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# A Convenient Method for the Preparation of Fluorous Tin Derivatives for the Fluorous Labeling Strategy

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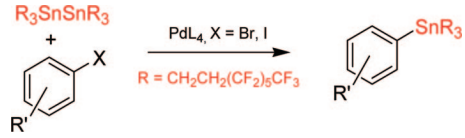


A convenient method for the preparation of fluorous aryl stannanes was developed as a means of expanding the general utility of the fluorous labeling strategy (FLS). Following the synthesis of a novel fluorous distannane, a palladium-catalyzed cross-coupling reaction was used to prepare the target compounds from aryl halides. The scope of the reaction was investigated by preparing a small library of model compounds where the reaction yields were similar to those reported for the analogous procedures employing hexamethyl- or hexabutyldistannanes. The utility of the reported methodology was demonstrated through the successful synthesis of fluorous precursors to two established molecular imaging and therapy agents (FIAU, IUdR). These were radiolabeled with iodine-125 and the desired products isolated in high yield and effective specific activity.

## Introduction

The desire to create molecular radioimaging agents and imaging biomarkers for protein targets that are expressed in low concentrations has created the need for methods of preparing radiotracers in high effective specific activity (ESA).[1] The removal of the excess starting material present following radiolabeling reactions is necessary to obtain radiotracers in high ESA. If this material is not removed, it can, in many cases, compete with the miniscule amounts of tracer for the target of interest, thereby increasing the amount of nonspecific binding.

Radiolabeled compounds can be isolated in high ESA by preparative HPLC. However, the method has significant practical drawbacks when working with radioactivity. The time required to isolate the desired product and remove the organic eluent is particularly undesirable for isotopes with short half-lives. In response to these issues, direct methods for the preparation of agents in high ESA are being developed. One approach utilizes solid supports where a precursor is coordinated to a cross-linked polymer in such a manner that the desired product is released into solution upon reaction with a radionuclide, while the unreacted starting material remains bound and can be removed by filtration. Methods for solid-phase labeling have been developed for isotopes of iodine[2−4]and for $^{99m}$Tc.[5,6]

One of the difficulties associated with solid-phase labeling is that the preparation of high purity polymer-supported precursors is often not trivial. Because purification of cross-linked supports is not an option, loading the resin must be accomplished in quantitative yield; otherwise, impurities can be introduced upon radiolabeling. To address this issue, we developed the fluorous labeling strategy (FLS), which is a solution-phase analogue of the solid-phase labeling strategy that employs a perfluoroalkyl moiety in place of a solid support. Upon labeling, the fluorous tag is released, rendering the desired product nonfluorous. Isolation of the desired product can be ac-

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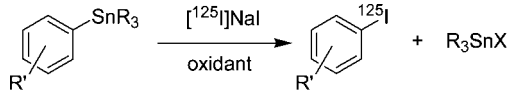
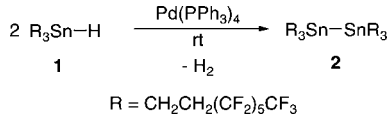
**SCHEME 1. Fluorous Labeling Strategy**




**SCHEME 2. Synthesis of a Fluorous Distannane**




complished by passing the reaction mixture through commercially available fluorous solid-phase extraction (FSPE) cartridges.[7,8] One of the main advantages of the FLS is that the fluorous precursors can be purified using standard chromatographic methods, making quantitative loading unnecessary, and all materials can be characterized using the conventional techniques employed for small molecules.

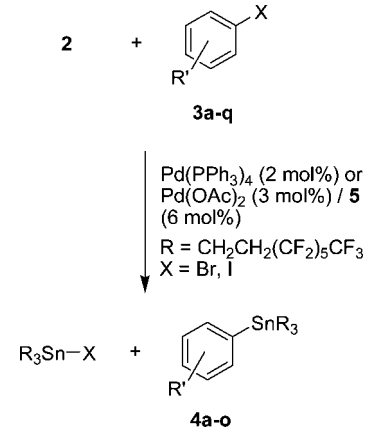
The FLS is based on halodestannylation chemistry (Scheme 1) where the fluorous precursors were originally prepared by combining organozinc reagents with commercially available fluorous tin bromides.[9] This synthetic approach, though effective, is incompatible with the functional groups present in many desirable targets.[7] To expand the general utility of the FLS, a new method for introducing fluorous supports was developed based on a palladium cross-coupling reaction between an aryl halide and a novel fluorous distannane.

## Results and Discussion

The majority of tin precursors used in radiopharmaceutical chemistry are produced using hexaalkyldistannanes. Despite the prior use of fluorous compounds in a range of palladium cross-coupling reactions,[9] there have been no reports in the literature of a palladium-catalyzed reaction being used to prepare fluorous trialkylstannyl derivatives. Consequently, the first objective was the preparation of the necessary fluorous distannane, which was initially attempted from a commercially available fluorous tin bromide, tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin bromide, via a zinc-catalyzed Wurtz-type coupling reaction reported by Marton et al.[10] This approach gave a complex mixture of products and was abandoned in favor of a palladium-catalyzed dehydrogenative coupling reaction with the fluorous tin hydride tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (**1**) (Scheme 2).[11]

The fluorous tin hydride **1** in toluene or THF was combined under a nitrogen atmosphere with a solution of $Pd(PPh_3)_4$, whereupon gas evolution and a color change from orange to yellow was evident. After 4 h, the desired product was isolated by extraction into FC-72 followed by silica gel chromatography to give the desired product as a colorless oil in excellent yield (91%). The $^1$H NMR showed two multiplets corresponding to the ethyl spacer groups on the fluorous chains. The $^{119}$Sn NMR spectrum contained a dominant peak at −52.5 ppm and a minor impurity at 14.5 ppm. The compound was stable for 1−2 weeks when exposed to light and several months when stored in a freezer.

**SCHEME 3. Cross-Coupling between an Aryl Halide and a Fluorous Distannane**[a]




[a] The R′ groups in **3a**−**q** and **4a**−**o** are listed in Table 1.

