Fluorous-Phase Synthesis of Heparan Sulfate Disaccharides & Low-Molecular Weight Additives for Enhancing the Performance of Lithium-Ion Batteries.

Matthew Daniel Casselman
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LOW-MOLECULAR WEIGHT ADDITIVES FOR ENHANCING THE PERFORMANCE
OF LITHIUM-ION BATTERIES

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

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David H. Thompson

Yu Xia

Mingji Dai

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Approved by Major Professor(s): Alexander Wei

Approved by: R. E. Wild  11-19-2013

Head of the Graduate Program Date
FLUOROUS-PHASE SYNTHESIS OF HEPARAN SULFATE DISACCHARIDES & LOW-MOLECULAR WEIGHT ADDITIVES FOR ENHANCING THE PERFORMANCE OF LITHIUM-ION BATTERIES

A Dissertation
Submitted to the Faculty
of
Purdue University
by
Matthew D. Casselman

In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

December 2013
Purdue University
West Lafayette, Indiana
For my parents Daniel and Teresa Casselman, and the rest of my family
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxy carbonyl</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
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<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
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<td>DMA</td>
<td>dimethylacetal</td>
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<tr>
<td>DMAP</td>
<td>N,N-dimethyl-4-aminopyridine</td>
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<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>DMSO</td>
<td>dimethylsulfoxide</td>
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equiv equivalent
en ethylenediamine
ESI electrospray ionization
Et ethyl
EtOAc ethyl acetate
FPSE fluorous solid-phase extraction
Glc glucose
GlcN glucosamine
GlcA glucuronic acid
h hour
HBP heparan binding protein
HS heparan sulfate
IBX 2-iodoxybenzoic acid
IR infrared
IdoA iduronic acid
LAH lithium aluminum hydride
LIB lithium-ion battery
Me methyl
min minute
NHS N-hydroxysuccinimide
NIS N-iodosuccinimide
Np p-nitrophenyl
MS mass spectrometry
MW  microwave
NMR  nuclear magnetic resonance
MP  4-methoxyphenyl
Nap  2-naphthylmethyl
Np  4-nitrophenyl
o/n  overnight
PFA  perfluoroalkyl
PFB  perfluorobutyl
PFH  perfluorohexyl
PFO  perfluoroctyl
Ph  phenyl
Phth  phthalic
PMB  p-methoxybenzyl
PMBDMA  p-methoxybenzyidine dimethyl acetal
pyr  pyridine
q  quartet
rt  room temperature
s  singlet
sat  saturated
SEM  trimethylsilylethoxymethyl
SEI  solid-electrolyte interface
t  triplet
TBAI  tetrabutylammonium iodide
<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TCEP</td>
<td>tris(2-carboxyethyl)phosphine</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethyl-1-piperidinyloxy</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFT</td>
<td>trifluorotoluene</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Tol</td>
<td>toluene</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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ABSTRACT

Casselman, Matthew D. Ph.D., Purdue University, December 2013. Fluorous-Phase Synthesis of Heparan Sulfate Disaccharides & Low-Molecular Weight Additives for Enhancing the Performance of Lithium-Ion Batteries. Major Professor: Alexander Wei.

Heparan sulfate is a complex cell-surface proteoglycan that serves many important roles in biology, such as growth and development, immune response and pathogenesis. Heparan sulfate is structurally heterogeneous due to the variable post-glycosylation modifications, particularly the generation of diverse sets of sulfate esters (sulfoforms) for any given disaccharide unit. In order to establish useful relationships between heparan sulfate structure and biological activity, a set of well-defined sulfoforms is necessary to support binding affinity screening. In this thesis, we describe the generation of diverse sulfoforms from heparan disaccharides using a fluorous tag to facilitate purification of highly charged intermediates, and their subsequent immobilization on substrates for affinity binding studies.

A library of heparan disaccharide sulfoforms was prepared from a single intermediate using an orthogonal protecting group system, to enable the controlled unmasking of hydroxyls or amines for subsequent sulfonation. A practical challenge of this approach is the need to carry highly polar intermediates through multiple synthetic steps. This was addressed by installing a perfluoroalkyl (fluorous) tag on the reducing
end of the orthogonally protected disaccharide. The fluorous tag facilitated the separation of polar intermediates from non-fluorous byproducts via a two-stage solid-phase extraction. In this manner, a library of 1,4-linked disaccharides comprised of glucuronic acid (GlcA) and glucosamine (GlcN) could be prepared with a variable set of sulfonated substituents. The fluorous tag was retained on the final product to enable their non-covalent adhesion onto perfluoroalkyl-functionalized glass slides in microarray format, for biological screening against L-selectin, FGF2, and urokinase.

Lithium ion batteries have quickly become an important energy source and storage medium for electronics in recent years. Increasing the useful lifetime of batteries is a key challenge in their wide use. A number of perfluoroalkyl-functionalized small molecules were prepared as performance-enhancing additives for lithium ion batteries. Perfluoroctyl ethylene carbonate was identified as a candidate that had positive effects on both cell cycling and cell impedance.
CHAPTER I – INTRODUCTION

1.1 Heparin and Heparan Sulfate – Structure and Biosynthesis

Carbohydrates are a class of biomolecules with importance in biology with respect to recognition and regulation of biochemical processes. Important classes of carbohydrates are the glycosaminoglycans, a family of related carbohydrates found on the cell surface as part of glycoproteins.\(^1\) Of particular interest to us are heparin and heparan sulfate. Heparin and heparin sulfate in their primary sequence are made up of a repeating disaccharide unit of glucoamine and hexuronic acid. The oligosaccharide is then made more complex by the presence of post-glycosational modifications that produce a diverse and heterogeneous set of substructures. These modifications include the presence of sulfate esters, at various positions, as well as the isomerization of the D-glucuronic acids (GlcA) into L-iduronic acid (IdoA) units (Figure 1.1). We collectively describe these modified heparan structures as sulfoforms.\(^2,3\)

![Figure 1.1 Basic structure of heparin and heparan sulfate. R = H, Ac, SO\(_3^-\). R’=H, SO\(_3^-\).](image-url)
The biosynthesis of heparin and heparan sulfate are similar in which N-acetyl glucosamine (GlcNAc) and D-glucuronic acid units are copolymerized from a peptide-bound core tetrasaccharide. Following the elongation of the heparan chain, a number of post-glycosylational modifications are effected by various enzymes (Figure 1.2).¹ Modification sites on GlcNAc include the amine (NHAc, NHSO₃⁻, or NH₂) and the sulfonation of the C3 or C6 hydroxyls. The D-glucuronic unit can be sulfonated at the C2 position and epimerized at the C5 position into L-iduronic acid. The first step in the biosynthesis involves N-deacetylation and sulfate transfer (NDST) to afford heparan N-sulfate. Epimerization (EPI) of the D-glucuronic acid to L-iduronic acid is next, followed by sulfonation at the C2 hydroxyl (2-OST) of the uronic acid unit and the C6 hydroxyl (6-OST) of glucosamine being the most common modification sites. Sulfonation of the C3 hydroxyl (3-OST) of glucosamine is the last step in the biosynthesis and is often considered an uncommon or rare modification (and a key signaling factor for various heparin-binding proteins.) This multistep, post-glycosylational biosynthesis results in a complex and heterogeneous structure, as each biosynthetic operation does not proceed with 100% efficiency, with segments that are highly modified (NS-domain), segments with few modifications (NA/NS-domain) and segments with no modifications (NA-domain) (Figure 1.3).

One disaccharide unit can generate up to 48 sulfoforms, though approximately half of the unique disaccharide sulfoforms have been isolated. When considered in the context of larger oligosaccharides, an inordinately large number of potential sulfoforms results. As an example, there are over 5.3 million sulfoforms are possible for heparan octasaccharides.
1.2 Role of Heparin and Heparan Sulfate in Biology

Heparin and HS have many documented roles in key biological processes. Perhaps the most well known example heparin plays in biological processes is its role in the blood coagulation pathway. Clinically heparin is used as an anti-coagulant:
interaction with antithrombin III (AT-III) leads to the inactivation of thrombin. This interaction is quite well studied, and a minimum size fragment (pentasaccharide) has been identified for activation of AT-III (Figure 1.4). This heparin fragment possesses the relatively uncommon 3-O-sulfate, which is critical for biological activity. This pentasaccharide has been synthesized and is now sold on the market under the name fondaparinux (trade name Arixtra).

![Figure 1.4 AT-III-binding heparin pentasaccharide, fondaparinux.](image)

Heparan sulfate is present on the surface of nearly all mammalian cells, and is well known to be a ligand for extracellular signaling proteins. It is implicated in the recruitment of growth factors, particularly fibroblast growth factor and vascular endothelial growth factor. Research suggests that heparin sulfoform expression is related to cellular conditions and environment. L-selectin, a cell-adhesion protein, is found on lymphocytes and is known to have some affinity for heparan sulfate. It is thought that interactions with heparan sulfate on endothelial cells can slow the rolling of the lymphocytes along the surfaces of blood vessels, giving more time for the interaction between highly specific receptors to take place.
A number of bacteria and viruses also have strong affinities for heparin. Human immunodeficiency virus (HIV) is one such example, specifically the envelope glycoprotein gp41. Herpes simplex virus also has affinity for heparin, and in vitro experiments have shown that exogenous heparin can inhibit infection of cells. Chlamydia has also been show to interact with heparin, and may be involved in the initial infection of human epithelial cells.

While many heparin-binding proteins (HBPs) have been identified, the converse is not well known. Very few sequences of heparin/HS have been characterized as high-affinity ligands for various HBPs. This is because well-defined structures of heparin/HS oligosaccharides are not easily isolated from natural sources, which presents an opportunity for synthetic organic chemists to obtain them abiotically.

1.3 Chemical Synthesis of Heparin-Like Oligosaccharides

Until very recently, all chemical synthesis of well-defined HS fragments has been completed by one of two synthetic approaches. The first is by a target-oriented approach, where a single sulfoform of HS is synthesized and screened for its biological activity; the second is by a diversity-oriented approach, where a library of HS sulfoforms is synthesized and screened for structure-activity relationships.

The target-oriented approach has found significant support in the literature for the synthesis of larger HS fragments. This approach typically involves the task of preparing a large library of monosaccharide intermediates that are differentially protected. These monosaccharide donors each require multiple steps of functionalization to afford each desired sulfoform pattern, and are coupled by a stepwise glycosylation approach, where
the oligosaccharide is built up one unit at a time with the sulfonation patterns pre-programmed at specific positions. Recently libraries of protected monosaccharides have been synthesized and used to make a small number of structurally complex and biologically active octasaccharide sulfoforms (Figure 1.5). The disadvantage of this approach is that structure-activity relationships for all possible sulfoforms is simply not possible due to the large number of possible oligosaccharide sulfoforms.

![Diagram of target-oriented synthesis of a bioactive oligosaccharide sulfoform](Image)

Figure 1.5 Target-oriented synthesis of a bioactive oligosaccharide sulfoform.  

More recently, chemical biology methods have been advanced to the extent where a number of sulfotransferases have been isolated, produced and purified from bacterial growths. These enzymes have since found use in the semi-synthetic synthesis of biologically relevant oligosaccharide sulfoforms. Core heparin structures were synthesized, the oligosaccharide chain was elongated enzymatically, and controlled sulfonation using sulfotransferase enzymes was used to prepare single sulfoforms with relatively high purity.
A complementary approach to the target-oriented synthesis of sulfoforms is the diversity-oriented synthesis of libraries consisting of shorter heparin-inspired fragments. In this strategy, a single monosaccharide or disaccharide fragment is synthesized with a unique protecting group system. This protecting group system allows for the selective deprotection of any one position to enable the conversion to a sulfonate ester. Further deprotection reveals the desired sulfoform. In this manner, a single intermediate can produce a library of all possible sulfoforms (Figure 1.6). This strategy also enables structure-activity relationships between sulfoform structure and protein to be identified. These relatively weak relationships may then be used to develop longer oligosaccharides, which may exhibit stronger and more specific interactions with heparin binding proteins. The synthesis of heparan sulfate sequences enables the discovery of high affinity ligands for individual heparan binding proteins.

Figure 1.6. Diversity-oriented approach to disaccharide sulfoform libraries.
1.4 New Technologies for Carbohydrate Synthesis

In addition to various synthetic strategies for sulfoform generation, a number of practical methods have been developed recently in the area of carbohydrate chemistry. Polypeptide synthesis was revolutionized by the introduction of solid-phase synthesis, enabling the automated, step-wise synthesis of large peptide fragments without the tedious manipulations of traditional solution-phase chemistry. The translation of solid-phase methods to carbohydrate chemistry has been on-going, and presents its own unique challenges.

More recently, solid-phase supported synthesis has been applied to sulfoform chemistry. Previous work in our research group has involved the development of solid phase methods for the generation of sulfoforms.\(^2\) By this method, differentially protected carbohydrates are tethered to standard polystyrene resins. Subsequent deprotection and sulfonation afford sulfoforms in good yields (Figure 1.7). The advantage of this approach is that reaction intermediates need not be handled between reactions and only a single purification at the end of the synthesis is necessary. However, these advantages are not without drawbacks. The use of the polystyrene resin makes all reactions heterogeneous in nature and thus reduces the reactivity of bound carbohydrates. This is most apparent in the sulfonation step itself, where generating highly charged molecules on resin is quite challenging and is the limiting step in this method.
1.5 Fluorous Separations

Fluorous-based separations involves the use of perfluoroalkyl chains (fluorous tags) that allow for the separation of tagged molecules from untagged molecules.\textsuperscript{19} The unique materials properties of perfluoroalkyl-functionalized molecules have been known for years\textsuperscript{20}, but only recently have their application towards separations been realized. Fluorous chains have the unique quality of having both hydrophobic and lipophobic qualities, and prefer to associate with other fluorous molecules, hence the term fluorous phase. In a fluorous separation, a mixture of tagged and untagged molecules is partitioned between fluorous and non-fluorous phases.\textsuperscript{21} Fluorous phases include fluorinated solvents, such as perfluorohexanes or hydrofluoroethers, or fluorinated solid phases, such as perfluoroalkyl-functionalized silica gel or Teflon surfaces. Using an organic solvent with a fraction of aqueous solvent effectively partitions fluorous-tagged molecules into the fluorous phase, while untagged molecules are left in the non-fluorous phase. Molecules with a single perfluoroalkyl chain are termed ‘light fluorous’ typically do not
partition efficiently into liquid fluorous phases, but can be partitioned and separated using fluorous solid-phase extraction. Molecules with multiple perfluoroalkyl groups are termed ‘heavy fluorous’ and can partition into liquid or solid fluorous phases.

The typical fluorous separation is completed by fluorous solid-phase extraction (FSPE). In this method, a mixture of compounds is loaded onto a small cartridge of fluorous silica gel, then eluted in two stages. The first elution is a fluorophobic solvent such as a mixture of methanol and water (in a 9:1 or lower ratio). The fluorous compounds are retained on the fluorous silica and any non-fluorous compounds are not. The second elution is a fluorophilic solvent, which is typically acetone, THF or anhydrous methanol. This wash elutes the fluorous compounds efficiently. A typical FSPE separation takes mere minutes, and the time savings over tedious column chromatography can be significant.

Fluorous methods have found use in a wide variety of organic synthesis applications, including diversity-oriented mixture synthesis, polypeptide and oligonucleotide synthesis. One area of organic synthesis that has seen significant adoption of fluorous methods is carbohydrate chemistry. Here the advantages in terms of carbohydrate synthesis are apparent: Carbohydrate synthesis typically involves multistep synthesis that requires purification after each step, whereas fluorous methods streamline purifications in such linear syntheses. Fluorous methods are also compatible with the use of large excesses of reagents to drive reactions to completion without concern for post-reaction purification, as fluorous separations are straightforward and efficient. In general, these syntheses use a fluorous protecting group to introduce the tag which is cleaved at the end of the synthesis to afford the desired product in high yield.
Fluorous compounds behave very similarly to their non-fluorous counterparts. They also can be monitored by standard solution-phase methods (TLC, NMR, IR, etc.), and are easily purified and isolated by FSPE, and thus have a significant advantage over both solid-phase and solution-phase purification methods.

