perhaps affording additional stabilizing interactions. This may explain the appreciable rate enhancement observed in the fluorinations of agents **14** and **18** (Tables 2 and 3).

CONCLUSION

We developed new 18-C-6-based CENCs giving high [^{18}F]potassium fluoride sequestration efficiency and rapid fluorinations and radiofluorinations of organosilicon compounds under mild conditions. A key feature of these ionophoric agents is that they contain a side-arm terminating in a hydroxyl group, which may activate the silicon towards fluorination. Our studies of these CENCs demonstrate that the length of the side-arm correlates with the rate of silicon fluorination. These observations are rationalized based on stabilization of a hypervalent silicon intermediate by an intramolecularly proximal potassium/18-C-6 complex.

EXPERIMENTAL SECTION

General Information: Reactions were performed in oven-dried glassware with magnetic stirring under an argon atmosphere (unless otherwise stated). Reaction products were purified with flash chromatography on silica gel (40–63 μ m). Extracts were concentrated with a rotary evaporator (bath temperatures up to 30 $^{\circ}$ C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high vacuum line at rt. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates (200 μ m). Plates were visualized under UV light (254 or 365 nm), followed by staining with vanillin, or potassium permanganate or silica/ I_2 and drying with a heat gun. 1H NMR spectra were acquired on a 400 MHz spectrometer and are reported as δ in ppm relative to TMS using solvent as an internal standard ($CDCl_3$ at δ 7.26 or CD_3CN at δ 1.94 ppm). Data are reported as br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext =

sextet, sept = septet, m = multiplet; coupling constants in Hertz (Hz). $^{13}C\{^1H\}$ NMR were measured on a 100 MHz spectrometer. Chemical shifts are reported as δ (ppm) relative to signal for TMS using solvent as an internal standard ($CDCl_3$ at δ 77.0 or CD_3CN at δ 1.39 and 118.69 ppm). High-resolution mass spectra were recorded by an ESI-TOF MS spectrometer (DART ion source). All reagents were obtained commercially and were used without further purification. Solvents were purchased in an anhydrous state, or purified and dried as required.

General procedure for synthesis of silane precursors:

A solution of bromophenyl/biphenyl substrate (1.0 eq.) in THF (0.5 M) was chilled to $-78^{\circ}C$. $n-BuLi$ (1.6 M in hexanes, 1.0 eq.) was added over 10 min. The mixture was stirred for 30 min at $-78^{\circ}C$, after which chlorodiisopropylsilane (1.0 eq.) was slowly added via syringe. After 1 h, the ice-bath was removed and the solution was allowed to warm to rt with stirring overnight. The reaction was quenched with saturated aq. NH_4Cl (5.0 mL) and extracted with ether (20 mL \times 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield a light-yellow oil which was purified by flash chromatography (1% EtOAc/hexane), affording the product as a colorless oil.

[1,1'-Biphenyl]-4-yl diisopropylsilane: Yield: 2.98 g (94%); 1H NMR ($CDCl_3$): δ (ppm) 1.06 (d, J = 7.2 Hz, 6H), 1.13 (d, J = 7.2 Hz, 6H), 1.24–1.34 (m, 2H), 4.02 (t, J = 3.2 Hz, 1H), 7.35–7.39 (m, 1H), 7.45–7.49 (m, 2H), 7.62–7.66 (m, 6H); ^{13}C NMR ($CDCl_3$): δ (ppm) 11.0(2C), 18.8(2C), 18.9(2C), 126.6(2C), 127.4(2C), 127.6, 129.0(2C), 133.1, 136.2(2C), 141.3, 141.9. ESI-HRMS: m/z [$M+H$] calcd for $C_{18}H_{24}Si$: 269.1726; found 269.1722.

Diisopropyl(4-(((tetrahydro-2H-pyran-2-yl)-oxy)-methyl)-phenyl)-silane (8**):** Yield: 1.88 g (92%); 1H NMR ($CDCl_3$): δ (ppm) 0.99 (d, J = 7.2 Hz, 6H), 1.06 (d, J = 7.2 Hz, 6H), 1.17–1.27 (m, 2H), 1.54–1.92 (m, 6H), 3.54–3.58 (m, 1H), 3.91–3.96 (m, 2H), 4.50 (d, J = 12.4 Hz, 1H), 4.74 (t, J = 4.0 Hz, 1H), 4.80 (d, J = 12.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ (ppm) 10.9(2C), 18.7(2C), 18.9(2C), 19.6, 25.7, 30.8, 62.3, 69.1, 98.1, 127.2(2C), 133.4, 135.8(2C), 139.4. NMR data of this material were consistent with reported values.^{4b}