**TABLE 1. Yields for the Preparation of Arylstannanes 4a−o**[a]

| entry | ArX | R′ = | X = | product | yield with $Pd(PPh_3)_4$ | yield with $Pd(OAc)_2$ and **5** (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | I | **4a** | 59 | 67 |
| 2 | **3b** | *p*-OMe | I | **4b** | 51 | 47 |
| 3 | **3c** | *p*-Me | I | **4c** | 60[1] | 24 |
| 4 | **3d** | *p*-Et | I | **4d** | 37 | 18 |
| 5 | **3e** | *p*-Cl | I | **4e** | 42 | 41 |
| 6 | **3f** | *p*-COOH | I | **4f** | 30 | 44 |
| 7 | **3g** | *p*-CN | Br | **4g** | 15 | 19 |
| 8 | **3h** | *p*-$NO_2$ | I | **4h** | 59 | 54 |
| 7 | **3i** | *m*-COOEt | I | **4i** | 24 | 20 |
| 10 | **3j** | *m*-OH | I | **4j** | 38 | 34 |
| 11 | **3k** | *o*-Me | I | **4k** | 22 | 12 |
| 12 | **3l** | *o*-CN | Br | **4l** | 28 | 22 |
| 13 | **3m** | *o*-OH | I | **4m** | 0 | 0 |
| 14 | **3n** | *p*-$NMe_2$ | Br | **4n** | 0 | 0 |
| 15 | **3o** | *o*-$NH_2$ | Br | **4o** | 0 | 0 |
| 16 | **3p** | H | Br | **4a** | 27 | 29 |
| 17 | **3q** | *p*-OMe | Br | **4b** | 21 | 24 |

[a] Yields given are isolated yields averaged over two experiments.

A series of trial reactions using the fluorous distannane **2** were performed in THF using iodobenzene **3a** and *p*-iodoanisole **3b** as substrates (Scheme 3). $Pd(PPh_3)_4$ (2 mol %) was added to a solution of **2** and the aryl halide in THF. The fluorous products were extracted into FC-72 (perfluorohexanes), leaving the catalyst and nonfluorous components in the THF layer. A stoichiometric amount of a fluorous tin halide byproduct was formed alongside the desired product. Removal of this byproduct was somewhat challenging for these substrates; however, the desired products were ultimately isolated in reasonable yield (51% **4a**, 60% **4b**) using chromatography on silica gel.

One of the advantages of the FLS over polymer-based methods is that the target products can be characterized using conventional techniques employed for small molecules. The ability to thoroughly characterize products is particularly important for those agents which are to be used in the clinical production of radiopharmaceuticals. Here, all final products were characterized by $^1$H, $^{13}$C, and $^{119}$Sn NMR, HRMS, and GC/MS or HPLC. $^1$H NMR was particularly useful in that it clearly indicated the successful introduction of the fluorous tin group and removal of the unreacted fluorous tin halide. Successful

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reactions showed a multiplet and a triplet with $^{119}$Sn satellites in the 1−3 ppm range (e.g., 2.295 and 1.276 ppm for **4b**), which was characteristic of the presence of the ethyl spacer groups of the tris(perfluoroalkyl)tin moiety. The signals arising from the corresponding tin halide were distinct from the signals arising from the ethyl spacer groups in **4a**−**l**. The appearance of $^{119}$Sn satellites on the signals corresponding to protons in the α-position relative to the tin atom provided further evidence for the introduction of the fluorous trialkylstannyl group.

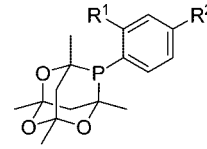
Initially, the fluorous distannane was isolated prior to performing the cross-coupling reactions. Isolation of ultrapure samples of **2** containing none of the impurity that appeared at 14.4 ppm in the Sn NMR proved difficult. Furthermore, it was difficult to obtain consistent elemental analysis or HRMS data even on batches of the same samples of **2**. Since the same catalyst and solvent were used in the cross-coupling reaction as in the preparation of the distannane, an attempt was made to prepare the distannane in situ.[12] The tin hydride and Pd were combined in THF at room temperature for 4 h prior to adding the aryl halide and heating the reaction to reflux. The isolated yield of the desired product was comparable to that obtained via the isolated distannane. The yield relative to tin hydride **1** was improved with the in situ method since no distannane was lost in the intermediate purification step. Because the in situ synthesis method was convenient and did not compromise the overall yield, it was the only method employed for all other examples presented here.

The scope of the in situ fluorous stannylation reaction was investigated using 17 different aryl halides. Reactions were performed in duplicate under nitrogen in a Radleys carousel reactor. The isolated yields for the model trialkylarylstannanes ranged from 15% to 59% (Table 1). These yields are comparable to the isolated yields reported for the analogous reactions involving hexabutyldistannane.[13,14]

Consistent with literature reports, aryl iodides afforded higher yields than the corresponding aryl bromides.[13,14] Three precursors gave no isolable product. With the *o*-hydroxyl group, some product was observed when the reaction mixture was analyzed by HPLC, but the product could not be isolated in sufficient purity. With the *o*-amino and *p*-*N*,*N*-dimethylamino groups, the reaction mixture immediately turned black likely due to the premature decomposition of the catalyst and the precipitation of Pd$^0$.

It was later shown (vide infra) that the method used to prepare compounds **4a**−**o** was unsuccessful when working with two radiopharmaceutical precursors. Consequently, the impact of changing the phosphine ligand was investigated. Capretta and co-workers have reported that phosphaadamantane ligands (Chart 1) are air-stable and that these electron-rich and sterically hindered ligands are highly active in Suzuki and Sonogashira reactions.[15−17] As a result, the utility of a series of these ligands for introducing the fluorous tin groups into the various aryl halides was investigated.

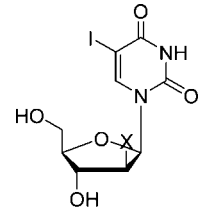
**CHART 1. Phosphaadamantane Ligand 5**




**5**

$R^1 = R^2 = OMe$

**CHART 2. Structures 6a and 6b**




**6a** (IUdR): X = H
**6b** (FIAU): X = F

The reaction conditions employed were similar to the original conditions used with $Pd(PPh_3)_4$, using THF and a reaction temperature of 65 °C. In place of $Pd(PPh_3)_4$, 3 mol % of $Pd(OAc)_2$ and 6 mol % of **5** were used as the catalysts. Although the separate components are air-stable solids, we found the catalyst system to be somewhat air-sensitive in solution; consequently, reactions were performed under argon. Reactions were monitored by GC, which indicated most reactions were complete within 24 h. In a few cases, an additional aliquot of the catalyst was added to the reaction when the precipitation of black Pd$^0$ was observed prior to complete consumption of the aryl halide. The yields observed (Table 1) were similar to that involving $Pd(PPh_3)_4$. Although no improvements in yields were observed with the phosphaadamantane−palladium system, the reaction rate was notably faster. Ultimately, this method proved more successful for the less reactive and highly functionalized precursors used in radiopharmaceutical chemistry.