Due to the solvophobic profiles of fluorous compounds, it is also possible to selectively immobilize them onto fluorous surfaces. This idea has been used to present fluorous-tagged molecules, including carbohydrates, for biological assays. Pohl and coworkers\textsuperscript{28} first demonstrated that fluorous-tagged carbohydrates could be printed onto perfluoroalkyl-functionalized glass slides and used to study protein-carbohydrate interactions in a microarray format. The microarrays proved to be robust and able to withstand aqueous washing, protein binding, and antibody hybridization over multiple steps. This provides additional motive to synthesize a library of heparin-like sulfoforms and to screen their affinity toward heparin-binding proteins, using fluorous methods for both phases of the project.
1.6 References


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CHAPTER II – SYNTHESIS OF HEPARAN SULFATE SULFONOMERS VIA FLUOROUS METHODS

2.1 Synthesis of Orthogonally Protected α-Glucosamines

Glucosamine donor 6 was synthesized according to modified literature conditions. Compound 1 was synthesized in 2 steps from glucosamine hydrochloride salt as a mixture of anomers via phthalimide protection of the amino moiety and subsequent per-O-acetylation in 51% yield. Thioglycoside 2 was prepared under Lewis-acid mediated conditions with p-thiocresol and boron trifluoride in 81% yield. Only the β anomer is formed, due to anchimeric assistance. Zemplén deacetylation and p-methoxybenzylidene protection of the resulting 4,6-diol afforded acetal 3 in 83% yield. Deprotection of the phthalimide with ethylenediamine and subsequent conversion of the free amine to the corresponding azide was completed by treatment with triflyl azide and copper sulfate in 80% yield. The intermediate azidosugar was then acetylated to afford 4. A modified procedure for azide transfer was utilized to minimize the amount of potentially explosive triflyl azide reagent. Regioselective acetal reduction using Bu₂BOTf and borane cleanly afforded primary alcohol 5 in 91% yield. Treatment with TBDPS-Cl afforded orthogonally protected glucoamine donor 6 in 95% yield after careful chromatographic separation from TBDPS byproducts. Overall yield from glucosamine was 24% (Figure 2.1).
2.2 Synthesis of First-Generation Fluorous Sulfoforms

Prior to undertaking this project, there were no examples of highly polar carbohydrates being prepared via a fluorous approach. We first tested the feasibility of such an approach with a simple perfluoroalkyl glycoside. The fluorous tag was synthesized by the radical-mediated addition of perfluorooctyl iodide to allyl alcohol in the presence of AIBN to afford halohydrin 7 in quantitative yield (Figure 2.2).\(^4\) Dehalogenation of 7 with tributyltin hydride produced alcohol 8 in good yield, but required tedious purification to remove all traces of tin byproducts as both product and reaction byproducts are sufficiently non-polar. FSPE separation of tin byproducts from 8 was not feasible due to the hydrophobic character of the fluorous silica used. However, treatment of halohydrin 7 with hydrazine and Raney nickel\(^5\) cleanly afforded alcohol 8 in 71% yield and high purity after filtering through a silica plug.
Synthesis of the fluorous-tagged glucosamine 13 was completed according to Figure 2.3. Compound 1 was treated with acceptor 8 under Lewis acid conditions to afford β-glycoside 9 in 55% yield. Deacetylation and protection of the 4,6-diol afforded p-methoxybenzylidene acetal 10 in 79% yield. Conversion of the phthalimide to azide was achieved first by treatment with ethylenediamine, then triflyl azide, followed by 3-O-acetylation in 86% yield over 3 steps. Regioselective reduction of the 4,6-acetal afforded the 4-O-PMB ether 12 in 65% yield, and subsequent TBDPS protection afforded orthogonally protected glucosamine 13 in 93% yield. Yields for this synthetic sequence were unaffected by the presence of the fluorous chain, despite the electron-withdrawing nature of the PFO moiety. Purifications were performed by either standard silica gel chromatography or fluorous solid phase extraction (FSPE) depending on the cleanliness and completeness of the reaction. In particular, decomposition byproducts with fluorous tags cannot be separated by FSPE.
With orthogonally protected glucosamine derivative 13 in hand, we evaluated the compatibility of deprotection and sulfonation conditions and efficacy of purification with FSPE (Figure 2.4). Standard FSPE conditions were used to separate the fluorous-tagged intermediates from reaction byproducts, using 80% aqueous methanol to retain fluorous compounds and 100% methanol to elute them. Deprotection of the azide with tributylphosphine and subsequent sulfonation using \( \text{SO}_3 \cdot \text{pyridine} \) under microwave conditions afforded an \( N \)-sulfonate, followed by TBDPS deprotection (using TBAF) and saponification (using NaOMe) to produce PMB-protected sulfoform 14. Stepwise deprotection of 6-\( O \)-TBDPS and 3-\( O \)-acetate and sulfonation of the corresponding hydroxyls afforded 3,6-di-\( O \)-sulfate 15. While standard FSPE conditions were used to isolate intermediates after the first few deprotection steps, these were less successful following sulfonation, and gave a lower yield was recovered. Compound 16 was prepared by TBDPS protection, acetate removal, azide reduction and finally sulfonation under
microwave conditions. Very little trisulfate 16 was isolated by FSPE following sulfonation; most of the fluorous compound was found in the methanolic wash with additional pyridinium salts.

The low recovery of 15 and 16 motivated us to example the fluorophobic fraction. Analysis of the fluorophobic fractions by TLC and NMR showed that some fluorous compound was present in the fluorophobic fractions. This indicated that retention on the fluorous silica gel was compromised by the presence of sulfate esters.

![Figure 2.4 Deprotection and sulfonation of orthogonally protected \( \beta \)-glucosaminoglycoside 13](image)

We then attempted to isolate sulfonated compounds 14, 15, and 16 by modifying FSPE conditions. These were first tested using fluorous thin layer chromatography, to predict whether a FSPE separation will be successful. Under FSPE separations, the polar
fluorophobic wash typically causes the fluorous compound to be retained onto the fluorous substrate while washing away any salts and non-fluorous byproducts. A retention factor of zero indicates a strong absorption onto the fluorous silica of the FSPE cartridge. 80% aqueous methanol was successful in separating and isolating monosulfate 14, but disulfate 15 and trisulfate 16 were not successfully isolated. The R_f values as determined by fluorous TLC reflect this trend (Table 2.1): The high mobilities of 15 and 16 initially suggest that the polar intermediates have low affinity for the fluorous solid support. Increasing the water content of the eluent to 40% decreased R_f values for 14, 15, and 16. But even at this eluent composition, some undesired elution of the more polar compounds is observed. Increasing the water fraction in the eluent to 80% resulted in complete retention, suggesting complete partitioning of the tagged sulfoforms onto the fluorous support. It is widely assumed that fluorophilicity is orthogonal to polarity. But the above results demonstrate that fluorous character is also influenced by polarity and amphiphilic tendencies.

Table 2.1. Retention factors of intermediates 14-16 on F-TLC.

<table>
<thead>
<tr>
<th>Compound</th>
<th>80% aq. MeOH</th>
<th>40% aq. MeOH</th>
<th>20% aq. MeOH</th>
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<td>0.3</td>
<td>0.1</td>
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<tr>
<td>16</td>
<td>0.8</td>
<td>0.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Given the challenges of retaining highly polar intermediates on fluorous-phase substrates with a single PFO tag, an alternative strategy was developed to better enable FPSE separations under standard conditions. Pohl and coworkers had shown that molecules with two fluorous tags permitted better separation by FSPE relative to compounds with just one. We also envisioned a "double PFO" tag would increase the partitioning ratio onto the fluorous silica solid phase (Figure 2.5). 3-PFO-propanol 8 was converted to tosylate 17 in 87% yield, which was used to alkylate methyl 3,5-dihydroxybenzoate to afford the bis-PFO labeled methyl ester 18 in 96% yield. Reduction of ester 18 by LiAlH₄ afforded bis-PFO benzyl alcohol 19 in 74% yield. Using alcohol 19 as an acceptor in NIS/TfOH-promoted glycosylation with thioglycoside 2 resulted in bis-PFO tagged glucosamine 20 in low yield (22%), which was saponified and sulfonated to afford the trisulfate 21. Fluorous thin layer chromatography with 80% aqueous methanol as eluent resulted in full immobilization, which suggests that FSPE separation under standard conditions would be successful. This proved to be the case and tri-O-sulfonate 21 was recovered in high yield. This result suggested that the low partitioning of highly polar sulfoforms could be mitigated using bis-PFO tags.
2.3 Synthesis of Bis-PFO Tags

Having confirmed that two PFO chains are able to impart fluorous character onto highly polar sulfoforms, the next goal would be to transition from a non-cleavable tag to one that can be cleaved after all deprotection and sulfonation steps are performed. In the original orthogonal protecting group system\(^1\), there is no linker or protecting group present at the reducing end. In this study we introduced a 2-aminoethyl linker at the reducing end protected by a benzyl carbamate (Cbz) analogue, which is orthogonal to the other protecting groups on glucosamine and presumed to be stable under sulfonation conditions.

The first attempt towards bis-PFO benzyl carbamate (Cbz) protecting group utilized benzyl alcohol 19, which was treated with triphosgene to form the chloroformate intermediate, and converted to NHS ester 22 in 40% overall yield (Figure 2.6).
Glycosyl donor 6 and Fmoc-protected aminoethanol were coupled using NIS/TfOH conditions to afford corresponding glycoside 23 in 88% yield as a 4:1 α:β mixture of anomers (Figure 2.7). The anomers could be efficiently separated by silica gel chromatography using a THF/hexane eluent gradient. α-Glycoside 23 was then treated with 20% piperidine in DMF to afford the free amine in nearly quantitative yield, and conjugation with the activated NHS-carbonate 22 afforded protected aminoethyl α-glycoside 24 in 80% overall yield. α:β
Bis-PFO-tagged glycoside 24 was then subjected to orthogonal deprotection and sulfonation conditions. Treatment with TBAF removed the TBDPS group efficiently, but also caused the unexpected cleavage of a fluorous tag. Analysis of the reaction mixture by mass spectrometry revealed fragment ions that suggested elimination of one or more ether-linked PFO chains. It was possible that the reaction conditions were sufficiently basic to cause elimination of the phenolic unit, aided by the inductive effects of the PFO chain on the β-hydrogens. This sensitivity to basic conditions was also potentially problematic for the clean removal of acetate. It was observed that compound 24 slowly decomposed when exposed to ambient conditions. It is known that the 3,5-dimethoxybenzyl carbamate group can be photolabile, which decreased the reliability of this unit as a linker for sulfoform generation via a multi-step sequence.

With the problematic reactivity of bis-PFO tag 22, an alterative fluorous motif was designed based on the cross coupling of perfluoroalkyl iodides with aryl iodides using a copper-catalyzed Ullmann reaction. Perfluoroctyl iodide was coupled with methyl 3,5-diiodobenzoate in the presence of copper bronze to afford bis-PFO-substituted benzoate 25 in 74% yield. Reduction of the methyl ester with LiAlH₄ afforded bis-PFO benzyl alcohol 26 in quantitative yield. Attempts to synthesize the activated NHS-carbonate were unsuccessful, but treatment with carbonyldiimidazole afforded imidazole carbamate 27 in 85% yield (Figure 2.8). Activation of the acyl imidazole for conjugation to amines is typically achieved by alkylation to afford the activated acylimidazolinium species, however treatment of 27 with either methyl iodide or trimethylxonium tetrafluoroborate did not result in an acyl imidazolium, but led instead to a complex mixture. We then treated alcohol 26 with p-nitrophenyl chloroformate to afford mixed
carbonate 28 in 87% yield. Carbonate 28 was sufficiently stable for purification by column chromatography, yet reactive enough to form carbamates under mild conditions. Conjugation of 28 with the aminoethyl α-glycoside was straightforward, resulting in bis-PFO tagged product 29 in 98% yield (Figure 2.9).

Figure 2.8 Synthesis of bis-PFO Cbz analogue 28.

Figure 2.9 Synthesis of Bis-PFO tagged aminoethyl α-Glucosaminoside 29.
Compared to the O-linked bis-PFO tag 24, the C-linked bis-PFO derivative 29 was quite stable at ambient conditions. Deprotection of TBDPS with TBAF, unbuffered or buffered with an equimolar amount of acetic acid, smoothly afforded the desired alcohol. Separation of reaction byproducts from the bis-PFO tagged carbohydrate was easily achieved under standard FSPE conditions. Deprotection of acetate by sodium methoxide also cleanly afforded the corresponding alcohol; simple neutralization of the reaction mixture with proton exchange resin cleanly afforded the desired product. Azide deprotection was slightly problematic; conditions previously used in our group involved: reduction with tributylphosphine, followed by hydrolysis of the aza-ylide.\(^1\) While reduction of the azide with excess tributylphosphine was facile, hydrolysis of the aza-ylide was often sluggish. To address this issue, alternative reducing agents were considered, including tris(2-carboxyethyl)phosphine (TCEP). TCEP is a water-soluble reducing agent often used in the reduction of disulfides, but it is also known to reduce azides to primary amines.\(^10\) A slight excess of TCEP could reduce 29 in “wet” DMF to afford the desired primary amine in as little as two hours, as opposed to 18-24 hours as needed with tributylphosphine. TCEP was also more easily separated from the desired reaction products; in fact, a simple aqueous wash in a separatory funnel was sufficient to remove water-soluble TCEP. Tributylphosphine, being fairly hydrophobic in character, was sometimes hard to remove under FSPE conditions when high fractions of water were used in the eluent, which cause the fluorous silica gel to act similarly to reversed-phase media.

The controlled reactivity of 29 under a variety of deprotection conditions did not seem significantly affected by the presence of the bis-PFO tags, however solubility was a
common problem. DMF and DMSO were often necessary to increase solvation, where non-polar solvents such as DCM and chloroform were ineffective. This was particularly true in cases where the products had a significant amphiphilic character, with a hydrophilic sulfoform “headgroup” and solvophobic PFO tails.

Furthermore, while deprotection of 29 was largely successful, using sulfonation of the free alcohols and amines was problematic (Figure 2.10). Using the standard conditions for sulfonation established in our group (SO$_3$•pyridine in 1:5 Et$_3$N/pyridine), very little product was isolated by FSPE under either standard or modified conditions. Analysis of the fluorous fractions by NMR revealed diminished peak intensities of the carbohydrate region, relative to the bis-PFO tag. ESI-MS negative mode analysis of the reaction mixture revealed peaks corresponding to the desired sulfonated product, but also a high intensity peak centered at 1023 m/z, which was attributed to cleavage of the bis-PFO Cbz tag. This result was unexpected, but appeared to be a significant problem only when $N$-sulfonation was attempted. When sulfonation was attempted in the presence of azide or NHAc derivative, cleavage of the bis-PFO Cbz linkage was greatly reduced.

Figure 2.10 Attempted sulfonation of bis-PFO-tagged $\alpha$-glucosaminoside 29, following azide reduction and $N$-sulfonation.
Having isolated fluorous decomposition product after sulfonation, we sought to understand how reaction byproduct was formed. Our hypothesis is proposed as in Figure 2.11: Following reduction of azide 29 and N-sulfonation, the corresponding sulfamate transfer its $\text{SO}_3$ group to the carbamate in an intramolecular fashion. It is already known that amides and carbamates can be sulfonated under certain conditions. It may be possible that N-to-N or N-to-O sulfate transfer may occur upon treatment with $\text{SO}_3\cdot\text{pyridine}$. Intramolecular $\text{S}_\text{N}2$ may follow and ultimately decarboxylation causes cleavage of sulfated benzylic alcohol 30 from the aminoethyl $\alpha$-glucosaminoside.
Given the lability of the carbamate linkage in glycoside 29, we hypothesized that the dual PFO moieties may activate the benzylic position by inductive effects. To mitigate this, additional methylene spacers should be introduced to sufficiently insulate
the carbamate center from the PFO groups. With this in mind, homologated fluorous alcohol 33 was prepared and converted to a mixed carbonate for amine functionalization (Figure 2.12A). Benzylic alcohol 26, it was oxidized with 2-iodoxybenzoic acid to afford the bis-PFO benzaldehyde 31 in 94% yield. Bis-PFO benzaldehyde 31 was then homologated under Horner-Wadsworth-Emmons reaction conditions to afford substituted cinnaminic acid 32 in 87% yield. Chemoselective hydrogenation and ester reduction using LiAlH₄ afforded bishomobenzylic alcohol 33 in 92% yield. Conversion to mixed carbonate 34 with nitrophenyl chloroformate was completed in 65% yield, and conjugation of 34 with aminoethyl α-glycoside 23 following Fmoc deprotection afforded bis-PFO labeled 35 in 72% yield (Figure 2.12B).