Procedure to synthesize 4-(diisopropylsilyl)-benzaldehyde (9**):** To a solution THP ether **8** (1.0 eq.) in ethanol (13 mL/mmol) was added p -toluenesulfonic acid monohydrate (1.0 eq.) and the mixture was stirred for 2 h at rt. The mixture was added to saturated aq. sodium bicarbonate and extracted with CH_2Cl_2 . The combined organic extracts were washed with brine and dried (Na_2SO_4). After filtration and removal of the solvent, the crude alcohol was used directly in the next step. Yield: 1.36 g (100%); 1H NMR ($CDCl_3$): δ (ppm) 0.99 (d, J = 7.2 Hz, 6H), 1.06 (d, J = 7.2 Hz, 6H), 1.18–1.28 (m, 2H), 1.90 (brs, 1H), 3.95 (t, J = 3.2 Hz, 1H), 4.69 (s, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ (ppm) 10.9(2C), 18.7(2C), 18.9(2C), 65.6, 126.5(2C), 133.7, 135.9(2C), 141.9. NMR data of this material were consistent with reported values.¹⁶

A solution of alcohol (1.0 eq.) in dry CH_2Cl_2 (0.4 M) was added to a suspension of activated MnO_2 (10 eq.) in dry CH_2Cl_2 (3.8 mL/mmol) at rt, and the mixture was stirred for 5 h. The black residue was filtered on a pad of celite and washed thoroughly with CH_2Cl_2 . The collected organic layer was passed through a silica gel bed. The filtrate was evaporated in vacuo to give the aldehyde as a colorless oil. Yield: 1.08 g (80%); ^1H NMR (CDCl_3): δ (ppm) 0.98 (d, $J = 7.2$ Hz, 6H), 1.07 (d, $J = 7.2$ Hz, 6H), 1.21–1.31 (m, 2H), 3.99 (t, $J = 3.2$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 2H), 10.02 (s, 1H); ^{13}C NMR (CDCl_3): δ (ppm) 10.8(2C), 18.6(2C), 18.8(2C), 128.7(2C), 136.2 (2C), 136.9, 143.4, 192.9. NMR data of this material were consistent with reported values.¹⁶

General procedure for the synthesis of silyl ethers: To a suspension of trichloroisocyanuric acid (0.33 eq.) in CH_2Cl_2 (0.3 M) was added the previously synthesized silane (1.0 eq.) in CH_2Cl_2 (0.5 M) at 0 °C under N_2 atmosphere. The mixture was stirred for 1 h at rt. Then the white solid was filtered off through a short pad of celite. The filtrate was concentrated under reduced pressure to give the chlorosilane, which is unstable. Therefore, this product was used immediately in the next step, as follows. A solution of the chlorosilane (1.1 eq.) in CH_2Cl_2 (0.5 M) at 0 °C under N_2 atmosphere was added to a mixture of corresponding alcohol (1.0 eq.) and imidazole (1.2 eq.) in CH_2Cl_2 (0.3 M). The mixture was warmed to rt and stirred for 4 h. After filtering off the white solid, the filtrate was concentrated and purified with flash column chromatography (5% EtOAc/hexane) to give product as a colorless oil.

[1,1'-Biphenyl]-4-yldiisopropyl(methoxy)-silane (1): Yield: 3.18 g (96%); ^1H NMR (CDCl_3): δ (ppm) 1.12 (d, $J = 7.2$ Hz, 6H), 1.17 (d, $J = 7.2$ Hz, 6H), 1.39 (sept, $J = 7.2$ Hz, 2H), 3.70 (s, 3H), 7.37–7.41 (m, 1H), 7.47–7.51 (m, 2H), 7.66–7.70 (m, 6H); ^{13}C NMR (CDCl_3): δ (ppm) 12.3(2C), 17.6(2C), 17.8(2C), 52.4, 126.6(2C), 127.4(2C), 127.7, 129.0(2C), 133.1, 135.4(2C), 141.3, 142.2. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{19}\text{H}_{26}\text{OSi}$: 299.1826; found 299.1821.

4-(Diisopropyl(methoxy)-silyl)-benzaldehyde (10): Yield: 1.10 g (90%); ^1H NMR (CDCl_3): δ (ppm) 1.00 (d, $J = 7.2$ Hz, 6H), 1.07 (d, $J = 7.2$ Hz, 6H), 1.32 (sept, $J = 7.2$ Hz, 2H), 3.64 (s, 3H), 7.72 (d, $J = 8.0$ Hz, 2H), 7.86 (d, $J = 8.0$ Hz, 2H), 10.03 (s, 1H); ^{13}C NMR (CDCl_3): δ (ppm) 12.1(2C), 17.4(2C), 17.5(2C), 52.4, 128.7(2C), 135.3(2C), 137.0, 143.3, 192.9. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Si}$: 251.1467; found 251.1464.