**Applications in Radiopharmaceutical Chemistry.** The utility of the fluorous distannane and associated cross-coupling reaction in radiopharmaceutical chemistry was investigated through the preparation of two agents that have attracted a great deal of attention for their use in a range of molecular imaging and therapy studies (Chart 2). IUdR (iodoxuridine, 5-iodo-2′-deoxyuridine, **6a**) is under investigation as a therapeutic agent due to its ability to deliver $^{125}$I or $^{131}$I in close proximity to the DNA of rapidly dividing tumor cells.[18,19] FIAU (**6b**) is of interest as an imaging agent because it is selectively phosphorylated by thymidine kinases of the herpes simplex virus and those of other pathogens and can therefore be used to image bacterial infections and tumors associated with the herpes simplex or Epstein−Barr viruses.[20−23] A further advantage to this choice of targets is that the syntheses of the tributylstannyl precursor of IUdR and the trimethylstannyl precursor of FIAU from the corresponding distannanes have been reported, allowing for direct comparison to the fluorous method described here.[24,25]

The syntheses of the fluorous precursors to FIAU and IUdR were attempted using the iodide **6a** and bromide **7**. Unfortu-

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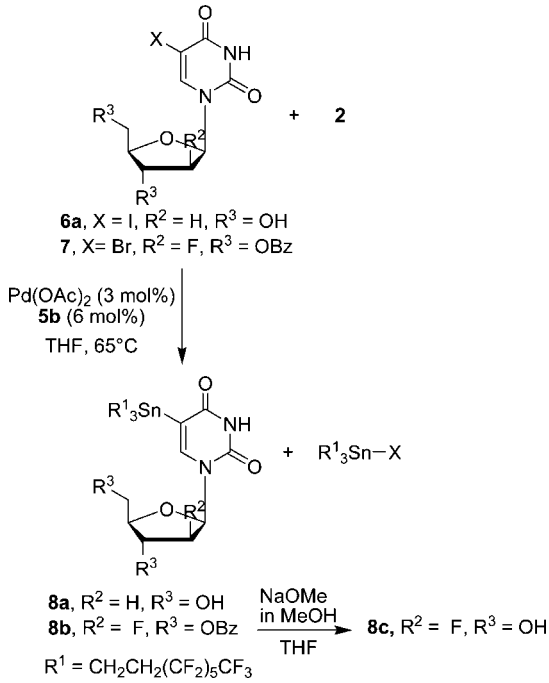
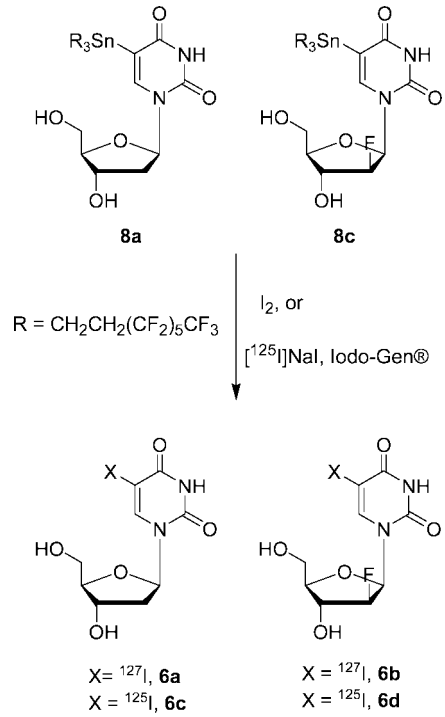
**SCHEME 4. Synthesis of Fluorous Precursors**




**SCHEME 5. Iodination of Fluorous Radiotracer Precursors**




nately, the procedure employing $Pd(PPh_3)_4$ as the catalyst did not yield the desired products **8a** and **8b**. The same reaction using the phosphaadamantane−palladium catalyst was, in contrast, successful. The halides were heated at 65 °C in THF in the presence of 6 mol % of **5** and 3 mol % of $Pd(OAc)_2$ or 1.5 mol % of $Pd_2(dba)_3$. No difference in yield was noted between the two palladium sources. Extraction with FC-72 removed the fluorous tin halide byproducts from the THF layer, while the products remained in the organic layer. The target products **8a** and **8b** were isolated by column chromatography in 21% and 48% yield, respectively. In comparison, yields reported for preparation of the analogous tributylstannyl and trimethylstannyl compounds were 80% and 36% for the IUdR and FIAU precursors, respectively.[24,25]

Removal of the benzoyl protecting groups on **8b** (which were required for the synthesis of **7**)[25] was not successful following the literature method of treating the ester with 80:20 methanol/aqueous $NH_4OH$ at room temperature[25] or *n*-butylamine in methanol at reflux.[26] Failure of these methods may have been caused by the poor solubility of **8b** in methanol. The deprotection was ultimately achieved in 80% yield by treating **8b** in THF with sodium methoxide in methanol (Scheme 4).[20] The reactions were monitored by HPLC (elution method B) and went to completion within 20 min, after which the product was conveniently isolated by FSPE. The opportunity to use fluorous chemistry to facilitate isolation of key precursors is an added advantage of the FLS.

**Radiochemistry.** Compounds **8a** and **8c** were subjected to direct iodinolysis with nonradioactive iodine prior to the preparation of the corresponding iodine-125 compounds [$^{125}$I]I-UdR and [$^{125}$I]FIAU (Scheme 5). Direct iodinolysis was used to verify the reactivity of the fluorous stannanes and to test the ability of the FSPE purification protocol to remove the unreacted precursor. To ensure that residual starting material was present at the end of the reaction, reactions were performed using 0.5 equiv of $I_2$. After 15 min, the reactions were quenched with sodium metabisulfite, and the crude reaction mixture was analyzed by HPLC (elution method A). The chromatogram (Figure 1) showed two signals which matched those of the precursors (**8a/8c**) and the products (**6a/6b**). Following FSPE purification, the chromatogram showed only the desired products.

For the radiolabeling procedures, 100 $\mu$g of HPLC-purified samples of each tin precursor was combined with [$^{125}$I]NaI in the presence of Iodo-Gen. After 3 min, the reaction mixture was quenched by the addition of 10 $\mu$L of 0.1 M aqueous sodium metabisulfite, diluted with 1 mL of water, and transferred to a conditioned FSPE cartridge (80:20 MeOH/water). The cartridge was then eluted with water followed by 80:20 MeOH/water and the eluent collected in 1.5 mL fractions whereupon the activity of each was measured in a dose calibrator. The purity of the fractions having the highest activity was examined by HPLC (elution method A). The average radiochemical yield for three trials was 94% for **6c** and 88% for **6d**. The average percentage of residual activity remaining on the cartridge was 4% for **6c** and 8% for **6d** indicating modest amounts of nonspecific binding. The remaining activity (2% for **6c** and 4% for **6d**) was found in a fraction containing both the desired products and [$^{125}$I]NaI.