![Diagram showing the synthesis of homologated bis-PFO tag 34 and bis-PFO labeled α-aminoethyl glycoside 35.](image)

Figure 2.12 A) Synthesis of homologated bis-PFO tag 34. B) Synthesis of bis-PFO labeled α-aminoethyl glycoside 35.
Once again, the compatibility of bis-PFO tagged glucosamine 35 was tested using our standard deprotection sequence conditions. No incompatibilities were noted during TBDPS, acetate or azide deprotections, and the deprotected intermediates were easily isolated and purified by FSPE under standard conditions. However, sulfonation with the free amine resulted in the formation of the analogous cleavage product and little desired carbohydrate product was recovered. Despite the additional two methylene units to “insulate” the carbamate from the effects of the PFO moieties, the cross reactivity of the carbamate with sulfonation conditions was not diminished. Furthermore, solubility of this compound was again problematic; the direct attachment of the PFO units to the arene ring may be the reason for poor solvation.

2.4 Synthesis of Mono-PFO Benzyl Carbamate

As discussed previously, the double PFO carbamate approach was problematic for two reasons: (i) the carbamate was reactive under sulfonation conditions, with possible activation by the dual PFO moieties, and (ii) the bis-PFO tagged intermediates displayed poor solubility and amphiphilic character. As shown in previous studies, sulfoforms bearing a single PFO tag were not well retained during FSPE under standard conditions, however modifying the elution conditions might improve separation and isolation of the mono-PFO tagged sulfoforms. We thus decided to revisit the single-PFO tag approach to see if both issues could be surmounted.

A single-PFO Cbz tag was synthesized according to the scheme in Figure 2.13A. Ethyl p-aminobenzoate was treated with amyl nitrite and BF$_3$•Et$_2$O to afford a diazonium tetrafluoroborate intermediate salt, which was coupled under Pd-catalyzed Heck
conditions\textsuperscript{12} to afford the fluorous alkene 36 in 69% yield. Reduction of the olefin and ester moieties afforded the fluorous benzyl alcohol 37 in 95% yield, and treatment of 37 with \textit{p}-nitrophenyl chloroformate afforded the activated mixed carbonate 38 in 92% yield. Subsequent conjugation of single-PFO Cbz tag 38 to aminoethyl \textit{\alpha}-glycoside 23 following \textit{Fmoc} deprotection afforded single-PFO tagged glycoside 39 in 84% yield (Figure 2.13B).

\[ \text{Figure 2.13 A) Synthesis of mono-PFO tag 38.} \]
\[ \text{B) Synthesis of mono-PFO tagged aminoethyl \textit{\alpha}-glycoside 39.} \]

Initial tests on the mono-PFO tagged 39 by stepwise deprotection followed the same pattern of compatibility as noted for compound 29. Sulfonation was again problematic, particularly when \textit{N}-sulfonation was attempted. ESI-MS analysis in negative mode suggested that Cbz cleavage once again resulted in a sulfonated benzyl alcohol, as evidenced by a peak at 634 m/z. It thus appears that the reactivity of the Cbz linkage is
not solely due to PFO activation, as the use of spacer methylenes does not significantly affect the rate of decomposition. The most likely explanation is the 2-aminoethyl linker on α-glucosamine is short enough that an intramolecular sulfonate transfer is facile and thus problematic.

Place glucosamine at the reducing end adjacent to the cleavable carbamate linker seems to be the root of the problem. If the C2 amino group is indeed responsible for the cleavage of the carbamate linkage, preparing a disaccharide with β-uronic acid at the reducing end may mitigate carbamate cleavage. To explore this strategy, a new orthogonally-protected disaccharide was prepared (Figure 2.14). Glucose pentaacetate was glycosylated with bromoethanol using BF$_3$•Et$_2$O then treated with sodium azide to afford the β-(2-azidoethyl) glucoside 40 in 57% yield. Deacetylation and protection as the 4,6-benzyldiene acetal afforded 2,3-diol 41 in 91% yield. Regioselective alkylation with p-methoxybenzyl chloride at the C3 hydroxyl was attempted using a stannylene acetal intermediate; however, a 3:2 mixture of 2- and 3-O-PMB ethers was obtained. The regioisomers were separated and desired 3-O-PMB ether was benzoylated to afford full protected glucoside 42 in 31% yield over three steps. Azide reduction using Zn and ammonium chloride$^{13}$ afforded the free amine, which was then protected with 38 to afford PFO-carbamate 43 in 72% yield over two steps. Removal of the benzyldiene acetal with camphorsulfonic acid in methanol afforded a 4,6-diol, which was protected or oxidized at the C6 position to afford various PFO-tagged GlcA donors 44-46 in good to high yields.
Figure 2.14 Synthesis of aminoethyl-GlcA acceptors 44 – 46.

Glycosylation using thioglycoside donor 47 and acceptor 44 was unsuccessful due to the sensitivity of trityl protecting group at the C6 position to Lewis acids, which resulted in the formation of 1,6-linked saccharides rather than the desired 1,4-linked disaccharide. Attempts to couple donor 47 with GlcA methyl ester 46 were attempted but the nucleophilicity of acceptor 46 was too low due to the electron withdrawing C5 carboxyl group. However, the 2-bromoisobutyryl (2-BiB) ester 45 proved to be a competent acceptor for glycosyl coupling, and the desired α-1,4-linked disaccharide 48 was obtained in 43% yield (Figure 2.15). Further deprotection of the 2-BiB ester,
TEMPO oxidation and methylation afforded orthogonally protected heparan disaccharide 49 in 76% yield.

Figure 2.15 Synthesis of orthogonally protected, PFO-tagged dissacharide 49.

With the orthogonally protected PFO-tagged disaccharide 49 in hand, we performed tests to determine if the carbamate linkage was stable under $N$-sulfonation conditions. Cleavage of alcohol protecting groups such as TBDPS, SEM and benzoate were successful, and subsequent sulfonation caused minimal decomposition of the mono-PFO Cbz linkage as evidenced by ESI-MS analysis in negative-ion mode. However, azide reduction and $N$-sulfonation, increased cleavage of the carbamate regardless of the choice of sulfonation conditions. This confirmed that the carbamate linkage itself is labile in the presence of $N$-sulfamates, despite its widespread use in organic synthesis.
2.5 Synthesis of Single-PFO Benzyl Glycosides

Having extensively explored the chemistry of sulfoforms with a Cbz-protected aminoethyl linker, we altered our synthetic goals and returned to the simpler objective of synthesizing PFO-tagged sulfoforms without a terminal aminoethyl linker, while retaining the ability to cleave the fluorous tag after generating and purifying the penultimate sulfoforms. We envisioned that a benzylic ether at the reducing end of the disaccharide should cleanly address these concerns. Cleavage of the fluorous tag would be accomplished by hydrogenation, as with the case with the benzyl carbamate linkage previously considered, but using a more stable ether linkage would prevent premature cleavage of the fluorous tag.

Glycosyl coupling of with glucosamine donor 6 and $p$-substituted (2-PFO)ethyl benzyl alcohol 37 afforded the PFO-tagged $\alpha$-glucosaminoside 50 in 95% yield as a single isomer (Figure 2.16). Donor 6 provided the highest coupling yield, replacing the 3-$O$-acetate with a SEM ether or Lev ester resulted in diminished yields. Exchange of the 3-$O$-acetate for the SEM ether and PMB deprotection was completed in three steps to afford $\alpha$-glucosamine acceptor 51 in 65% yield. Intermediates were isolated solely by FSPE, and the final donor was purified by column chromatography to ensure efficient glycosylation in the next step.
A new thioglycosyl donor was synthesized as a GlcA donor equivalent (Figure 2.17): Glucose pentaacetate was treated with thiophenol and BF$_3$•Et$_2$O to afford β-thioglycoside 52 in 57% yield$^{14}$; Zemplén deacetylation and protection as the 4,6-anisilidene acetal afforded 53 in 81% yield$^{15}$; Regioselective alkylation of the 2,3-stannylene acetal with PMB-Cl and subsequent benzoylation afforded 54 in 79% yield. In contrast to the poor regioselectivity of 2,3-stannylene acetals prepared from O-glycosides, that of the S-glycoside exclusively afforded the 3-O-PMB product. Regioselective reduction of the p-methoxybenzylidene acetal resulted in the 4-O-PMB ether 55 in 91% yield. Protection of the C6 hydroxyl as the p-nitrobenzoyl (PNBz) ester afforded thioglycoside donor 56 in 86% yield (29% total yield over 8 steps).
Glycosyl coupling with acceptor 51 and donor 56 under NIS-promoted conditions afforded disaccharide 57 in fair to low yields (Figure 2.18). It was generally observed that the donor was fully consumed, but decomposed prior to coupling. Other acceptors were explored, by replacing 3-0-SEM ether with acetate or Lev esters, but no desired product was isolated in these cases. Alternative activating reagents were also explored, such as replacing triflic acid with silver triflate, however neither the yield nor efficiency of this reaction could be improved. Lowering the temperature did not have a positive effect on reaction outcome, and simply increased the amount of time needed for donor activation without increasing overall disaccharide yield. Glycosylation promoted by (benzenesulfonyl)piperidine (BSP) and triflic anhydride was also attempted, but no successful coupling products were isolated in this case. Isolation of decomposition products by column chromatography and NMR analysis suggested loss of one or both of
the PMB ethers on the glycosyl donor as a potential source of problems. There are documented examples of PMB ethers being deprotected \textit{in situ} under acid-catalyzed coupling conditions.\textsuperscript{17}

![Figure 2.18 Synthesis of disaccharide 57.](image)

We reasoned that replacing the PMB ethers with less acid-labile protecting groups should improve the glycosylation yield under NIS/TfOH-mediated conditions. We choose to investigate the 2-naphthylmethyl (Nap) ether as a more stable alternative to the PMB ether, but one that is selectively cleaved under oxidative conditions.\textsuperscript{18} Nap-protected donor 61 was synthesized in an analogous manner to donor 56 (Figure 2.19): Protection of thiophenyl glucoside 52 as the 4,6-naphthylidene acetal 58 was completed in 2 steps in 76\% yield; regioselective 3-O-alkylation with 2-(bromomethyl)naphthylene and subsequent 2-O-benzylation afforded 59 in 75\% yield; Regioselective cleavage of the naphthylidene acetal was accomplished with dibutyl boron triflate and borane to afford primary alcohol 60 in 80\% yield. The C6 alcohol was protected as the \textit{p}-nitrobenzoate to afford donor 61 in 82\% yield.
With Nap-protected donor 61 in hand, glycosylation of acceptor 51 was conducted under NIS/TfOH-mediated conditions to afford disaccharide 62 in modest yield (Figure 2.20). Analysis of the reaction by TLC appears to be significantly cleaner than with the PMB-protected donor, although the conversion is still incomplete: Despite using 1.5 eq of donor to 1 eq of acceptor, the latter was still left over in appreciable quantity. This suggested that the nucleophilicity of the acceptor needed to be boosted. The low coupling yield suggests that the glucosamine acceptor 51 may be a difficult coupling partner in this reaction, possibly the result of high steric hindrance due to the 6-\(O\)-TBDPS ether.
With disaccharide 62 synthesized, all that is needed to generate the library of disaccharide sulfoforms is stepwise deprotection and sulfonation. Conditions for deprotecting other orthogonally protected heparan sulfate ligands have been previously established, except for Nap ether deprotection, and are summarized Table 2.2. To ensure the stability of the fluorous tag linkage, the azide was deprotected with TCEP and subsequently sulfonated. ESI-MS of the reaction mixture did not indicate linker cleavage; only the expected molecular ion peak was observed. Similarly, the cleavage of the Nap ethers was explored in the presence of the PFO-Bn ether. Treatment of 62 under hydrogenation conditions with Pd/C did not show any reaction after 24 hours, but treatment with CAN quickly afforded the 3,4-diol.

Table 2.2. Deprotection and sulfonation conditions for disaccharide 62.

<table>
<thead>
<tr>
<th>Operation</th>
<th>Conditions</th>
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</thead>
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<td>TCEP (1.5 eq), DMF, rt.</td>
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<tr>
<td>SEM Deprotection</td>
<td>MgBr₂•Et₂O (10 eq), MeNO₂ (20 eq), Et₂O, rt.</td>
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<tr>
<td>TBDPS Deprotection</td>
<td>TBAF (3 eq), THF, rt.</td>
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<td>Bz Deprotection</td>
<td>NaOMe (1 eq), MeOH, rt.</td>
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<tr>
<td>Nap Deprotection</td>
<td>CAN (3 eq/Nap), 90% aq. MeCN, rt.</td>
</tr>
<tr>
<td>O-Sulfonation</td>
<td>SO₃•Me₃N (10 eq/OH), DMF, 100 °C.</td>
</tr>
<tr>
<td>N-Sulfonation</td>
<td>SO₃•pyridine (5 eq), pH 8 buffer, rt.</td>
</tr>
</tbody>
</table>
2.6 Materials and Methods

All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents were freshly distilled prior to use. \(^1\)H NMR spectra were recorded at 300 or 400 MHz; \(^{13}\)C NMR spectra were recorded at 75 or 100 MHz. \(^{19}\)F NMR spectra were recorded at 282 MHz. \(^{31}\)P NMR spectra were recorded at 121 MHz. Chemical shifts were referenced to the solvent used (\(\delta 7.27\) and 77.00 for CDCl\(_3\), \(\delta 3.31\) and 49.15 for CD\(_3\)OD, and \(\delta 4.80\) in D\(_2\)O). Mass spectra were acquired using either a Hewlett-Packard 5989B or a Finnigan 40000 mass spectrometer. Optical rotations were measured by polarimetry at room temperature.

1,3,4,6-Tetra-\(O\)-acetyl-2-phthalimido-2-deoxy-\(\beta\)-D-glucopyranoside (1).

Glucosamine hydrochloride (30.0 g, 1 equiv) was suspended in 1 M NaOMe solution (1 equiv, 135 mL) and stirred for 4 hours until dissolved. Phthalic anhydride (22.8 g, 1.1 equiv) and triethylamine (22 mL, 1.1 equiv) were added in 2 portions at rt. The reaction was mechanically stirred for 2 days. The reaction was cooled to \(-20^\circ\)C and the solids were removed by filtration. The filtered solids were then dissolved in a pyridine and acetic anhydride mixture (2:1) and stirred at rt for 2 days. Solvent was removed by rotary evaporation and the residue was azeotroped with toluene. The material was dissolved in DCM and passed through a silica plug to remove much of the highly colored byproducts. The residue was recrystallized from ethanol to afford 23.1 g (51\%) of tetraacetate 1 as an off-white solid. \(^1\)H NMR was compared to literature reported values and confirmed correct product was obtained.\(^{19}\)
**Thiotolyl 3,4,6-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (2).**

Tetraacetate 1 (1.72 g, 1 equiv) and p-thiocresol (578 mg, 1.3 equiv) were dissolved in 3 mL of dry DCM at 0 °C. BF$_3$•Et$_2$O (0.6 mL, 1.3 equiv) was added dropwise. The reaction allowed to warm to rt and stirred for 40 hours. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with DCM. The organic extracts were washed with brine and dried over sodium sulfate. The organic extracts were then concentrated by rotary evaporation. The residue was purified by column chromatography using a 33% EtOAc in hexane to afford 1.59 g (81%) of 2 as an off-white solid. $^1$H NMR was compared to literature reported values and confirmed correct product was obtained.