Procedure to synthesize 4-(diisopropyl(methoxy)silyl)benzoic acid (11): The aldehyde **10** (1.0 eq.) was dissolved in a mixture of $^i\text{BuOH}$ -acetonitrile (2:1, 0.03 M) and 2-methyl-1-butene (5.0 eq.) was added. The mixture was cooled to 0 °C. NaH_2PO_4 (3.5 eq.) and NaClO_2 (3.125 eq.) were then added. The mixture was then slowly warmed to rt over 5 h before it was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$. After common work-up, the obtained product was dissolved in dry CH_2Cl_2 (2 mL) and purified with flash chromatography (5–20% EtOAc/hexane) to furnish product as a colorless oil. Yield: 0.45 g (65%); ^1H NMR (CDCl_3): δ (ppm) 1.02 (d, $J = 7.2$ Hz, 6H), 1.08 (d, $J = 7.2$ Hz, 6H), 1.33 (sept, $J = 7.2$ Hz, 2H), 3.65 (s, 3H), 7.68 (d, $J = 8.0$ Hz, 2H), 8.11 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3): δ (ppm) 12.1(2C), 17.4(2C), 17.6(2C), 129.1(2C), 130.5, 134.9(2C), 142.2,

172.6. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{Si}$: 267.1411; found 267.1407.

General procedure for oxidative amidations: Aldehyde **10** (1.0 eq.), amine (1.5 eq.) and 2-methylbut-2-ene (5.0 eq.) were added to toluene (0.6 M) and allowed to stir for 5 min. NaClO_2 (3.125 eq.) and NaH_2PO_4 (3.5 eq.) were then added to the mixture, which was then stirred at 40 °C for 15–26 h. Reaction progress was monitored with TLC. After the reaction was complete, the mixture was diluted with anhydrous CH_2Cl_2 (5.0 mL), filtered and concentrated under reduced pressure. The residue was purified with flash chromatography (5–10% EtOAc/hexane) to afford the product as a gum.

N-Benzyl-4-(diisopropyl(methoxy)silyl)-benzamide (12): Yield: 1.19 g (75%); ^1H NMR (CDCl_3): δ (ppm) 1.00 (d, $J = 7.2$ Hz, 6H), 1.06 (d, $J = 7.2$ Hz, 6H), 1.30 (sept, $J = 7.2$ Hz, 2H), 3.62 (s, 3H), 4.65 (d, $J = 5.6$ Hz, 2H), 6.57 (brs, 1H), 7.28–7.35 (m, 5H), 7.61 (d, $J = 8.0$ Hz, 2H), 7.79 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3): δ (ppm) 12.1(2C), 17.4(2C), 17.6(2C), 44.3, 52.3, 126.2(2C), 127.8, 128.1(2C), 129.0(2C), 135.0(2C), 135.2, 138.4, 139.1, 167.8. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_2\text{Si}$: 356.2040; found 356.2038.

Methyl (4-(diisopropyl(methoxy)silyl)benzoyl)glycyl-L-phenylalaninate (23): Yield: 0.18 g (65%); ^1H NMR (CDCl_3): δ (ppm) 1.00 (d, $J = 7.2$ Hz, 6H), 1.06 (d, $J = 7.2$ Hz, 6H), 1.31 (sept, $J = 8.0$ Hz, 2H), 3.05–3.18 (m, 2H), 3.63 (s, 3H), 3.72 (s, 3H), 4.11 (s, 2H), 4.85–4.90 (m, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 7.07–7.17 (m, 5H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.79 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CDCl_3): δ (ppm) 12.1(2C), 17.4(2C), 17.6(2C), 38.0, 43.7, 52.7, 53.5, 126.3(2C), 127.4, 128.9(2C), 129.4(2C), 134.2, 135.0(2C), 135.8, 139.6, 168.1, 168.9, 171.9. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_5\text{Si}$: 485.2466; found 485.2464.