The $\gamma$-HPLC chromatograms showed the formation of a single product in both reactions with the retention times of the

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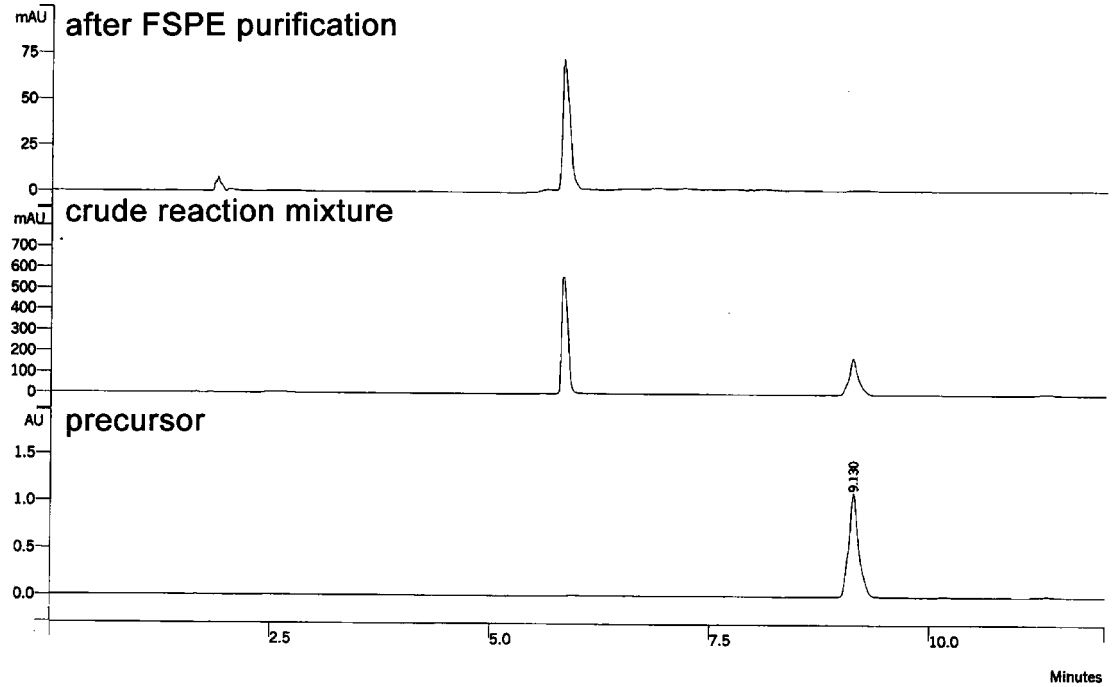


**FIGURE 1.** UV−HPLC chromatograms (elution method A) of the various stages involved in the iodinolysis and purification of **8a**.

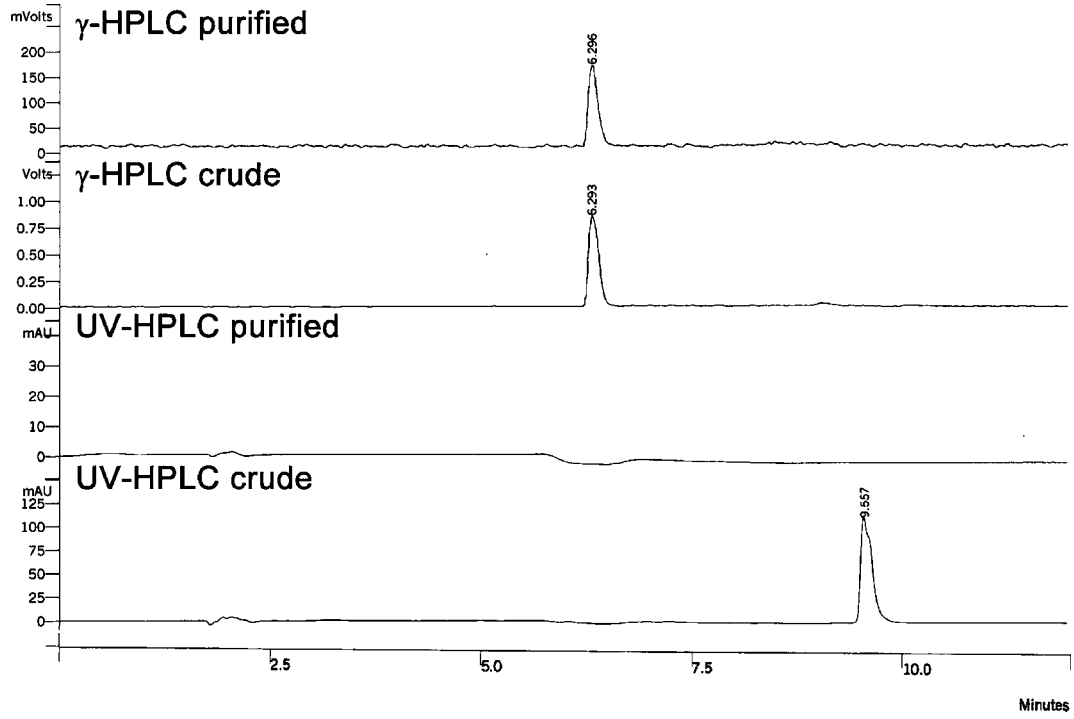


**FIGURE 2.** HPLC chromatograms (elution method A) of the various stages involved in the radiolabeling and purification of **6a**.

products corresponding to that of authentic nonradioactive standards. In concert, the UV−HPLC chromatograms showed that the FSPE was highly effective at removing the tin precursor from the crude reaction mixture (Figure 2). After FSPE purification, neither of the precursors was observed in the UV−HPLC chromatogram, within the detection limit of the instrument (75 $\mu$g/mL). The radiolabeled product, present in trace amounts in the HPLC aliquot, also could not be observed in the UV chromatogram. The organic solvent remaining after FSPE was removed quickly on a Biotage V10 evaporator at 40 °C, and the activity was taken up into a sterile isotonic solution ready for injection.