**Thiotolyl 4,6-O-anisilidine-2-deoxy-2-phthalimido-β-D-glucopyranoside (3).**

Triacetate 2 (2.01 g, 1 equiv) was dissolved in DCM and methanol (3:2, 16 mL) and cooled to –30 °C. NaOMe (1M in MeOH, 1.6 mL, 0.3 equiv) was added and the reaction was stirred from –30 °C to –10 °C until TLC indicated reaction was complete. The reaction was quenched with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated by rotary evaporation to afford the intermediate triol as a white solid in quantitative yield.

The crude triol was azeotroped with toluene three times and then dissolved in toluene (25 mL). PMBDMA (1.3 mL, 2 equiv) and CSA (182 mg, 0.2 equiv) were added. The reaction was stirred at 90 °C for 2 hours. Additional portions of PMBDMA (1.3 mL, 2 equiv) and CSA (182 mg, 0.2 equiv) were added and the reaction was stirred for an additional 1 hour at 90 °C until reaction was complete. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with ethyl acetate. The organic extracts were dried over
sodium sulfate and concentrated by rotary evaporation. The residue was crystallized from ethanol to afford 567 mg (29%) of acetal 3 as a white solid. The mother liquors were subjected to column chromatography (gradient 10% to 50% EtOAc in hexane) to afford 1.07 g (54%) of acetal 3. Combined yield of 3 was 1.63 g (83%). $^1$H NMR was compared to literature reported values and confirmed correct product was obtained.\(^{21}\)

**Thiotolyl 3-O-acetyl-4,6-O-anisilidine-2-azido-2-deoxy-\(\beta\)-D-glucopyranoside (4).**

Acetal 3 (83 mg, 1 equiv) was suspended in \(n\)-butanol (1 mL) in a sealed reaction tube. Ethylenediamine (250 \(\mu\)L, 24 equiv) was added and the mixture was stirred at 100 °C for 16 hours, at which time the solution was homogeneous. The reaction mixture was concentrated by rotary evaporation and azeotroped with toluene to afford the intermediate amine used crude in the next step.

Trifyl azide (TfN\(_3\)) was prepared according to the procedure of Yan et al.\(^2\)

**Caution:** Trifyl azide is potentially explosive and should only be handled as a dilute solution and in small amounts. It should only be prepared and handled behind a blast shield in a fume hood. It should be used immediately after preparation and not stored. NaN\(_3\) (62 mg, 4.5 equiv) was suspended in pyridine (3 mL). At 0 °C, triflic anhydride (125 \(\mu\)L, 4 equiv) was added dropwise. The reaction was stirred for 3 hours at 0 °C until it was ready for use.

The crude amine, triethylamine (70 \(\mu\)L, 2 equiv), copper sulfate (4 mg) were dissolved in pyridine (1 mL) and cooled to 0 °C. The TfN\(_3\) solution was then added dropwise by disposable glass pipette. The reaction was then stirred from 0 °C to rt
overnight. The reaction was concentrated under rotary evaporation to remove solvent. The residue was dissolved in pyridine and acetic anhydride (1:1, 5 mL) and stirred at rt until reaction was deemed complete by TLC. The reaction was concentrated and residue was purified by column chromatography (20% to 40% EtOAc in hexane) to afford 54 mg (81%) of azide 4 as a white solid. \(^1\)H NMR was compared to literature reported values and confirmed that correct product was obtained.\(^1\)

**Thiotolyl 3-O-acetyl-2-azido-4-O-methoxybenzyl-2-deoxy-\(\beta\)-D-glucopyranoside (5).** Azide 4 (3.25 g, 1 equiv) was dissolved in BH\(_3\)•THF (1 M in THF, 35 mL, 5 equiv) and cooled to 0 °C. Bu\(_2\)BOTf (1 M in toluene, 7 mL, 1.1 equiv) was added dropwise and the reaction was stirred at 0 °C for 2 hours. The reaction was cooled to –78 °C and quenched with triethylamine (1.5 equiv) and methanol. It was warmed slowly to room temperature, then concentrated by rotary evaporation to afford crude 4-O-PMB ether. The residue was dissolved in methanol and concentrated three times. The residue was then purified by column chromatography (20% to 30% EtOAc in hexane) to afford 3.24 g (91%) of 4-O-PMB ether 5 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.45 (d, J = 8.1 Hz, 2H), 7.17 (dd, J = 8.2, 3.1 Hz, 4H), 6.86 (d, J = 8.6 Hz, 2H), 5.13 (t, J = 9.5 Hz, 1H), 4.60 – 4.36 (m, 3H), 3.89 (dd, J = 12.3, 2.5 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J = 12.2, 3.9 Hz, 1H), 3.54 (t, J = 9.5 Hz, 1H), 3.39 (ddd, J = 9.7, 3.9, 2.5 Hz, 1H), 3.27 (t, J = 10.0 Hz, 1H), 2.37 (s, 3H), 2.04 (s, 3H), 0.00 (s, 9H).

**Thiotolyl 3-O-acetyl-2-azido-4-O-benzyl-6-O-(tert-butyldiphenylsilyl)-2-deoxy-\(\beta\)-D-glucopyranoside (6).** Alcohol 5 (3.24 g, 1 equiv) and imidazole (1260 mg, 3 equiv) were dissolved in DMF (15 mL). At room temperature, TBDPS-Cl (3.3 mL, 1.2 equiv) was
added and the reaction was stirred at rt overnight. The reaction was concentrated by rotary evaporation and was purified by column chromatography (0-20% EtOAc in hexane) to afford 4.63 g (95%) of silyl ether 13 as crystalline white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.76 (ddd, J = 6.9, 3.5, 1.6 Hz, 4H), 7.57 – 7.34 (m, 8H), 7.24 – 7.16 (m, 2H), 7.14 – 7.07 (m, 2H), 6.90 (dd, J = 8.7, 1.2 Hz, 2H), 5.65 (dd, J = 5.5, 1.1 Hz, 1H), 5.58 – 5.39 (m, 1H), 4.68 (d, J = 1.6 Hz, 2H), 4.49 – 4.31 (m, 1H), 4.12 – 3.86 (m, 4H), 3.83 (s, 3H), 2.37 (s, 3H), 2.15 (s, 3H), 1.17 (s, 9H).

2-iodo-3-perfluorooctyl-proan-1-ol (7). Perfluorooctyl iodide (3.0 mL, 1 equiv) and 1 M aq Na$_2$S$_2$O$_3$ (3 mL) are placed in a flask. The reaction mixture is heated to 80 °C and a solution of 5% AIBN in allyl alcohol (2 mL) is added dropwise over 30 minutes. After 2 hours, the reaction is cooled to room temperature and extracted with DCM. The organic extracts were dried over sodium sulfate and concentrated by rotary evaporation to afford crude halohydrin 7 as a white solid in quantitative yield.

3-perfluorooctyl-proan-1-ol (8). Halohydrin 7 (183 mg, 1 equiv) was dissolved in methanol (2 mL). A small amount of Raney Nickel (a spatula tip) was added as a slurry in water. The reaction flask was purged with argon and cooled to 0 °C. Hydrazine hydrate (50 µL, 2 equiv) was added dropwise. Upon addition, small bubbles of gas are formed on the catalyst surface. The reaction was stirred for 1 hour at 0 °C to rt. The catalyst was removed by filtration, the reaction mixture was diluted with water, extracted with DCM and dried over sodium sulfate. The organic extracts were treated with activated carbon
and filtered through a pad of celite. The extracts were concentrated by rotary evaporation to afford 107 mg (71%) alcohol 8 as a white solid. \( ^1 \text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.73 (t, \( J = 6.1 \) Hz, 2H), 2.32 – 2.09 (m, 2H), 1.93 – 1.77 (m, 2H).

**(3-perfluorooctyl)propyl 3,4,6-O-acetyl-2-deoxy-2-phthalimido-\( \beta \)-D-glucopyranoside (9).** Tetraacetate 2 (227 mg, 1.3 equiv) and alcohol 8 (205 mg, 1 equiv) were dissolved in DCM (5 mL) and cooled to 0 °C. BF\(_3\)•Et\(_2\)O (1 mL, 8 equiv) was added and the reaction was stirred and warmed to rt. The reaction was quenched with sat. aq. NaHCO\(_3\) and extracted with DCM. The organic extracts were washed with brine and dried over sodium sulfate, then concentrated by rotary evaporation. The residue was purified by column chromatography using a 20% EtOAc in hexane eluent to afford 226 mg (55%) of 9 as an off-white solid. \( ^1 \text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.82 (dd, \( J = 5.5, 3.1 \) Hz, 2H), 7.70 (dd, \( J = 5.5, 3.1 \) Hz, 2H), 5.76 (dd, \( J = 10.8, 9.1 \) Hz, 1H), 5.37 (d, \( J = 8.5 \) Hz, 1H), 5.16 (dd, \( J = 10.1, 9.1 \) Hz, 1H), 4.39 – 4.24 (m, 2H), 4.15 (dd, \( J = 12.3, 2.3 \) Hz, 1H), 3.97 – 3.78 (m, 2H), 3.53 (ddd, \( J = 10.0, 7.1, 4.8 \) Hz, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H), 1.83 – 1.68 (m, 2H).

**(3-perfluorooctyl)propyl 4,6-O-anisilidine-2-deoxy-2-phthalimido-\( \beta \)-D-glucopyranoside (10).** Triacetate 9 (1881 mg) was dissolved in DCM and methanol (3:2, 50 mL) and treated with NaOMe (1M in methanol, 600 µL, 0.3 equiv) at -20 °C for 14 hours. The reaction was quenched with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated under rotary evaporation to afford intermediate triol used crude in the next step.
The crude triol was azeotroped with toluene and dissolved in THF. PMBDMA (1.3 mL, 4 equiv) and CSA (25 mg, 5 mol%) were added in a single portion and the reaction was refluxed at 70 °C overnight. The reaction was cooled to rt and quenched with sat. aq. NaHCO₃. The reaction was extracted with ethyl acetate, dried over sodium sulfate and concentrated by rotary evaporation. The residue was crystallized from EtOAc/hexane to afford 1.17 g of acetal 10 as white solid. The mother liquors were purified by column chromatography (20% EtOAc in hexane with 1% Et₃N) to afford 313 mg of acetal 10. Combined yield of acetal 10 was 1.48 g (79%).

(3-perfluorooctyl)propyl 3-O-acetyl-4,6-O-anisilidine-2-azido-2-deoxy-β-D-glucopyranoside (11). Acetal 10 (51 mg, 1 equiv) was treated with ethylenediamine (100 µL, 24 equiv) in n-butanol (2 mL) at 100 °C in a sealed tube for 14 hours. The reaction mixture was concentrated by rotary evaporation and azeotroped with toluene. The intermediate amine was used crude in the next step.

The crude amine, copper sulfate and triethylamine were dissolved in pyridine (2 mL) was treated with a solution of TfN₃ in pyridine (8 equiv) at 0 °C for 14 hours. (See 4 for the preparation of TfN₃.) The reaction was concentrated by rotary evaporation and treated with acetic anhydride and pyridine (1:1, 5 mL) for 12 hours. The reaction was concentrated by rotary evaporation and purified by column chromatography (10-20% EtOAc in hexane) to afford 39 mg (86%) of azide 11 as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.42 – 7.29 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.45 (s, 1H), 5.13 (t, J = 9.8 Hz, 1H), 4.48 (d, J = 7.9 Hz, 1H), 4.31 (dd, J = 10.5, 4.9 Hz, 1H), 4.01 (dt, J = 9.6,
5.8 Hz, 1H), 3.79 (s, 3H), 3.72 (dd, J = 16.8, 10.0 Hz, 2H), 3.60 (t, J = 9.5 Hz, 1H), 3.54 – 3.42 (m, 2H), 2.25 (ddp, J = 14.8, 11.4, 3.5 Hz, 2H), 2.13 (s, 3H), 2.04 – 1.89 (m, 2H).

(3-perfluorooctyl)propyl 3-O-acetyl-2-azido-4-O-methoxybenzyl-2-deoxy-β-D-glucopyranoside (12). Azide 11 (734 mg, 1 equiv) was dissolved in 6 mL BH₃•THF (1 M in THF, 5 equiv) at 0 °C. Bu₂BOTf (1M in DCM, 940 µL, 1.1 equiv) was added dropwise and the reaction was stirred at 0 °C for 2 hours. The reaction was cooled to −78 °C and quenched with triethylamine (2 equiv) and methanol (2 equiv). The reaction mixture was concentrated by rotary evaporation to afford the crude 4-O-PMB product. The residue was dissolved in methanol and concentrated three times. The residue was then purified by column chromatography (20% to 30% EtOAc/hexane) to afford 514 mg (65%) of 4-O-PMB ether 12 as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.19 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.03 (dd, J = 10.4, 9.3 Hz, 1H), 4.53 (d, J = 1.1 Hz, 2H), 4.39 (d, J = 8.0 Hz, 1H), 4.00 (dt, J = 9.7, 5.7 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.78 (s, 4H), 3.68 – 3.57 (m, 2H), 3.43 – 3.27 (m, 2H), 2.37 – 2.06 (m, 3H), 2.05 (s, 3H), 2.01 – 1.85 (m, 2H).

(3-perfluoroctyl)propyl 3-O-acetyl-2-azido-2-deoxy-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-β-D-glucopyranoside (13). Primary alcohol 12 (514 mg, 1 equiv) and imidazole (129 mg, 3 equiv) were dissolved in DMF (2 mL). At room temperature, TBDPS-Cl (340 µL, 2 equiv) was added and the reaction was stirred overnight. The reaction mixture was applied directly to an FSPE cartridge, washed with 5 volumes (25 mL) of 90% aq. methanol, and eluted with 100% methanol to afford 617 mg (93%) of silyl ether 13 as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.71 (tt, J = 8.0, 1.5 Hz,
4H), 7.51 – 7.30 (m, 6H), 7.10 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.03 (dd, J = 10.4, 9.3 Hz, 1H), 4.63 – 4.47 (m, 2H), 4.36 (d, J = 8.0 Hz, 1H), 4.06 – 3.94 (m, 1H), 3.91 (d, J = 2.7 Hz, 2H), 3.84 – 3.71 (m, 4H), 3.59 (dt, J = 9.5, 6.1 Hz, 1H), 3.48 – 3.31 (m, 2H), 2.26 (s, 2H), 2.07 (d, J = 1.1 Hz, 2H), 1.99 (q, J = 7.1, 6.6 Hz, 2H), 1.09 (s, 8H).

**Typical FSPE procedure under standard conditions:** Typical samples separated on a 5 gram FSPE cartridge were 30-500 mg in size. FSPE cartridges upon first use were washed with DMF to remove any plasticizer or other contaminants. The FSPE cartridges were then pre-conditioned using methanol and water (4:1) (10–20 mL). The reaction mixture was dissolved in 0.5 mL DMF (minimum volume) and loaded on the top of the FSPE cartridge. A gentle vacuum is applied to lower the sample into the silica bed. A drop rate of 1–2 drops per second is ideal. Another 0.5 mL DMF is used to wash the flask and is loaded onto the FSPE cartridge as before. After loading, the cartridge is first eluted with 4–5 column volumes of fluorophobic eluent (20–25 mL, methanol/water 4:1) and is collected as a single fraction. The FSPE cartridge is then eluted until nearly dry, then eluted with 4–5 column volumes of fluorophilic eluent (20–25 mL, methanol, acetone, or THF) and is collected as a single fraction. A small amount of ethanol is typically added to the fluorous fraction prior to concentration by rotary evaporation to avoid foaming and bumping. Reducing the vacuum on the rotary evaporator may be beneficial in reducing the tendency of samples to foam and bump. If foaming and bumping is problematic, a centrifugal evaporator may be useful to avoid these problems.