Procedure to synthesize 2-methoxymethyl-18-C-6 (5): 2-hydroxymethyl-18-C-6 **4** (1.0 eq.) was added to a suspension of NaH (1.5 eq) in THF (0.1 M) and the mixture was stirred for 2 h. Methyl iodide (2.0 eq.) was added, and the mixture was stirred for 20 h and then refluxed for 10 h. The cooled solution was then concentrated under reduced pressure and purified with flash chromatography on neutral alumina using EtOAc as eluent to afford product as a colorless oil. Yield: 0.23 g (59%); ^1H NMR (CDCl_3): δ (ppm) 3.31 (s, 3H), 3.52–3.69 (m, 24H), 3.81–3.85 (m, 1H); ^{13}C NMR (CDCl_3): δ (ppm) 59.4, 68.4, 70.0, 70.03 (4C), 70.11 70.13, 70.4, 70.5, 71.6, 71.65, 77.6. Proton and carbon NMR data of this material were consistent with reported values.¹⁷

Procedure to synthesize 18-C-6-methoxy-ethoxy-ethoxy-ethanol (18): The compound **18**, a colorless oil, was prepared using the standard reported procedure.¹⁴ Yield: 2.59 g (48%); ^1H NMR (CDCl_3): δ (ppm) 2.79 (brs, 1H), 3.55–3.82 (m, 37H); ^{13}C NMR (CDCl_3): δ (ppm) 61.7, 69.9, 70.3, 70.5, 70.58, 70.59, 70.61, 70.65, 70.67, 70.7, 70.75 (2C), 70.81, 70.82, 70.84, 71.3, 71.6, 72.5, 78.3. ESI-HRMS: m/z [M+H] calcd for $\text{C}_{19}\text{H}_{38}\text{O}_{10}$: 427.2543; found 427.2538.

General procedure for fluorination: In an oven-dried vial purged with argon was added a CENC (0.10 mmol) and anhydrous KF (0.10 mmol) in anhydrous MeCN (0.5 mL). After the complexation reaction, the solvent was removed under vacuum and the residue was kept under high vacuum over-

night followed by discharging under argon for 15 min. A solution of silyl ether substrate (0.20 mmol) in anhydrous CD₃CN (0.1 M) was added to the CENC/KF complex. The mixture was directly transferred in a dry NMR tube and the ¹H NMR was acquired in 5 min intervals up to 25 min. The percent conversions were then estimated based on comparisons of integrations of the isopropyl group signals in the ¹H NMR of starting material versus product. Compounds **20** and **24** were also characterized in solution by LC/MS because of their instabilities in the absence of solvent. (see SI for more details).

General procedure for radiofluorination: No-carrier-added (NCA) [¹⁸F]fluoride ion was obtained through the ¹⁸O(p,n)¹⁸F nuclear reaction by irradiating [¹⁸O]water (95 atom %) for 90–120 min with a proton beam (17 MeV; 20 μA) generated with a PETTrace cyclotron (GE Medical Systems, Milwaukee, WI). Cyclotron-produced NCA [¹⁸F]fluoride ion (1.1–3.7 GBq) in [¹⁸O]water (150–250 μL), and K₂CO₃/PTA stock solution (0.66/1.32 μmol; 15 μL) were loaded into a 5-mL glass V-vial. MeCN (500 μL) was added and water/MeCN was azeotropically removed at 110 °C under a stream of N₂ gas (200 mL/min) and vacuum (< 20 mmHg). The azeotropic process was repeated three more times to obtain dry [¹⁸F]fluoride ion agent. The vial was cooled with several dry-ice pellets over 4 min to rt. A solution of **12** or **23** (2.0 mg) was dissolved in MeCN (450 μL) and transferred to the drying vial at rt. The reaction mixture was allowed to stand at rt for 20 min before dilution with water (1 mL) and injected onto a semi-preparative scale HPLC column (Luna C18, 10 μm, 250 × 10 mm) for separation of products. The reaction mixture was eluted at 6 mL/min, with a mixture of aq. ammonium formate (A, 25 mM) and MeCN (B), with B initially 40% for 3 min, and then increasing linearly to 90% over 2 min. The fractions at *t*_R = 14.7–14.9 min ([¹⁸F]**20**) or 13.4–13.9 min ([¹⁸F]**24**) were collected and measured for radioactivity. Identities of [¹⁸F]**20** and [¹⁸F]**24** were verified by LC-MS analysis of associated carrier as *m/z* = 344.2 and 473.2 for [M⁺+H], respectively.

For radiofluorination in the presence of added MeOH or ethylene glycol, the alcohol was added along with **12**.

ASSOCIATED CONTENT

Supporting Information. Copies of ¹H and ¹³C NMR spectra of all new compounds. NMR-based percent conversion silicon fluorination data. HPLC chromatograms of [¹⁸F]**20** and [¹⁸F]**24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

[†]* E-mail: slepore@fau.edu

[‡]* E-mail: shuiyu.lu@mail.nih.gov

Author Contributions

[§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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