## Conclusions

A fluorous distannane was prepared in effectively quantitative yield by dehydrogenative coupling of a fluorous tin hydride in the presence of a palladium catalyst. From the distannane generated in situ, a series of model compounds were prepared from aryl halides in the presence of either $Pd(PPh_3)_4$ or a phosphaadamantane ligand and $Pd(OAc)_2$ or $Pd_2(dba)_3$, with

yields ranging from 15% to 67%. The phosphaadamantane−palladium catalyst was also used to prepare fluorous trialkylstannyl precursors of IUdR and FIAU. The fluorous precursors were radiolabeled with iodine-125 and the products were isolated by FSPE to afford [$^{125}$I]IUdR and [$^{125}$I]FIAU in high radiochemical yields (94% and 88%). The labeled products were obtained in high effective specific activity, as no tin precursor could be detected after purification. The ability to introduce the fluorous tin groups in a manner similar to the one used for trimethyl- and tributylstannanes will expand the general utility of the FLS and offer researchers a convenient means of producing labeled compounds with high ESA.

## Experimental Section

**Synthesis of Hexa(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)distannane (2).** To a stirred solution of tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (120 mg, 0.10 mmol) in toluene or THF (3.8 mL) under a nitrogen atmosphere was added 1.2 mg of $Pd(PPh_3)_4$ in toluene (1.2 mL). The reaction mixture was protected from light and stirred for 4 h, after which it was extracted with FC-72 (3 × 3 mL). The combined fluorous layers were dried over sodium sulfate, and the solvent was removed to afford a pale yellow oil which was purified by column chromatography on silica (eluent: 5:1 hexanes/EtOAc) to give a colorless oil (106 mg, 91%): TLC $R_f$ = 0.70 (5:1 hexanes/EtOAc), 0.06 (99:1 hexanes/EtOAc); $^1$H NMR (FC-72, 600 MHz) $\delta$ 2.48 (m, 6H, $CF_2CH_2$), 1.37 (m, 6H, $CH_2Sn$); $^{13}$C NMR (FC-72, 150 MHz) $\delta$ 28.0, −1.5; $^{119}$Sn NMR (FC-72, 186 MHz) $\delta$ −52.5; IR (cm$^{-1}$) 1238, 1204, 1145.

**Generalized Cross-Coupling Reactions.** The synthesis of tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzene (**4a**) is used as a representative example.

**Method A: From Purified Distannane.** To a stirred solution of hexa(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)distannane (116 mg, 50 $\mu$mol) in THF (3.9 mL) was added $Pd(PPh_3)_4$ (1.2 mg, 1 $\mu$mol) in THF (0.6 mL) and a solution of iodobenzene (5 mg, 24.5 $\mu$mol) in THF (0.5 mL). The reaction mixture was brought to reflux and stirred for 72 h. The reaction mixture was extracted with FC-72 (3 × 5 mL), and the combined fluorous layers were dried with sodium sulfate and concentrated by rotary evaporation. The desired product was isolated as a colorless oil (27 mg, 22 $\mu$mol, 48%) by flash chromatography on silica gel using an eluent mixture of hexanes and ethyl acetate (199/1 v/v).

**Method B: Distannane Formed In Situ.** To a stirred solution of tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (174 mg, 150 $\mu$mol) in THF (4.2 mL) was added $Pd(PPh_3)_4$ (1.7 mg, 1.5 $\mu$mol) in THF (0.85 mL) under an inert atmosphere. The reaction mixture was protected from light and stirred at room temperature. After 4 h, a solution of iodobenzene (14 mg, 68.6 $\mu$mol) in THF (0.35 mL) and an additional 0.5 mg of $Pd(PPh_3)_4$ in THF (0.25 mL) were added. The mixture was heated at reflux temperature for 72 h or until completion of the reaction had been observed by GC. Aliquots of ∼0.1 mL were taken for analysis by GC using a glass syringe and then diluted with hexanes to 1 mL and filtered through glass wool prior to GC analysis. Upon completion of the reaction, the reaction mixture was extracted with FC-72 (3 × 3 mL). The combined fluorous layers were dried over sodium sulfate, and the solvent was removed by rotary evaporation to yield a yellow oil. The product was isolated by column chromatography on silica gel (hexanes/EtOAc, 199/1 v/v). The fractions containing product were combined and the solvent was removed to afford a colorless oil (43 mg, 51%).

**Method C: One-Pot Procedure Used with Phosphaadamantane Ligands.** A solution of tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (232 mg, 200 $\mu$mol) in THF (4 mL) was added to a reaction vessel which had been evacuated and purged with argon. A solution of 1,3,5,7-tetramethyl-2,4,8-trioxa-(2,4-dimethoxyphenyl)-6-phosphaadamantane **5** (2.1 mg, 12 $\mu$mol) in THF (1 mL) was added to the reaction vessel, followed by a solution of palladium acetate (0.7 mg, 6 $\mu$mol) in THF (1 mL). After the reaction mixture was stirred for 10 min, during which time evolution of hydrogen was observed, iodobenzene (18 mg, 90 $\mu$mol) in THF (1 mL) was added. The mixture was heated at reflux temperature for 72 h or until completion of the reaction had been observed by GC. Upon completion, the reaction mixture was extracted with FC-72 (3 × 3 mL). The combined fluorous layers were dried over sodium sulfate, and the solvent was removed by rotary evaporation. The product was isolated by flash chromatography on silica gel (hexanes/EtOAc, 199:1) to afford a colorless oil (75 mg, 67%).

**Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzene (4a):** colorless oil; yield 48% (from iodobenzene, method A), 51% (from iodobenzene, method B), 27% (from bromobenzene, method B), 67% (method C); TLC $R_f$ = 0.78 (5:1 hexanes/EtOAc), 0.37 (199:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.44 ppm (m, 5H, H-aryl), 2.31 (m, 6H, $CF_2CH_2$), 1.31 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) 136.6, 136.2, 129.8, 129.2, 27.9, −1.3; $^{119}$Sn NMR ($CDCl_3$, 186 MHz) $\delta$ −29.4; IR (cm$^{-1}$) 1239, 1207, 1145; HRMS (ES-) *m*/*z* calcd for $C_{30}H_{17}F_{39}Sn$ ([M + TFA]$^-$) 1350.9586, found 1350.9567; HPLC (230 nm) $t_R$ = 20.3 min; GC/MS $t_R$ = 10.3 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylanisole (4b):** colorless oil; yield 60% (from 4-iodoanisole, method B), 21% (from 4-bromoanisole, method B); TLC $R_{f/>}$ = 0.29 (99:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.30 (m, 2H, H-aryl), 6.98 (d, 2H, $^3$J = 8.4 Hz, H-aryl), 3.82 (s, 3H, $OCH_3$), 2.30 (m, 6H, $CF_2CH_2$), 1.27 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 161.0, 137.3, 126.5, 115.1, 55.3, 27.9, −1.3; $^{119}$Sn NMR ($CDCl_3$, 224 MHz) $\delta$ −25.6; IR (cm$^{-1}$) 1240, 1207, 1145; HRMS (ES-) *m*/*z* calcd for $C_{31}H_{19}F_{39}SnO$ ([M + acetate]$^-$) 1326.9976, found 1326.9965; HPLC (230 nm) $t_R$ = 19.8 min; GC/MS $t_R$ = 11.2 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannyltoluene (4c):** colorless oil; yield 60% (method B with 2 equiv of distannane **1**), 24% (method C); TLC $R_{f/>}$ = 0.33 (hexanes); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.25 (m, 4H, H-aryl), 2.37 (s, 3H, $CH_3$), 2.30 (m, 6H, $CF_2CH_2$), 1.24 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 139.9, 139.8, 136.1, 132.5, 130.0, 27.9, 21.6, −1.4; $^{119}$Sn NMR ($CDCl_3$, 186 MHz) $\delta$ −28.3; IR (cm$^{-1}$) 2933, 1239, 1204, 1145; HRMS (ES-) *m*/*z* calcd for $C_{31}H_{19}F_{39}Sn$ ([M + acetate]$^-$) 1311.0026, found 1311.0037; HPLC (230 nm) $t_R$ = 21.4 min; GC/MS $t_R$ = 10.6 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylethylbenzene (4d):** colorless oil; yield 37% (method B), 18% (method C); TLC $R_{f/>}$ = 0.34 (hexanes); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.27 (m, 4H, H-aryl), 2.66 (q, 2H, $^3$J = 7.5 Hz, $\underline{CH_2}CH_3$), 2.30 (m, 6H, $CF_2CH_2$), 1.29 (m, 9H, $CH_3$, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 146.1, 136.2, 132.9, 128.8, 29.0, 27.9, 15.5, −1.4; $^{119}$Sn NMR ($CDCl_3$, 186 MHz) $\delta$ −28.5; IR (cm$^{-1}$) 2974, 2942, 1239, 1202; HRMS (ES-) *m*/*z* calcd for $C_{32}H_{21}F_{39}Sn$ ([M + acetate]$^-$) 1325.0183, found 1325.0189; HPLC (230 nm) $t_R$ = 22.0 min; GC/MS $t_R$ = 10.9 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylchlorobenzene (4e):** colorless oil; yield 42% (method B), 41% (method C); TLC $R_{f/>}$ = 0.44 (hexanes); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.36 (m, 4H, H-aryl), 2.26 (m, 6H, $CF_2CH_2$), 1.30 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 137.3, 136.4, 134.9, 129.4, 27.9, −1.0; $^{119}$Sn NMR ($CDCl_3$, 186 MHz) $\delta$ −26.0; IR (cm$^{-1}$) 2944, 1239, 1203, 1145; HRMS (ES-) *m*/*z* calcd for $C_{30}H_{16}F_{39}SnCl$ ([M + TFA]$^-$) 1384.9190, found 1384.9188; HPLC (230 nm) $t_R$ = 20.5 min; GC/MS $t_R$ = 11.0 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzoic acid (4f):** colorless oil; yield 30% (method B), 44% (method C); TLC $R_{f/>}$ = 0.19−0.40 (1:1 hexanes/diethyl ether); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.11 (d, 2H, $^3$J = 8.0 Hz, H-3′, H-5′), 7.53 (m, 2H, H-2′, H-6′), 2.33 (m, 6H, $CF_2CH_2$), 1.35 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 171.4, 145.1, 136.3, 130.3, 130.1, 27.8, −1.0; $^{119}$Sn NMR ($CDCl_3$, 186 MHz) $\delta$ −28.1; IR (cm$^{-1}$) 2927, 1698, 1238,

1205, 1144; HRMS (ES-) *m/z* calcd for $C_{31}H_{17}F_{39}SnO_2$ ([M + TFA]$^-$) 1394.9556, found 1394.9596; HPLC (254 nm) $t_R$ = 18.1 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzonitrile (4g):** colorless oil; yield 15% (method B), 19% (method C); TLC $R_{f/>}$ = 0.27 (95:5 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.40 (d, 2H, $^3$J = 7.9 Hz, H-aryl), 7.31 (m, 2H, H-aryl), 2.30 (m, 6H, $CF_2CH_2$), 1.34 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 137.3, 136.4, 132.2, 129.4, 27.9, −1.2; $^{119}$Sn NMR ($CDCl_3$, 224 MHz) $\delta$ −26.1; IR (cm$^{-1}$) 2943, 2364, 1576, 1239, 1145; HRMS (ES-) *m/z* calcd for $C_{31}H_{16}F_{39}SnN$ ([M + acetate]$^-$) 1321.9822, found 1321.9824; HPLC (230 nm) $t_R$ = 20.6 min; GC/MS $t_R$ = 11.0 min.

***p*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylnitrobenzene (4h):** colorless oil; yield 59% (method B), 54% (method C); TLC $R_{f/>}$ = 0.23 (95:5 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.23 (d, 2H, $^3J$ = 8.5 Hz, H-aryl), 7.60 (m, 2H, H-aryl), 2.34 (m, 6H, $CF_2CH_2$), 1.38 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 149.2, 147.3, 136.9, 123.2, 27.7, −0.7; $^{119}$Sn NMR ($CDCl_3$, 224 MHz) $\delta$ −25.7; IR (cm$^{-1}$) 2932, 1523, 1351, 1239, 1202, 1145; HRMS (ES-) *m/z* calcd for $C_{30}H_{17}F_{39}SnNO_2$ ([M + TFA]$^-$) 1395.9437, found 1395.9430; HPLC (230 nm) $t_R$ = 18.1 min; GC/MS $t_R$ = 12.2 min.