**(3-perfluorooctyl)propyl 2-deoxy-2-N-sulfonato-4-O-p-methoxybenzyl-β-D-glucopyranoside** (14). **13** (36 mg, 1 equiv) was dissolved in DCM (1 mL) and treated with
tributylphosphine (40 µL, 3 equiv) at rt for 5 hours. Water (1.5 mL) was added to hydrolyze the intermediate ylide. The reaction was vigorously stirred at rt overnight. The layers were separated and the aqueous layer was extracted with DCM. The organic extracts were concentrated and the residue was purified by FSPE under standard conditions to afford the free amine. The deprotected carbohydrate was then dissolved in acetonitrile (2 mL). SO$_3$•pyridine (50 mg, 9 equiv) and pyridine (80 µL, 10 equiv) were added. The reaction was heated to 70 °C under microwave conditions for 1 hour. The reaction mixture was then concentrated and subjected to FSPE purification to isolate the desired sulfoform. The intermediate sulfoform was dissolved in THF (2 mL) and treated with TBAF (1 M in THF, 150 µL, 3 equiv) at rt overnight. The reaction mixture was concentrated by rotary evaporation and purified by FSPE under standard conditions to afford the intermediate alcohol. The intermediate was then dissolved in methanol (2 mL) and treated with NaOMe (1M in MeOH, 30 µL, 0.3 equiv) at rt, overnight, then the reaction was neutralized with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated to afford the diol. $^1$H NMR (300 MHz, MeOH-$d_4$) δ 7.30 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.85 (d, J = 10.5 Hz, 1H), 4.58 (d, J = 10.7 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 4.04 – 3.92 (m, 1H), 3.78 (s, 3H), 3.64 (dt, J = 9.9, 3.9 Hz, 2H), 3.47 – 3.34 (m, 4H), 3.31 (p, J = 1.6 Hz, 1H), 2.63 (dd, J = 9.5, 8.0 Hz, 1H), 2.44 – 2.18 (m, 2H), 1.98 – 1.85 (m, 3H), 1.84 – 1.69 (m, 11H), 1.62 – 1.38 (m, 22H), 0.97 (t, J = 7.2 Hz, 16H).

(3-perfluorooctyl)propyl 2-azido-2-deoxy-3,6-di-O-sulfonato-4-O-p-methoxybenzyl-β-D-glucopyranoside (15). 13 (31 mg, 1 equiv) was dissolved in THF (2 mL) and treated
with TBAF (1 M in THF, 150 µL, 3 equiv) at rt overnight. Then the reaction mixture was
concentrated by rotary evaporation and purified by FSPE under standard conditions to
afford the intermediate alcohol. The intermediate alcohol was then dissolved in methanol
(3 mL) and treated with NaOMe (1M in MeOH, 20 µL, 0.3 equiv) at rt overnight. The
reaction was neutralized with acidic ion-exchange resin (Dowex-50WX8), filtered and
concentrated to afford the diol. The deprotected carbohydrate was then dissolved in
acetonitrile (2 mL). \( \text{SO}_3 \text{•pyridine} \) (103 mg, 18 equiv) and pyridine (80 µL, 20 equiv)
were added. The reaction was heated to 70 °C under microwave conditions for 1 hour.
The reaction mixture was then concentrated and subjected to FSPE purification to isolate
the desired sulfoform. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.31 – 7.26 \) (m, 2H, 6.90 (d, \( J = 8.6 \)
Hz, 2H), 4.81 – 4.61 (m, 2H), 4.33 (d, \( J = 8.0 \) Hz, 1H), 4.07 – 3.92 (m, 1H), 3.87 (dd, \( J = 
12.2, 2.7 \) Hz, 1H), 3.80 (s, 3H), 3.74 (dd, \( J = 12.1, 4.1 \) Hz, 1H), 3.63 (dt, \( J = 9.6, 6.2 \) Hz,
1H), 3.53 – 3.44 (m, 2H), 3.38 – 3.23 (m, 2H), 2.35 – 2.13 (m, 2H), 1.95 (m, 2H).

(3-perfluorooctyl)propyl 2-deoxy-2,3,6-tri-\( N,O,O \)-sulfonato-4-\( O \)-p-methoxybenzyl-\( \beta \)-
D-glucopyranoside (16). 13 (45 mg, 1 equiv) was dissolved in THF (1 mL) and treated
with TBAF (1 M in THF, 130 µL, 3 equiv) at rt overnight. The reaction mixture was
concentrated by rotary evaporation and purified by FSPE under standard conditions to
afford the intermediate alcohol. The intermediate alcohol was then dissolved in methanol
(1.5 mL) and treated with NaOMe (1M in MeOH, 15 µL, 0.3 equiv) at rt, overnight. The
reaction was neutralized with acidic ion-exchange resin (Dowex-50WX8), filtered and
concentrated to afford the diol. The diol was then dissolved in DCM (1.5 mL) and treated
with tributylphosphine (40 µL, 3 equiv) at rt for 5 hours. Water (1.5 mL) was added to
hydrolyze the intermediate ylide. The reaction was vigorously stirred at rt overnight. The layers were separated and the aqueous layer was extracted with DCM. The organic extracts were concentrated and the residue was purified by FSPE under standard conditions to afford the free amine. The deprotected carbohydrate was then dissolved in pyridine and triethylamine (5:1, 3 mL) and SO$_3$•pyridine (160 mg, 30 equiv) was added. The reaction was heated to 70 °C under microwave conditions for 1 hour. The reaction mixture was then concentrated and subjected to FSPE purification to isolate the desired sulfoform. $^1$H NMR (300 MHz, $d_4$-MeOH) $\delta$ 7.32 (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.83 – 4.77 (m, 1H), 4.51 – 4.43 (m, 2H), 4.25 (t, $J = 8.5$ Hz, 1H), 4.03 (d, $J = 10.5$ Hz, 1H), 3.96 (s, 1H), 3.78 (s, 2H), 3.70 (s, 3H), 3.66 (d, $J = 5.1$ Hz, 1H), 3.60 (d, $J = 9.9$ Hz, 2H).

(3-perfluorooctyl)propyl 4-methylbenzenesulfonate (17). Alcohol 8 (750 mg, 1 equiv), 4-methylbenzenesulfonyl chloride (460 mg, 1.5 equiv) and pyridine (200 µL, 1.5 equiv) were dissolved in DCM (15 mL) and stirred at rt. Silver oxide (440 mg, 1.5 equiv) was added and the reaction commenced with formation of white precipitate. The reaction was filtered through Celite and concentrated by rotary evaporation. The residue was purified by column chromatography (0% to 20% EtOAc in hexane) to afford 865 mg (87%) of tosylate 17 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 8.3$ Hz, 2H), 7.37 (dt, $J = 8.1$, 0.7 Hz, 2H), 4.11 (t, $J = 5.9$ Hz, 2H), 2.46 (s, 4H), 2.28 – 1.88 (m, 4H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -82.25, -82.29, -82.33, -115.99, -116.05, -116.11, -123.48, -124.27, -125.02, -127.62, -127.67.
Methyl 3,5-bis((3-perfluorooctyl)propyloxy)benzoate (18). Tosylate 17 (549 mg, 2.2 equiv), methyl 3,5-dihydroxybenzoate (68 mg, 1 equiv) and potassium carbonate (210 mg, 5 equiv) were dissolved in 3 mL of DMF. The reaction was heated to 50 °C for 14 hours. The reaction was diluted with diethyl ether and washed with water to remove DMF and inorganic salts. The organic extracts were dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by column chromatography to afford 448 mg (98%) of methyl ester 18 as an off-white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)). \(\delta \) 7.19 (dd, J = 2.5, 0.7 Hz, 2H), 6.64 (td, J = 2.3, 0.7 Hz, 1H), 4.07 (t, J = 5.8 Hz, 4H), 3.91 (d, J = 0.7 Hz, 3H), 2.30 (td, J = 18.3, 9.8 Hz, 4H), 2.18 – 2.02 (m, 4H).

(3,5-bis((3-perfluorooctyl)propyloxy)phenyl)methanol (19). Methyl ester 18 (483 mg, 1 equiv) was dissolved in DCM (20 mL). The reaction was cooled to –78 °C and diisobutylaluminum hydride (1M in hexane, 1.3 mL, 3 equiv) was added dropwise. The reaction mixture was stirred and warmed to rt. The reaction then was cooled to 0 °C and quenched with solid Glauber’s salt. Solids were removed by filtration and the organic fraction was concentrated. The residue was purified by column chromatography to afford 306 mg (72%) of benzyl alcohol 19 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)). \(\delta \) 6.65 – 6.51 (m, 2H), 6.42 (t, J = 2.3 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.13 (t, J = 6.0 Hz, 3H), 2.46 (tt, J = 19.2, 8.5 Hz, 4H), 2.18 – 2.05 (m, 4H).

3,5-bis((3-perfluorooctyl)propyloxy)benzyl 3,4,6-tri-\(\text{O}\)-acetyl-2-deoxy-2-N-phthalimido-\(\beta\)-D-glucopyranoside (20). Benzyl alcohol 19 (104 mg, 1 equiv) and GlcN donor 2 (63 mg, 1.5 equiv) azeotroped with toluene, dried on a high vacuum line, and then dissolved in dry DCM (1.5 mL). 4 Å MS (50 mg) were added and the reaction was
stirred at room temperature for 30 minutes. NIS (90 mg, 2 equiv) was added and the reaction mixture was cooled to 0 °C. TfOH (5 µL, 0.3 equiv) was added and the reaction was stirred at 0 °C until TLC indicates consumption of donor. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of Celite, and concentrated. The residue was purified by column chromatography to afford 30 mg (22%) of glucoside 20. \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.89 – 7.49 (m, 4H), 6.97 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 6.0 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.42 – 4.95 (m, 4H), 4.45 – 4.15 (m, 3H), 2.36 (m, 4H), 2.13 (s, 3H), 2.01 (s, 3H), 1.84 (s, 3H).

3,5-bis((3-perfluorooctyl)propyloxy)benzyl 3,4,6-tri-O-sulfonato-2-deoxy-2-N-phthalimido-\(\beta\)-D-glucopyranoside (21). Glucoside 20 was dissolved in methanol and trifluorotoluene (2:1, 6 mL), cooled to −30 °C and treated with NaOMe (1M in MeOH, 50 µL, 0.3 equiv). The reaction was slowly warmed to −10 °C and after 5 hours the reaction was neutralized with acidic ion-exchange resin (Dowex-50WX8) to afford the intermediate tri-alcohol. The intermediate triol was then dissolved in acetonitrile (2 mL) and treated with SO\(_3\)•pyridine (95 mg, 27 equiv) and pyridine (60 µL, 30 equiv). The mixture was heated to 70 °C under microwave conditions to afford tri-O-sulfonate 21. Half of the reaction mixture was subjected to standard FSPE conditions with slow loading (1 drop per 3 seconds) and slow fluorophobic elution (1 drop per second). Fluorophillic elution with 100% methanol afforded the desired sulfoform as 15 mg (88%)
of a white solid. $^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 7.88 – 7.47 (m, 3H), 5.34 (t, J = 8.9 Hz, 1H), 5.14 – 4.94 (m, 2H), 4.29 – 3.89 (m, 4H), 3.71 – 3.49 (m, 1H), 2.59 – 2.30 (m, 2H), 2.17 – 1.96 (m, 2H).

3,5-bis((3-perfluorooctyl)propyloxy)benzyl (N-hydroxysuccinimidyl)carbonate (22).

Benzyl alcohol 19 (74 mg, 1 equiv) was dissolved in DCM (4 mL) at rt. Triphosgene (33 mg, 4 equiv) and triethylamine (40 µL, 4 equiv) were added and the reaction was stirred at room temperature overnight. NHS (50 mg, 8 equiv) and triethylamine (80 µL, 8 equiv) were added and the reaction stirred at room temperature for 2 hours. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with DCM. The organic extracts were dried over sodium sulfate and concentrated via rotary evaporation. The residue was purified by column chromatography (0% to 20% EtOAc/hexane) to afford 33 mg (40%) of NHS carbonate 22. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.53 (d, J = 2.2 Hz, 2H), 6.45 (t, J = 2.2 Hz, 1H), 5.24 (s, 2H), 4.04 (t, J = 5.8 Hz, 4H), 2.84 (s, 4H), 2.30 (td, J = 18.3, 9.1 Hz, 4H), 2.11 (dt, J = 10.3, 5.5 Hz, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.41, 159.91, 135.53, 106.58, 102.08, 72.25, 66.38, 27.80, 25.33, 20.39.

2'-(9H-Fluoren-9-yl)methoxycarbonylaminoethyl 3-O-acetyl-2-azido-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-2-deoxy-\(\alpha\)-D-glucopyranoside (23).

GlcN donor 6 (477 mg, 1 equiv) and Fmoc-protected ethanolamine (237 mg, 1.2 equiv) were azeotroped with toluene in a flame-dried flask and dried on vacuum line. The compounds were dissolved in a mixture of DCE and Et$_2$O (1:3, 20 mL) with flame-dried 4 Å MS (1 gram). The reaction was stirred for 30 minutes before addition of NIS (189 mg, 1.2 equiv). The reaction mixture was cooled to -20 °C and TfOH (20 µL, 0.3 equiv)
was added to the reaction mixture and was stirred at −20 °C for 5 hours. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of Celite, and concentrated by rotary evaporation. The residue was purified by column chromatography (0% to 20% THF in hexane) to afford 513 mg (88%, 4:1 α/β) of α-aminoethyl glucoside 23. 1H NMR (300 MHz, CDCl3) δ 7.78 – 7.72 (m, 2H), 7.68 – 7.52 (m, 2H), 7.47 – 7.33 (m, 9H), 7.32 – 7.27 (m, 5H), 7.21 – 7.14 (m, 2H), 5.66 – 5.52 (m, 1H), 5.36 (t, J = 6.0 Hz, 1H), 4.99 (d, J = 3.5 Hz, 1H), 4.64 (s, 2H), 4.34 (d, J = 7.2 Hz, 2H), 4.20 (t, J = 7.2 Hz, 1H), 3.99 – 3.83 (m, 3H), 3.79 (d, J = 5.6 Hz, 3H), 3.55 (dt, J = 9.8, 4.8 Hz, 2H), 3.39 – 3.23 (m, 1H), 3.14 (dd, J = 10.7, 3.5 Hz, 1H), 2.07 (s, 3H), 1.09 (s, 9H).

2'-3,5-bis((3-perfluorooctyl)propyl)oxy)benzylxycarbonylaminoethyl 3-O-acetyl-2-azido-2-deoxy-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (24). Glucoside 23 (25 mg, 1 equiv) was deprotected with 20% piperidine in DMF at room temperature for 30 minutes. The reaction mixture was concentrated by rotary evaporation and was purified by a short silica plug to afford 21 mg (quantitative) of the intermediate free amine.

The intermediate amine (21 mg, 1 equiv) and NHS carbonate 22 were dissolved in acetonitrile (1 mL) with triethylamine (3 µL, 1 equiv) and stirred at rt o/n. The reaction mixture was concentrated and directly purified by column chromatography (0-20% EtOAc in hexane) to afford 38 mg (80%) of tagged glucoside 24 as a colorless oil. 1H NMR (300 MHz, CDCl3) δ 7.79 – 7.57 (m, 4H), 7.51 – 7.31 (m, 5H), 7.05 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.49 (d, J = 2.2 Hz, 2H), 6.37 (t, J = 2.3 Hz, 1H), 5.60 –
5.45 (m, 1H), 5.26 (d, J = 8.5 Hz, 1H), 5.01 (s, 2H), 4.97 (d, J = 3.5 Hz, 1H), 4.59 – 4.46 (m, 2H), 4.01 (t, J = 5.8 Hz, 3H), 3.87 (s, 2H), 3.78 (s, 3H), 3.74 (s, 2H), 3.55 (t, J = 8.8 Hz, 2H), 3.32 (s, 1H), 3.12 (dd, J = 10.7, 3.5 Hz, 1H), 2.28 (dd, J = 17.5, 9.6 Hz, 4H), 2.15 – 2.00 (m, 7H), 1.07 (s, 9H).