**Ethyl *m*-tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzoate (4i):** colorless oil; yield 24% (method B), 20% (method C); TLC $R_{f/>}$ = 0.44 (9:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.07 (m, 2H, H-aryl), 7.48 (m, 2H, H-aryl), 4.39 (q, 2H, $^3$J = 7.0 Hz, $OCH_2$), 2.32 (m, 6H, $CF_2CH_2$), 1.30 (m, 9H, $CH_2Sn$, $CH_3$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 166.7, 140.3, 137.3, 136.9, 131.0, 130.8, 129.0, 61.4, 27.8, 14.4, −1.0; $^{119}$Sn NMR ($CDCl_3$, 187 MHz) $\delta$ −27.1; IR (cm$^{-1}$) 2964, 1715, 1238, 1200, 1143; HRMS (ES-) *m/z* calcd for $C_{33}H_{21}F_{39}SnO_2$ ([M + acetate]$^-$) 1369.0082, found 1369.0081; HPLC (220 nm) $t_R$ = 19.9 min; GC/MS $t_R$ = 11.8 min.

***m*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylphenol (4j):** colorless oil; yield 38% (method B), 34% (method C). TLC $R_{f/>}$ = 0.23 (9:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.30 (m, 1H, H-aryl), 6.86 (m, 3H, H-aryl), 4.79 (s, 1H, OH), 2.30 (m, 6H, $CF_2CH_2$), 1.29 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 155.2, 137.6, 129.6, 127.7, 121.8, 116.0, 27.1, −2.0; $^{119}$Sn NMR ($CDCl_3$, 224 MHz) $\delta$ −27.3; IR (cm$^{-1}$) 1238, 1205; HRMS (ES-) *m/z* calcd for $C_{30}H_{17}F_{39}SnO$ ([M + TFA]$^-$) 1366.9536, found 1366.9547; HPLC (230 nm) $t_R$ = 17.3 min.; GC/MS $t_R$ = 11.5 min.

***o*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannyltoluene (4k):** colorless oil; yield 22% (method B), 12% (method C); TLC $R_{f/>}$ = 0.28 (hexanes); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.28 (m, 4H, H-aryl), 2.37 (s, 3H, $CH_3$), 2.28 (m, 6H, $CF_2CH_2$), 1.32 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 144.1, 136.8, 136.3, 130.1, 126.1, 28.0, 25.2, −0.9; $^{119}$Sn NMR ($CDCl_3$, 187 MHz) $\delta$ −26.2; IR (cm$^{-1}$) 2924, 1238, 1196, 1144; HRMS (ES-) *m/z* calcd for $C_{31}H_{19}F_{39}Sn$ ([M + TFA]$^-$) 1364.9744, found 1364.9728; HPLC (220 nm) $t_R$ = 20.8 min; GC/MS $t_R$ = 10.6 min.

***o*-Tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannylbenzonitrile (4l):** colorless oil; yield 28% (method B), 22% (method C); TLC $R_{f/>}$ = 0.33 (9:1 hexanes/EtOAc); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.73 (d, 1H, $^3$J = 7.7 Hz, H-aryl), 7.61 (m, 1H, H-aryl), 7.50 (m, 2H, H-aryl), 2.39 (m, 6H, $CF_2CH_2$), 1.48 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 144.3, 136.8, 133.4, 132.7, 130.0, 120.7, 120.1, 27.8, −0.4; $^{119}$Sn NMR ($CDCl_3$, 187 MHz) $\delta$ −23.7; IR (cm$^{-1}$) 2945, 2222, 1238, 1206, 1144; HRMS (ES-) *m/z* calcd for $C_{31}H_{16}F_{39}SnN$ ([M + formate]$^-$) 1307.9666, found 1307.9680; HPLC (230 nm) $t_R$ = 18.3 min; GC/MS $t_R$ = 11.1 min.

**Synthesis of 1-(2′-Deoxy-β-D-ribofuranosyl)-5-tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannyluracil (8a).** THF (2 mL) was added to tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (232 mg, 200 μmol) and 5-iodo-1-(2′-deoxy-β-D-ribofuranosyl)uracil (32 mg, 90 μmol) under argon followed by a solution of 1,3,5,7-tetramethyl-2,4,8-trioxa-(2,4-dimethoxyphenyl)-6-phosphaadamantane **5** (2 mg, 12 μmol) in THF (1 mL). A solution of tris(dibenzylideneacetone)dipalladium (2 mg, 3 μmol) in THF (1 mL) was added, and the reaction mixture was heated to 65 °C and stirred under argon. The progress of the reaction was monitored by HPLC (elution method B). Upon completion of the reaction, the reaction mixture was diluted with THF (10 mL) and extracted with FC-72 (3 × 5 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to afford a brown oil from which the desired product was isolated by column chromatography on a Biotage SP1 automated chromatography unit (stationary phase: silica gel, mobile phase: gradient of 0−10% MeOH in DCM (0−10 column volumes), 10% MeOH in DCM (10−20 column volumes). After concentration, the residue was dissolved in 80% MeOH−water (250 μL) and loaded onto an FSPE cartridge that had been conditioned with DMF (1 mL) and 80% MeOH−water (5 mL). The column was washed with 80% MeOH−water (5 mL) and then MeOH (5 mL) to elute the desired product which was isolated, following concentration of the methanol fraction by rotary evaporation, as a white foam (26 mg, 21%): TLC $R_{f/>}$ = 0.65 (9:1 DCM/MeOH); $^1$H NMR ($CD_3OD$, 200 MHz) 7.90 (s, 1H, H-6), 6.29 (t, 1H, H−1′), 4.39 (m, 1H, H-3′), 3.92 (m, 1H, H-4′), 3.73 (m, 2H, H-5′), 2.47 (m, 6H, $CF_2CH_2$), 2.33 (m, 2H, H-2′), 1.26 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CD_3OD$, 150 MHz) $\delta$ 169.4, 152.8, 147.7, 110.9, 89.5, 87.0, 72.7, 62.9, 41.8, 28.8, 0.1; $^{119}$Sn NMR ($CD_3OD$, 186 MHz) $\delta$ −25.5; IR (cm$^{-1}$) 3437, 1649, 1237, 1197, 1142; HRMS (ES-) *m/z* calcd for $C_{33}H_{23}F_{39}SnO_5N_2$ ([M + TFA]$^-$) 1500.9865, found 1500.9869; HPLC (254 nm) $t_R$ = 13.3 min.

**Synthesis of 1-(3′,5′-Dibenzoyl-2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-5-tris(2-perfluorohexylethyl)stannyluracil (8b).** 1,3,5,7-Tetramethyl-2,4,8-trioxa-(2,4-dimethoxyphenyl)-6-phosphaadamantane **5** (2.1 mg, 12 μmol) in THF (1 mL) and palladium acetate (0.7 mg, 12 μmol) in THF (1 mL) were added to a solution of tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)tin hydride (232 mg, 200 μmol) in THF (2 mL) under argon. The reaction mixture was stirred at room temperature for 10 min, during which time evolution of hydrogen was observed. A solution of 1-(3′,5′-dibenzoyl-2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-5-bromouracil (48 mg, 90 μmol) in THF (1 mL) was added and the reaction mixture heated at reflux. Progress of the reaction was monitored by HPLC (elution method B). If the progress of the reaction appeared to stop before complete consumption of the starting material or if a color change from yellow-orange to black was observed, further portions of the phosphaadamantane ligand and palladium(II) acetate were added in the same amounts stated above. Upon completion of the reaction, the reaction mixture was filtered through a 1 cm bed of silica with 0.5 cm layers of Celite above and below, and the silica was washed with THF (10 mL). The pale brown solution was extracted with FC-72 (3 × 5 mL) to remove the fluorous tin halide and distannane byproducts, and the organic layer was concentrated by rotary evaporation to afford an orange-brown oil. The oil was purified by column chromatography using by silica gel chromatography (hexanes and diethyl ether). The fractions containing product were concentrated by rotary evaporation to yield white foam (70 mg, 48%): TLC $R_{f/>}$ = 0.54 (1:1 hexanes/$Et_2O$); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.48 (s br, 1H, NH), 8.06 (m, 4H, H-2″, H-6″), 7.53 (m, H-6, H-3″, H-4″, H-5″), 6.35 (m, 1H, H−1′), 5.60 (m, 1H, H-3′), 5.35 (m, 1H, H-2′), 4.84, 4.71 (m, 1H, H-5′), 4.54 (m, 1H, H-4′), 2.30 (m, 6H, $CF_2CH_2$), 1.17 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 166.2, 166.1, 165.4, 150.4, 145.8, 134.5, 133.7, 130.2, 129.8, 129.7, 129.0, 128.7, 128.3, 109.4, 93.4, 92.1, 85.4, 85.3, 82.1, 76.7, 63.5, 27.6, −0.7; $^{119}$Sn NMR ($CDCl_3$, 187 MHz) $\delta$ −23.3; IR (cm$^{-1}$) 3438, 1726, 1239, 1207, 1145; HRMS (ES-) *m/z* calcd for $C_{47}H_{30}F_{40}SnO_7N_2$ ([M − H]$^-$) 1613.0358, found 1613.0389; HPLC (254 nm) $t_R$ = 16.1 min.

**Synthesis of 1-(2′-Deoxy-2′-fluoro-β-D-arabinofuranosyl)-5-tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)stannyluracil (8c).** To a solution of 5-tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-1-(3′,5′-dibenzoyl-2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)uracil (80.6 mg, 50 μmol) in THF (2 mL) was added a 0.5 M solution of sodium methoxide in MeOH (0.3 mL, 150 μmol). The reaction was monitored by HPLC (elution

method B) where upon completion the reaction mixture was neutralized with glacial acetic acid (approximately 30 $\mu$L) and loaded onto an FSPE cartridge which had been conditioned with 6 mL of 80:20 MeOH/water. The cartridge was then washed with 80:20 MeOH/water (8 mL) and MeOH (8 mL). Evaporation of the MeOH fractions afforded the product as a white foam (57 mg, 80%): TLC $R_{f/>} = 0.69$ (9:1 DCM/MeOH); $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 7.74 (m, 1H, H-6), 6.33 (m, 1H, H-1′), 5.10 (m, 1H, H-2′), 4.40 (m, 1H, H-3′), 4.02 (m, 1H, H-4), 3.83 (m, 2H, H-5′), 2.52 (m, 6H, $CF_2CH_2$), 1.35 (m, 6H, $CH_2Sn$); $^{13}$C NMR ($CD_3OD$, 125 MHz) $\delta$ 169.2, 152.5, 148.0, 110.0, 97.2, 86.0, 85.5, 75.3, 62.0, 28.8, 0.2; $^{119}$Sn NMR (acetone-$d_6$, 186 MHz) $\delta$ −24.9; IR (cm$^{-1}$) 3437, 2922, 1124; HRMS (ES-) *m*/*z* calcd for $C_{33}H_{22}F_{40}SnO_5N_2$ ([M + acetate]$^-$) 1465.0052, found 1465.0084; HPLC (265 nm) $t_R = 13.4$ min.

**General Procedure for Cold Iodination.** To a vial containing 10 mg of the desired trialkylstannyl precursor was added acetonitrile (200 $\mu$L) and a solution of iodine in MeCN (10 mg/mL, 2 $\mu$L). After being stirred for 15 min, the reaction was quenched by the addition of an aqueous solution of sodium metabisulfite (10 $\mu$L, 0.01 M). The crude reaction mixture was analyzed by HPLC (elution method A) and then diluted with water (2 mL) and loaded onto a fluorous solid-phase extraction cartridge that had been conditioned with DMF (1 mL) and 80% MeOH−water (6 mL). After loading, the reaction vial was rinsed with water (2 mL) which was added to the FSPE cartridge. The product was then eluted using 80% MeOH−water (12 mL). The MeOH−water fractions were combined and evaporated, and the residue was dissolved in MeCN (1 mL) for analysis by HPLC (elution method A).

**General Radiolabeling Procedure.** Glass vials were coated with Iodo-Gen (1,3,4,6-tetrachloro-3α,6α-diphenylglycouril) by concentrating a solution of the oxidant in chloroform (2 $\mu$L, 1 mg/mL) under reduced pressure. Vials were stored in the freezer until immediately before use. To an Iodo-Gen coated vial was added a solution of the trialkylstannyl precursor in methanol (100 $\mu$L, 1 mg/mL), glacial acetic acid (1 $\mu$L), and aqueous sodium [$^{125}$I]iodide (1 $\mu$L, 925−1455 kBq). The reaction mixture was allowed to stand for 3 min with occasional swirling and was then quenched by the addition of aqueous sodium metabisulfite (10 $\mu$L, 0.01 mol/L). The reaction mixture was immediately diluted with water (1 mL) and then loaded onto a FSPE cartridge which had been conditioned with 80% MeOH−water (6 mL). The reaction vial was rinsed with water (1 mL), which was added to the FSPE cartridge. The cartridge was then eluted with additional water (5 mL) followed by 80% MeOH−water (6 mL, collected in 1.5 mL fractions). The activities of all collected fractions were measured using a dose calibrator and the purity assessed by HPLC.

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**Supporting Information Available:** Characterization data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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