**Methyl 3,5-bis(perfluorooctyl)benzoate (25).** Methyl 3,5-diiodobenzoate (770 mg, 1 equiv) and perfluorooctyl iodide (1600 µL, 3 equiv) were dissolved in DMSO. Freshly activated Cu dust (800 mg, 6 equiv) was added and the reaction mixture was degassed for 15 minutes by bubbling Ar through the solution. The reaction was heated to 125 °C in a sealed flask under Argon o/n. The reaction mixture was then cooled, filtered through a bed of Celite, diluted with water and extracted with diethyl ether. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated by rotary evaporation. The residue was used in the next step of the reaction without purification. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.53 – 8.43 (m, 2H), 7.98 (s, 1H), 4.01 (s, 3H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -82.62, -112.85, -122.87, -123.52, -124.49, -127.93.

**(3,5-bis(perfluorooctyl)phenyl)methanol (26).** Crude methyl ester 25 was dissolved in THF and LAH (1M in THF, 3 mL, 1.5 equiv) was added to the reaction at room temperature. The reaction was stirred for 4 hours at room temperature. The reaction was quenched by the careful addition of sat. aq. NH$_4$Cl and extracted with diethyl ether. The organic extracts were dried over sodium sulfate and concentrated to afford the crude benzyl alcohol 26. The crude reaction mixture was crystallized from hexane to afford 755 mg of benzyl alcohol 26. The mother liquors were purified by column chromatography (0% to 20% EtOAc in hexane) to afford 631 mg of alcohol 26. Combined yield of 26
over 2 steps was 1386 mg (74%). $^1$H NMR (300 MHz, Acetone-$d_6$) $\delta$ 8.06 (d, $J$ = 1.7 Hz, 2H), 7.80 (s, 1H), 4.91 (s, 2H).

3,5-bis(perfluoroctyl)benzyl 1H-imidazole-1-carboxylate (27). Benzyl alcohol 26 (118 mg, 1 equiv) and carbonyl diimidazole (180 mg, 5 equiv) were dissolved in THF (12 mL) stirred o/n at rt. The reaction mixture was concentrated by rotary evaporation and the residue was passed through a silica plug to afford 110 mg (85%) of imidazole carbamate 27 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.95 – 7.89 (m, 2H), 7.85 (d, $J$ = 1.8 Hz, 1H), 7.48 – 7.35 (m, 1H), 7.10 (t, $J$ = 1.2 Hz, 1H), 5.55 (s, 2H). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -82.36 (t, $J$ = 9.9 Hz), -112.68 (t, $J$ = 14.3 Hz), -122.74 , -123.43 (m), -124.32 (s), -127.73 (t, $J$ = 13.8 Hz).

3,5-bis(perfluoroctyl)benzyl (4-nitrophenyl) carbonate (28). Benzyl alcohol 26 (490 mg, 1 equiv) and p-nitrophenyl chloroformate (220 mg, 2 equiv) were dissolved in THF (10 mL) at rt. Triethylamine (150 µL, 2 equiv) was added and the reaction was stirred at rt for 2h. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with diethyl ether, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (0–50% chloroform in hexane) to afford 498 mg (87%) of carbonate 28 as a pale-yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.35 – 8.25 (m, 2H), 7.90 (d, $J$ = 1.9 Hz, 2H), 7.83 (s, 1H), 7.45 – 7.33 (m, 2H), 5.42 (s, 2H).

2’,3,5-bis((3-perfluoroctyl)benzyloxycarbonylaminoethyl 3-O-acetyl-2-azido-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (29). Glucoside 23 (89 mg, 1 equiv) was treated with 20% piperidine in DMF at rt for 30 minutes. The
reaction mixture was concentrated by rotary evaporation and was purified by a short silica plug to afford quantitative recovery of the intermediate free amine. The intermediate free amine and carbonate 28 (140 mg, 1.2 equiv) were dissolved in DCM (5 mL) with a catalytic grain of DMAP and triethylamine (15 µL, 1.2 equiv). The reaction was stirred at rt o/n. The reaction mixture was then quenched with sat. aq. NaHCO₃, extracted with DCM, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10-30% EtOAc in hexane) to afford 150 mg (90%) of tagged glucosamine 29 as an off-white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.84 – 7.64 (m, 6H), 7.46 – 7.32 (m, 5H), 7.26 – 7.14 (m, 3H), 7.05 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.54 (dd, J = 10.7, 7.9 Hz, 1H), 5.38 (d, J = 6.1 Hz, 1H), 5.28 – 5.10 (m, 2H), 4.96 (d, J = 3.5 Hz, 1H), 4.52 (d, J = 4.3 Hz, 2H), 3.87 (d, J = 2.4 Hz, 2H), 3.76 (d, J = 11.1 Hz, 6H), 3.55 (dd, J = 14.2, 6.1 Hz, 2H), 3.39 – 3.24 (m, 1H), 3.12 (dd, J = 10.7, 3.5 Hz, 1H), 2.08 (s, 3H), 1.07 (s, 9H).

3,5-bis(perfluoroctyl)benzaldehyde (31). Benzyl alcohol 26 (222 mg, 1 equiv) and 2-iodosoxybezene (152 mg, 2 equiv) were dissolved in a mixture of DMSO and TFT (1:1, 10 mL). The reaction was heated at 40 °C until 2-iodosoxybezene dissolved into solution and stirred at that that temperature for 3 hours. The reaction mixture was then partitioned between water and diethyl ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to cleanly afford 197 mg (89%) of benzaldehyde 31 as an amorphous white solid. ¹H NMR (300 MHz, CDCl₃) δ 10.16 (s, 1H), 8.34 (d, J = 1.5 Hz, 1H), 8.05 (d, J = 1.9 Hz, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ -
81.88 – 82.95 (m), -112.06 – -113.54 (m), -122.71, -123.45 (d, J = 48.5 Hz), -124.34, -127.75 (d, J = 17.4 Hz).

(E)-ethyl 3-(3,5-bis(perfluorooctyl)phenyl)acrylate (32). Benzaldehyde 31 (197 mg, 1 equiv) and triethyl phosphonoacetate (85 µL, 1.5 equiv) were dissolved in THF (15 mL). NaH (60% dispersion in mineral oil, 18 mg, 1.5 equiv) was added and the reaction was stirred at rt o/n. The reaction quenched with sat. aq. NH₄Cl and extracted with diethyl ether. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (0–50% chloroform in hexane) to afford 185 mg (87%) of alkene 32 as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, J = 1.5 Hz, 2H), 7.84 – 7.66 (m, 2H), 6.59 (dd, J = 16.0, 0.8 Hz, 1H), 4.36 – 4.23 (m, 2H), 1.38 – 1.32 (m, 3H).

3-(3,5-bis(perfluorooctyl)phenyl)propan-1-ol (33). Alkene 32 (185 mg, 1 equiv) was dissolved in THF (10 mL) with HOAc (10 drops) added. Pd/C (ca. 20 mg) was added and the reaction was stirred under hydrogen for 36 hours. The reaction was then filtered through a pad of Celite and concentrated under reduced pressure to afford the reduced product in quantitative yield. The crude product was used in the next step without purification.

The crude ethyl ester was dissolved in THF (6 mL) and cooled to -78 °C with stirring. A solution of LAH (1M in THF, 200 µL, excess) was added and the reaction was allowed to warm to rt over 3h. The reaction was carefully quenched with sat. aq. NH₄Cl and extracted with diethyl ether. The organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was passed through
a silica gel plug to afford 164 mg (92% over 2 steps) of homologated alcohol 33 as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.64 (s, 3H), 3.70 (t, $J = 6.2$ Hz, 2H), 2.99 – 2.81 (m, 2H), 1.93 (ddt, $J = 9.8$, 7.9, 6.2 Hz, 2H).

3-(3,5-bis(perfluorooctyl)phenyl)propyl (4-nitrophenyl) carbonate (34). Homologated alcohol 33 (42 mg, 1 equiv) and $p$-nitrophenyl chloroformate (19 mg, 2 equiv) were dissolved in THF (2 mL) at rt. Triethylamine (15 µL, 2 equiv) was added and the reaction was stirred at rt for 2h. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with diethyl ether. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (0–50% chloroform in hexane) to afford 32 mg (65%) of carbonate 34 as a pale-yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.35 – 8.21 (m, 2H), 7.68 (s, 3H), 7.43 – 7.33 (m, 2H), 4.34 (t, $J = 6.2$ Hz, 2H), 2.96 (dd, $J = 9.2$, 6.5 Hz, 2H), 2.15 (dq, $J = 9.9$, 6.2 Hz, 2H).

2'-3-(3,5-bis(perfluorooctyl)phenyl)propyloxycarbonylaminoethyl 3-O-acetyl-2-azido-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-$\alpha$-D-glucopyranoside (35). Glucoside 23 (292 mg, 1 equiv) was treated with 20% piperidine in DMF at rt for 30 minutes. The reaction mixture was concentrated by rotary evaporation and was purified by a short silica plug to afford quantitative recovery of the intermediate free amine.

The intermediate free amine and carbonate 34 (465 mg, 1.2 equiv) were dissolved in DCM (10 mL) with a catalytic grain of DMAP and triethylamine (100 µL, 1.2 equiv). The reaction was stirred at rt o/n. The reaction mixture was then quenched with sat. aq. NaHCO$_3$ and extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified
by column chromatography (10–30% EtOAc in hexane) to afford 496 mg (72%) of tagged glucosamine 35 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.75 – 7.58 (m, 7H), 7.50 – 7.31 (m, 6H), 7.05 (d, J = 8.5 Hz, 2H), 6.85 – 6.73 (m, 2H), 5.66 – 5.43 (m, 1H), 5.21 (s, 1H), 4.98 (d, J = 3.6 Hz, 1H), 4.63 – 4.43 (m, 2H), 4.19 – 4.01 (m, 3H), 3.87 (s, 2H), 3.83 – 3.66 (m, 6H), 3.65 – 3.43 (m, 3H), 3.40 – 3.21 (m, 2H), 3.13 (dd, J = 10.6, 3.5 Hz, 1H), 2.82 (t, J = 8.0 Hz, 2H), 2.08 (d, J = 0.8 Hz, 3H), 1.94 (d, J = 8.1 Hz, 2H), 1.08 (s, 9H).

(E)-ethyl 4-(1H,1H,2H,2H-perfluorodec-1-en-1-yl)benzoate (36). Benzocaine (500 mg, 1 equiv) was dissolved in THF (15 mL) and cooled to −20 °C. BF$_3$•Et$_2$O (900 µL, 3 equiv) and isoamyl nitrite (800 µL, 2 equiv) were added dropwise sequentially. The reaction was stirred at −20 °C until a cloudy suspension resulted. The reaction warmed to 0 °C and then was diluted with diethyl ether to precipitate the diazonium salt. The solid was filtered and used crude in the next step of the reaction sequence.

The intermediate diazonium tetrafluoroborate salt was suspended in methanol (15 mL). 1H,1H,2H-perfluorodecene (450 µL, 1 equiv) and Pd(OAc)$_2$ (20 mg, 5 mol%) were added and reaction was stirred at 40 °C. At 40 °C the reaction commenced with effervescence and was refluxed for 30 minutes. The reaction mixture was cooled and concentrated under reduced pressure. The residue was redissolved in DCM and passed through a short silica plug to remove Pd salts. The organic fraction was concentrated by rotary evaporation and 1.20 g (69%) of alkene 36 was isolated as a white solid without purification. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.12 – 8.00 (m, 2H), 7.60 – 7.43 (m, 2H), 7.20 (d, J = 16.6 Hz, 1H), 6.30 (dt, J = 16.1, 12.0 Hz, 1H), 4.39 (qd, J = 7.1, 1.2 Hz, 2H),
1.44 – 1.36 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.71, 138.56, 137.37, 131.68, 129.98, 127.35, 116.50, 61.11, 14.05. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -82.61 (t, J = 10.0 Hz), -113.21 (d, J = 12.6 Hz), -122.77 – -123.36 (m), -123.66 (tt, J = 19.5, 10.0 Hz), -124.49 (d, J = 16.4 Hz), -124.64 – -125.02 (m), -127.60 – -128.69 (m).

(4-(1H,1H,2H,2H-perfluorodecyl)phenyl)methanol (37). Alkene 36 (1.20 g, 1 equiv) was dissolved in a mixture of THF and methanol (1:4, 20 mL) at room temperature. A small amount of Pd/C was added and the reaction mixture was stirred under hydrogen o/n. The reaction mixture was filtered through a pad of Celite to afford 1.20 g (quantitative) of the hydrogenated intermediate.

The intermediate ester was then dissolved in THF (30 mL) and cooled to 0 °C. Diisobutylaluminum hydride solution (1M in hexane, 8 mL, 3 equiv) was added and the reaction was stirred at 0 °C to rt o/n. The reaction was quenched with EtOAc and treated with sat. aq. Rochelle’s salt solution. The mixture was extracted with diethyl ether and washed with brine. The extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was passed through a silica plug to afford 1.06 g (95% over 2 steps) of benzyl alcohol 37 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.40 – 7.13 (m, 4H), 4.99 (s, 2H), 3.09 – 2.76 (m, 2H), 2.42 (dq, J = 18.3, 9.8, 9.1 Hz, 2H).

4-(1H,1H,2H,2H-perfluorodecyl)benzyl (4-nitrophenyl) carbonate (38). Beznyl alcohol 37 (3.38 g, 1 equiv) and p-nitrophenyl chloroformate (1.87, 1.5 equiv) were dissolved in THF (70 mL) at 0 °C. Triethylamine (2.0 mL, 2 equiv) was added and the reaction was stirred from 0 °C to rt o/n. The reaction was quenched with sat. aq NaHCO$_3$ and extracted with diethyl ether. The organic extracts were dried over sodium sulfate and
concentrated under reduced pressure. The residue was purified by column chromatography (0–50% chloroform in hexane) to afford 4.02 mg (92%) of carbonate 38 as a pale-yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 – 8.20 (m, 2H), 7.47 – 7.32 (m, 4H), 7.28 (d, J = 7.8 Hz, 2H), 5.28 (s, 2H), 3.06 – 2.85 (m, 2H), 2.40 (dq, J = 18.6, 9.3 Hz, 2H).

2'-{(4-(1H,1H,2H,2H-perfluorodecyl)benzyloxy carbonyl)aminoethyl} 3-O-acetyl-2-azido-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-β-D-glucopyranoside (13). Glucoside 23 (738 mg, 1 equiv) was treated with 20% piperidine in DMF at rt for 30 minutes. The reaction mixture was concentrated by rotary evaporation and was purified by a short silica plug to afford quantitative recovery of the intermediate free amine.

The intermediate free amine and carbonate 38 (804 mg, 1.2 equiv) were dissolved in THF (20 mL) with a catalytic grain of DMAP and triethylamine (180 µL, 1.2 equiv). The reaction was stirred at rt o/n. The reaction mixture was then quenched with sat. aq. NaHCO$_3$ and extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10–30% EtOAc/hexane) to afford 998 mg (84%) of tagged glucosamine 39 as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.73 – 7.64 (m, 4H), 7.48 – 7.33 (m, 6H), 7.29 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.54 (ddd, J = 10.7, 6.3, 2.7 Hz, 1H), 5.27 (t, J = 5.9 Hz, 1H), 5.06 (s, 2H), 4.97 (d, J = 3.5 Hz, 1H), 4.62 – 4.46 (m, 2H), 3.88 (t, J = 1.7 Hz,
2H), 3.77 (d, J = 9.1 Hz, 6H), 3.62 – 3.45 (m, 2H), 3.39 – 3.26 (m, 1H), 3.14 (dd, J = 10.7, 3.5 Hz, 1H), 2.95 – 2.85 (m, 2H), 2.46 – 2.25 (m, 2H), 2.09 (s, 3H), 1.08 (s, 9H).

2'-azidoethyl per-O-acetyl-β-D-glucopyranoside (40). Per-O-acetyl-β-D-glucose (7.8 g, 1 equiv) and 2-bromoethanol (2.8 mL, 2 equiv) were dissolved in DCM (35 mL) at rt. BF₃•Et₂O (5.0 mL, 2 equiv) was added dropwise and the reaction mixture was sonicated for 40 minutes. The reaction mixture was quenched with sat. aq. NaHCO₃ and extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by dry column vacuum chromatography to afford 5.48 g (61%) of 2-bromoethyl β-glucoside as an amorphous solid.

2-Bromoethyl β-glucoside (5.48 g, 1 equiv) and sodium azide (3.16 g, 4 equiv) were dissolved in a mixture of acetone and water (4:1, 50 mL). The reaction mixture was refluxed o/n. The reaction was then extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate and concentrated to afford 4.82 g (96%, 57% over 2 steps) of azidoethyl β-glucoside 40 as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 5.17 (td, J = 9.5, 1.1 Hz, 1H), 5.11 – 4.91 (m, 2H), 4.54 (dd, J = 8.0, 1.1 Hz, 1H), 4.27 – 4.16 (m, 1H), 4.16 – 4.04 (m, 2H), 3.92 – 3.81 (m, 2H), 3.77 (m, 1H), 3.71 – 3.62 (m, 1H), 3.53 – 3.37 (m, 3H), 2.09 – 1.92 (m, 12H).

2'-azidoethyl 4,6-O-benzylidine-β-D-glucopyranoside (41). Tetraacetate 40 (3.17 g, 1 equiv) was dissolved in DCM and methanol (1:1, 50 mL) and cooled to 0 °C. NaOMe (1M in MeOH, 3 mL, 0.3 equiv) was added and the reaction was stirred at 0 °C.
The reaction was quenched with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated by rotary evaporation to afford the intermediate tetraol in quantitative yield.

The crude tetraol was azeotroped with toluene three times and then dissolved in THF (30 mL). Benzyldiene dimethyl acetal (2.5 mL, 2 equiv) and CSA (50 mg, 3 mol%) were added. The reaction was refluxed o/n. The reaction was quenched with sat. aq. NaHCO₃ and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by dry column vacuum chromatography to afford 2.42 g (87%) of acetal 41 as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.40 (s, 1H), 4.63 (d, J = 3.8 Hz, 1H), 4.22 (dd, J = 10.1, 4.9 Hz, 1H), 4.05 (t, J = 9.3 Hz, 1H), 3.93 (td, J = 9.6, 3.5 Hz, 1H), 3.65 (dd, J = 9.3, 4.0 Hz, 1H), 3.55 (t, J = 10.3 Hz, 1H), 3.41 (t, J = 9.4 Hz, 2H), 3.35 (s, 4H), 3.06 – 2.91 (m, 2H), 2.69 (dd, J = 5.7, 4.4 Hz, 2H).

2'-azidoethyl 2-O-benzoyl-4,6-O-benzyldiene-3-O-p-methoxybenzyl-β-D-glucopyranoside (42). Acetal 41 (690 mg, 1 equiv) and dibutyl tin oxide (767, 1.5 equiv) were dissolved in toluene. The reaction was heated to reflux and when the reaction mixture was homogeneous, the reaction was cooled to rt. The solvent was removed under reduced pressure and the residue was azeotroped three times with toluene to afford the crude stannylene acetal.

The stannylene acetal intermediate was dissolved in THF and DMF (10:1, 30 mL). PMB-Cl (900 µL, 3 equiv), CsF (450 mg, 1.5 equiv) and TBAI (100 mg, 10 mol%) were added. The reaction was stirred at rt o/n. The reaction mixture was then filtered through a pad of Celite and concentrated to afford a mixture of alkylated products. The
residue was purified by column chromatography to afford 320 mg of the desired 3-\(\text{O}\)-PMB ether. The product was treated with 3 equiv benzoyl chloride in pyridine and passed through a silica plug to afford 259 mg (31% over 3 steps) of glucoside 42 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 8.07 – 7.93 (m, 2H), 7.65 – 7.54 (m, 1H), 7.52 – 7.39 (m, 4H), 7.11 – 7.01 (m, 2H), 6.99 – 6.89 (m, 2H), 6.68 – 6.55 (m, 2H), 5.58 (s, 1H), 5.37 – 5.21 (m, 1H), 4.81 – 4.56 (m, 3H), 4.38 (dd, J = 10.5, 4.9 Hz, 1H), 4.04 – 3.90 (m, 3H), 3.90 – 3.78 (m, 6H), 3.70 (s, 3H), 3.62 – 3.44 (m, 1H), 3.44 – 3.23 (m, 2H).

\(2'-(4-(1H,1H,2H,2H\text{-perfluorodecyl})\text{benzyloxy carbonyl})\text{aminoethyl 2-O-benzoyl-4,6-O-benzylidine-3-O-p-methoxybenzyl-\(\beta\)-D-glucopyranoside (43).}\) Azidoethyl \(\beta\)-glucoside 42 (259 mg, 1 equiv) was dissolved in a mixture of EtOAc, ethanol and water (1:4:4, 10 mL) and treated with Zn powder (50 mg, 2 equiv) and sat. aq. NH\(_4\)Cl (100 µL, 4 equiv). The reaction was refluxed for 1h. The intermediate amine was isolated after organic extraction in 228 mg (93%) yield.

The intermediate free amine (738 mg) and carbonate 38 (1.29 g, 1.2 equiv) were dissolved in THF (40 mL) with a catalytic grain of DMAP and triethylamine (500 µL, 2 equiv). The reaction was stirred at rt o/n. The reaction mixture was then quenched with sat. aq. NaHCO\(_3\) and extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10–30% EtOAc in hexane) to afford 1345 mg (87%, 72% over 2 steps) of tagged glucosamine 43 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 8.01 – 7.88 (m, 2H), 7.59 – 7.47 (m, 3H), 7.47 – 7.35 (m, 5H), 7.21 (q, J = 8.5, 8.1 Hz, 4H), 7.06 (d, J = 8.6 Hz, 2H), 6.65 – 6.57 (m, 2H), 5.61 (s, 1H), 5.23 (t, J = 8.3 Hz, 2H).
$\text{Hz, } 1\text{H})$, 5.09 (t, $J = 5.8 \text{ Hz, } 1\text{H})$, 5.05 – 4.81 (m, 2H), 4.81 – 4.60 (m, 2H), 4.58 (d, $J = 7.9 \text{ Hz, } 1\text{H})$, 4.37 (dd, $J = 10.5, 4.9 \text{ Hz, } 1\text{H})$, 3.92 – 3.75 (m, 4H), 3.70 (s, 3H), 3.67 – 3.43 (m, 2H), 3.31 (s, 2H), 2.97 – 2.85 (m, 2H), 2.48 – 2.25 (m, 2H).

2'-(4-(1H,1H,2H,2H-perfluorodecyl)benzyloxycarbonyl)aminoethyl 2-O-benzoyl-3-O-methoxybenzyl-6-O-monomethoxytrityl-$\beta$-D-glucopyranoside (44). Acetal 43 (504 mg, 1 equiv) was dissolved in a mixture of methanol and DCM (1:1, 10 mL), treated with CSA (ca. 10 mg) and refluxed for 3 hours. FSPE purification under standard conditions afforded 420 mg (90%) of the intermediate 4,6-diol.

The intermediate diol (420 mg, 1 equiv) was dissolved in DCM and pyridine (5:1, 6 ml) and treated with monomethoxytrityl chloride (1.7 equiv, 200 mg) and catalytic DMAP. The reaction was refluxed 6 hours. The reaction mixture was concentrated under reduced pressure and purification by column chromatography (20–50% EtOAc in hexane afforded 430 mg (81%) of trityl ether 44. $^1\text{H NMR (300 MHz, CDCl}_3\text{)}$ δ 8.03 (dt, $J = 7.2, 1.4 \text{ Hz, } 2\text{H}), 7.65 – 7.58 (m, 1\text{H}), 7.56 – 7.44 (m, 8\text{H}), 7.38 – 7.25 (m, 19\text{H}), 7.19 (q, $J = 8.2 \text{ Hz, } 4\text{H}), 7.14 – 7.09 (m, 2\text{H}), 6.79 – 6.63 (m, 2\text{H}), 5.36 (dd, $J = 9.4, 7.9 \text{ Hz, } 1\text{H}), 4.91 (d, J = 12.6 \text{ Hz, } 1\text{H}), 4.70 (d, J = 12.8 \text{ Hz, } 1\text{H}), 4.63 (d, J = 6.5 \text{ Hz, } 1\text{H}), 4.58 (d, J = 8.0 \text{ Hz, } 1\text{H}), 4.47 (s, 2\text{H}), 3.86 (t, J = 9.1 \text{ Hz, } 1\text{H}), 3.72 (d, J = 1.2 \text{ Hz, } 3\text{H}), 3.60 (t, J = 9.2 \text{ Hz, } 1\text{H}), 3.53 (t, J = 6.0 \text{ Hz, } 2\text{H}), 3.49 – 3.42 (m, 3\text{H}), 2.87 (s, 1\text{H}), 2.50 (s, 1\text{H}), 2.35 – 2.10 (m, 2\text{H}), 1.92 (dq, J = 12.1, 6.3 \text{ Hz, } 2\text{H}).

2'-(4-(1H,1H,2H,2H-perfluorodecyl)benzyloxycarbonyl)aminoethyl 2-O-benzoyl-6-O-(2-bromo)isobutyryl-3-O-methoxybenzyl-$\beta$-D-glucopyranoside (45). Intermediate diol (as prepared as in 44, 220 mg, 1 equiv), catalytic DMAP (ca. 10 mg), and DIPEA (45
µL, 1.5 equiv) were dissolved in DCM (3 mL). 2-bromoisobutyryl bromide (40 µL, 1.4 equiv) was added and the reaction was stirred at 0 °C for 2 hours. The reaction was quenched with sat. aq. NaHCO₃ and extracted with DCM. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (20–50% EtOAc in hexane) to afford 240 mg (95%) of ester 45 as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 8.10 – 7.93 (m, 2H), 7.65 – 7.49 (m, 1H), 7.49 – 7.32 (m, 2H), 7.32 – 7.05 (m, 6H), 6.73 (dd, J = 8.5, 1.5 Hz, 2H), 5.27 – 5.12 (m, 2H), 5.08 – 4.82 (m, 2H), 4.73 – 4.47 (m, 4H), 4.41 (dd, J = 11.8, 5.1 Hz, 1H), 3.81 (d, J = 5.1 Hz, 1H), 3.72 (s, 2H), 3.70 – 3.56 (m, 4H), 3.37 – 3.27 (m, 2H), 3.02 – 2.80 (m, 3H), 2.38 (dq, J = 17.4, 9.9, 9.0 Hz, 2H), 2.03 – 1.84 (m, 6H).

2'-((4-(1H,1H,2H,2H-perfluorodecyl)benzyloxycarbonyl)aminoethyl 2'-O-benzoyl-3-O-p-methoxybenzyl-β-D-gluronate methyl ester (46). Intermediate diol (as prepared as in 44, 140 mg, 1 equiv), bis(acetoxy)iodobenzene (134 mg, 3 equiv) and TEMPO (6 mg, 0.4 equiv) were dissolved in DCM and water (2:1, 8 mL). The reaction was stirred vigorously at rt for 45 min. The reaction was extracted with DCM and concentrated. The residue was purified by FSPE under standard conditions to afford 130 mg (92%) of the intermediate GlcA acid.

The intermediate free acid was dissolved in DCM (5 mL). Iodomethane (0.5 mL), tetraoctylammonium bromide (ca. 10 mg), and sat. aq. NaHCO₃ (1 mL) were added. The reaction was stirred o/n at rt. The organic layer was separated and concentrated. The residue was purified by FSPE under standard conditions to afford 131 mg (90% yield) of methyl ester 46 as a white solid.
Thiotolyl 2-azido-4-O-benzyl-6-O-(tert-butyldiphenylsilyl)-3-O-(2-trimethylsilyl-ethoxymethyl)-β-D-glucopyranoside (47). Thioglycoside 6 (260 mg, 1 equiv) was dissolved in methanol and DCM (1:1, 10 mL) and treated with potassium carbonate (ca. 50 mg). When the reaction was complete, the mixture was concentrated under reduced pressure and the residue was used crude in the next step.

The crude alcohol (250 mg, 1 equiv) was dissolved in DCM (4 mL) and treated with SEM-Cl (270 µL, 4 equiv), TBAI (27 mg, 10 mol%) and DIPEA (400 µL, 5 equiv). The reaction was refluxed for 6 hours until deemed complete by TLC. The reaction mixture was concentrated and purified by column chromatography to afford 205 mg (69%) of SEM ether 92 as a colorless oil. Note: 2-trimethylsilylethanol (by-product of the protection) can be removed high vacuum rotary evaporation at 45 °C after 30 minutes.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.84 – 7.77 (m, 2H), 7.77 – 7.70 (m, 2H), 7.59 – 7.52 (m, 2H), 7.50 – 7.30 (m, 6H), 7.12 – 6.99 (m, 4H), 6.84 – 6.74 (m, 2H), 4.99 (d, J = 6.4 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.69 (d, J = 10.2 Hz, 1H), 4.60 (d, J = 10.3 Hz, 1H), 4.40 (d, J = 10.1 Hz, 1H), 4.01 (dd, J = 11.4, 3.3 Hz, 1H), 3.91 (dd, J = 11.4, 3.3 Hz, 1H), 3.84 – 3.77 (m, 4H), 3.75 – 3.61 (m, 2H), 3.60 – 3.51 (m, 1H), 3.55 – 3.23 (m, 2H), 2.33 (s, 3H), 1.12 (s, 9H), 1.03 – 0.92 (m, 2H), 0.01 (s, 9H).

$^2$-(4-(1H,1H,2H,2H-perfluorodecyl)benzoyloxycarbonyl)aminoethyl 2-O-benzoyl-6-O-(2-bromo)isobutryl-3-O-p-methoxybenzyl-β-D-glucopyranosyl)-3-O-acetyl-2-azido-2-deoxy-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-β-D-glucopyranoside (48). GlcN donor 6 (103 mg, 1 equiv) and GlcA acceptor 45 (240 mg, 1.5 equiv) were carefully azeotroped with toluene, dried on a high vacuum line, and then
dissolved in dry DCM (2.5 mL). 4 Å MS (100 mg) were added and the reaction was stirred at room temperature for 30 minutes. NIS (90 mg, 2 equiv) was added and the reaction mixture was cooled to 0 °C. TfOH (1 µL, 0.1 equiv) was added and the reaction was stirred at 0 °C until TLC indicates consumption of donor. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of celite, and concentrated. The residue was purified by column chromatography to afford 104 mg (73%) of disaccharide 48 as a clear oil. 1H NMR (300 MHz, CDCl3) δ 8.10 – 8.01 (m, 1H), 7.73 – 7.60 (m, 5H), 7.56 (t, J = 7.4 Hz, 2H), 7.51 – 7.29 (m, 11H), 7.25 – 7.08 (m, 9H), 6.79 (m, 4H), 5.67 (d, J = 3.9 Hz, 1H), 5.27 (t, J = 8.6 Hz, 1H), 5.12 (d, J = 5.5 Hz, 1H), 5.04 (t, J = 6.9 Hz, 2H), 5.00 – 4.87 (m, 3H), 4.82 – 4.70 (m, 3H), 4.70 – 4.52 (m, 5H), 4.15 (dd, J = 11.9, 5.1 Hz, 1H), 3.89 (dt, J = 14.2, 3.6 Hz, 9H), 3.80 (s, 4H), 3.74 (s, 3H), 3.72 – 3.60 (m, 6H), 3.31 (s, 3H), 3.12 (dd, J = 10.4, 3.9 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.48 – 2.26 (m, 2H), 1.07 (s, 9H), 1.04 (m, 2H), 0.03 (s, 9H).

2′-(4-(1H,1H,2H,2H-perfluorodecyl)benzylloxycarbonyl)aminoethyl 2-O-benzoyl-3-O-p-methoxybenzyl-β-D-glucuronate)-3-O-acetyl-2-deoxy-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-β-D-glucopyranoside methyl ester(49).

Dissaccharide 48 (255 mg, 1 equiv) was dissolved in a mixture of methanol and THF (1:1) and treated with DBU (25 µL, 1 equiv) at rt o/n. The reaction mixture was concentrated under reduced pressure and the residue was purified by FSPE under standard conditions to afford 240 mg of 6-OH disaccharide.

Intermediate 6-OH alcohol (240 mg, 1 equiv), bis(acetoxy)iodobenzene (62 mg, 3 equiv) and TEMPO (2 mg, 0.4 equiv) were dissolved in DCM and water (2:1, 3 mL). The
reaction was stirred vigorously at rt for o/n. The reaction was extracted with DCM and concentrated. The residue was treated with an excess of diazomethane and carefully concentrated. The residue was purified by FSPE under standard conditions to afford 180 mg (76% over 3 steps) of disaccharide 49 as a clear oil. \( ^1 \text{H NMR} \ (300 \text{ MHz, CDCl}_3) \delta 8.03 \text{ (d, } J = 7.7 \text{ Hz, } 2\text{H}), 7.73 – 7.61 \text{ (m, } 5\text{H}), 7.55 \text{ (t, } J = 7.4 \text{ Hz, } 1\text{H}), 7.37 \text{ (dt, } J = 22.3, 6.9 \text{ Hz, } 10\text{H}), 7.16 \text{ (dt, } J = 18.6, 9.5 \text{ Hz, } 9\text{H}), 6.86 – 6.78 \text{ (m, } 2\text{H}), 6.78 – 6.71 \text{ (m, } 2\text{H}), 5.50 \text{ (d, } J = 3.6 \text{ Hz, } 1\text{H}), 5.31 \text{ (t, } J = 7.7 \text{ Hz, } 1\text{H}), 5.12 \text{ (d, } J = 6.1 \text{ Hz, } 1\text{H}), 5.05 – 4.93 \text{ (m, } 3\text{H}), 4.89 \text{ (d, } J = 6.0 \text{ Hz, } 2\text{H}), 4.68 \text{ (ddd, } J = 22.2, 12.9, 8.6 \text{ Hz, } 6\text{H}), 4.20 \text{ (d, } J = 8.5 \text{ Hz, } 1\text{H}), 4.07 – 3.85 \text{ (m, } 7\text{H}), 3.81 \text{ (s, } 6\text{H}), 3.73 \text{ (s, } 4\text{H}), 3.66 – 3.56 \text{ (m, } 3\text{H}), 3.50 \text{ (s, } 3\text{H}), 3.42 – 3.23 \text{ (m, } 4\text{H}), 3.10 \text{ (dd, } J = 10.4, 3.7 \text{ Hz, } 1\text{H}), 2.96 – 2.86 \text{ (m, } 2\text{H}), 2.37 \text{ (dq, } J = 18.0, 9.2, 8.5 \text{ Hz, } 2\text{H}), 1.07 \text{ (s, } 9\text{H}), 1.04 – 1.00 \text{ (m, } 2\text{H}), 0.02 \text{ (s, } 9\text{H}).

4-(1H,1H,2H,2H-perfluorodecyl)benzyl 3-O-acetyl-2-azido-4-O-p-methoxybenzyl-6-O-(tert-butyldiphenylsilyl)-\( \alpha \)-D-glucopyranoside (50). GlcN donor 6 (184 mg, 1 equiv) and benzyl alcohol 37 (240 mg, 1.5 equiv) were azeotroped with toluene in a flame-dried flask and dried on vacuum line. The compounds were dissolved in a mixture of diethyl ether and DCM (9:1, 5 mL) with flame-dried 4 Å MS (0.5 gram). The reaction was stirred for 30 minutes before addition of NIS (78 mg, 1.5 equiv). The reaction mixture was cooled to –20 °C and TfOH (6 µL, 0.3 equiv) was added to the reaction mixture. The reaction was stirred at –20 °C for 5 hours until TLC indicated the disappearance of donor. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of celite, and concentrated. The residue was purified by column chromatography (0% to 20% EtOAc in hexane) to afford 264 mg (89%, \( \alpha \) only) of benzyl
glycoside 50 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.82 – 7.61 (m, 4H), 7.56 – 7.35 (m, 7H), 7.35 – 7.23 (m, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.15 – 7.04 (m, 2H), 6.92 – 6.77 (m, 2H), 5.67 – 5.54 (m, 1H), 5.04 (d, J = 3.5 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.63 – 4.50 (m, 3H), 3.99 – 3.66 (m, 7H), 3.17 (ddd, J = 10.6, 3.6, 0.9 Hz, 1H), 2.97 – 2.82 (m, 2H), 2.36 (tt, J = 17.7, 7.8 Hz, 2H), 2.15 – 2.02 (m, 3H), 1.12 (d, J = 1.0 Hz, 9H).

4-(1H,1H,2H,2H-perfluorodecyl)benzyl 3-O-(2-trimethylsilylethoxymethyl)-2-azido-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (51). Glucoside 50 (264 mg, 1 equiv) was treated with potassium carbonate in MeOH to afford the 3-OH intermediate. The crude alcohol was dissolved in DCM (2 mL) and refluxed with SEM-Cl (35 µL, 1.1 equiv), DIPEA (80 µL, 1.5 equiv) and TBAI (10 mg, 0.1 equiv). The reaction was concentrated under reduced pressure and the residue was subjected to FSPE under standard conditions to afford 181 mg (65%) of intermediate 3-O-SEM ether.

The intermediate 3-O-SEM ether (181 mg, 1 equiv) was dissolved acetone, acetonitrile and water (4:4:1, 10 mL) and treated with CAN (750 mg, 9 equiv). The reaction mixture was directly applied to an FSPE cartridge and the 4-OH product 51 was isolated in 89 mg (55%) yield as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.81 – 7.66 (m, 4H), 7.49 – 7.35 (m, 7H), 7.35 – 7.29 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 5.03 – 4.90 (m, 2H), 4.79 (d, J = 7.3 Hz, 1H), 4.77 – 4.71 (m, 1H), 4.64 (d, J = 1.2 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.01 – 3.74 (m, 6H), 3.66 – 3.53 (m, 2H), 3.35 (dd, J = 10.2, 3.6 Hz, 1H), 2.98 – 2.83 (m, 2H), 2.49 – 2.25 (m, 2H), 1.09 (s, 9H), 1.05 – 0.95 (m, 2H), 0.02 (s, 9H).
**Thiophenyl per-O-acetyl-β-D-glucopyranoside (52).** Per-O-acetyl-β-D-glucose (8.9 g, 1 equiv) and thiophenol (2.2 mL, 1 equiv) were dissolved in DCM (50 mL) at rt. BF₃•Et₂O (2.8 mL, 1 equiv) was added dropwise and the reaction mixture was sonicated for 60 minutes. The reaction mixture was quenched with sat. aq. NaHCO₃ and extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by dry column vacuum chromatography to afford 5.48 g (57%) of thioglycoside 52 as a cream-colored solid. ¹H NMR was compared to literature reported values and confirmed that the correct product was obtained.¹⁴

**Thiophenyl 4,6-O-p-methoxybenzylidine-β-D-glucopyranoside (53).** Tetraacetate 52 (2.13 g, 1 equiv) was dissolved in methanol (50 mL) and cooled to 0 °C. NaOMe (1M in MeOH, 3 mL, 0.3 equiv) was added and the reaction was stirred at 0 °C. The reaction was quenched with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated by rotary evaporation to afford the intermediate tetraol in quantitative yield.

The crude tetraol was azeotroped with toluene three times and then dissolved in THF (30 mL). PMBDMA (1.2 mL, 1.5 equiv) and CSA (112 mg, 10 mol%) were added. The reaction was refluxed o/n. The reaction was quenched with sat. aq. NaHCO₃ and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by dry column vacuum chromatography to afford 1.52 g (81%) of acetal 53 as a white solid. ¹H NMR was compared to literature reported values and confirmed that the correct product was obtained.¹⁵
Thiophenyl 2-O-benzoyl-3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidine-β-D-glucopyranoside (54). Acetal 53 (1.45 mg, 1 equiv) and dibutyl tin oxide (1.39 g, 1.5 equiv) were dissolved in toluene. The reaction was heated to reflux and when the reaction mixture was homogeneous, the reaction was cooled to rt. The solvent was removed under reduced pressure and the residue was azeotroped three times with toluene to afford the crude stannylene acetal.

The stannylene acetal intermediate was dissolved in THF and DMF (10:1, 30 mL). PMB-Cl (1.5 mL, 3 equiv), CsF (836 mg, 1.5 equiv) and TBAI (80 mg, 10 mol%) were added. The reaction was stirred at rt o/n. The reaction mixture was then filtered through a pad of Celite and concentrated to afford the desired 3-O-PMB ether. The crude ether was treated with benzoyl chloride in pyridine and purified by column chromatography to afford 1.85 g (79% over 3 steps) of glycoside 54 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 8.06 – 7.94 (m, 2H), 7.67 – 7.57 (m, 1H), 7.53 – 7.39 (m, 6H), 7.34 – 7.22 (m, 3H), 7.10 – 7.00 (m, 2H), 7.00 – 6.87 (m, 2H), 6.66 – 6.54 (m, 2H), 5.57 (s, 1H), 5.35 – 5.18 (m, 1H), 4.84 (d, J = 10.1 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.41 (dd, J = 10.5, 4.9 Hz, 1H), 3.93 – 3.73 (m, 7H), 3.69 (s, 3H), 3.65 – 3.51 (m, 1H).

Thiophenyl 2-O-benzoyl-3-O-p-methoxybenzyl-4-O-p-methoxybenzyl-β-D-glucopyranoside (55). Glycoside 54 (1.47 g, 1 equiv) was dissolved in BH\(_3\)•THF (1 M in THF, 12.5 mL, 5 equiv) and cooled to 0 °C. Bu\(_2\)BOTf (1 M in toluene, 5 mL, 1.1 equiv) was added dropwise and the reaction was stirred for 2 hours. The reaction was cooled to –78 °C and quenched with triethylamine (1.5 equiv) and methanol. It was warmed slowly
to room temperature. The reaction mixture was concentrated by rotary evaporation to afford the crude 4-O-PMB ether. The residue was dissolved in methanol and concentrated three times. The residue was then purified by column chromatography (20% to 30% EtOAc in hexane) to afford 1.42 g (91%) of 4-O-PMB ether 55 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.11 – 7.95 (m, 2H), 7.68 – 7.53 (m, 1H), 7.53 – 7.35 (m, 4H), 7.31 – 7.23 (m, 5H), 7.11 – 6.99 (m, 2H), 6.94 – 6.81 (m, 2H), 6.70 – 6.58 (m, 2H), 5.24 (dd, J = 10.1, 9.0 Hz, 1H), 4.81 (dd, J = 10.3, 5.6 Hz, 2H), 4.75 – 4.55 (m, 3H), 3.96 – 3.87 (m, 1H), 3.81 (s, 4H), 3.73 (td, J = 3.8, 1.4 Hz, 1H), 3.69 (s, 4H), 3.48 (ddd, J = 9.7, 4.8, 2.6 Hz, 1H).

**Thiophenyl 2-O-benzoyl-3-O-p-methoxybenzyl-4-O-p-methoxybenzyl-6-O-p-nitrobenzoyl-\(\beta\)-D-glucopyranoside (56).** Alcohol 55 (1.42 g, 1 equiv) and \(p\)-nitrobenzoyl chloride (871 mg, 1.5 equiv) were dissolved in DCM (20 mL). Catalytic DMAP and triethylamine (700 \(\mu\)L, 2 equiv) were added. The reaction was stirred at rt o/n. The reaction was quenched with sat. aq. NaHCO\(_3\) and extracted with DCM. The organic extracts were dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10–30% EtOAc in hexane) to afford 1.61 g (97%) of donor 56 as a white solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.34 – 8.20 (m, 2H), 8.15 – 8.00 (m, 4H), 7.68 – 7.56 (m, 1H), 7.56 – 7.36 (m, 4H), 7.26 – 7.01 (m, 6H), 6.80 – 6.73 (m, 2H), 6.73 – 6.60 (m, 2H), 5.25 (dd, J = 10.0, 9.1 Hz, 1H), 4.81 (dd, J = 10.5, 2.3 Hz, 2H), 4.75 – 4.50 (m, 4H), 4.43 (dd, J = 11.9, 4.5 Hz, 1H), 3.89 (t, J = 8.7 Hz, 1H), 3.71 (dd, J = 2.5, 0.9 Hz, 7H).
2-O-benzoyl-3,4-O-p-methoxybenzyl-6-O-p-nitrobenzoyl-β(1,4)-D-glucopyranosyl-(4-(1H,1H,2H,2H-perfluorodecyl)benzyl)-2-azido-3-O-(2-trimethylsilylethoxymethyl)-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (57).

GlcN donor 56 (103 mg, 1 equiv) and GlcA acceptor 51 (240 mg, 1.5 equiv) were carefully azeotroped with toluene, dried on a high vacuum line, and then dissolved in dry DCM (2.5 mL). 4 Å MS (100 mg) were added and the reaction was stirred at room temperature for 30 minutes. NIS (90 mg, 2 equiv) was added and the reaction mixture was cooled to 0 °C. TfOH (1 µL, 0.1 equiv) was added and the reaction was stirred at 0 °C until TLC indicates consumption of donor. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of Celite, and concentrated. The residue was purified by column chromatography to afford 104 mg (40%) of disaccharide 57 as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 8.32 – 8.23\) (m, 2H), 8.16 (dd, \(J = 8.9, 1.3\) Hz, 2H), 7.81 – 7.73 (m, 4H), 7.69 (dd, \(J = 6.7, 1.4\) Hz, 2H), 7.57 – 7.27 (m, 10H), 7.18 (dd, \(J = 12.2, 7.9\) Hz, 4H), 7.06 (d, \(J = 8.2\) Hz, 2H), 7.00 (d, \(J = 7.9\) Hz, 2H), 6.76 (dd, \(J = 8.6, 1.3\) Hz, 2H), 6.68 (dd, \(J = 8.7, 1.3\) Hz, 2H), 5.32 – 5.21 (m, 1H), 5.00 – 4.86 (m, 3H), 4.83 – 4.69 (m, 3H), 4.62 – 4.51 (m, 4H), 4.51 – 4.36 (m, 2H), 4.01 (p, \(J = 8.9\) Hz, 2H), 3.70 (dd, \(J = 8.8, 1.2\) Hz, 10H), 3.54 – 3.39 (m, 1H), 3.29 (q, \(J = 9.2, 8.8\) Hz, 2H), 2.92 (dd, \(J = 9.5, 3.9\) Hz, 1H), 2.86 – 2.72 (m, 2H), 2.41 – 2.15 (m, 2H), 1.04 (s, 9H), 0.88 – 0.70 (m, 2H), -0.08 (s, 9H).

Thiophenyl 4,6-O-(2-naphthylidene)-β-D-glucopyranoside (58). Tetraacetate 52 (1.50 g, 1 equiv) was dissolved in methanol (20 mL) and cooled to 0 °C. NaOMe (1M in MeOH, 2 mL, 0.3 equiv) was added and the reaction was stirred at 0 °C. The reaction
was quenched with acidic ion-exchange resin (Dowex-50WX8), filtered and concentrated by rotary evaporation to afford the intermediate tetraol in quantitative yield.

The crude tetraol was azeotroped with toluene three times and then dissolved in THF (30 mL). 2-naphthaldehyde dimethyl acetal (875 mg, 1.5 equiv) and CSA (80 mg, 10 mol%) were added. The reaction was refluxed o/n. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by dry column vacuum chromatography to afford 551 mg (39%) of acetal 58 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.03 – 7.79 (m, 5H), 7.65 – 7.44 (m, 6H), 7.40 – 7.24 (m, 3H), 5.74 (d, J = 4.5 Hz, 1H), 4.88 – 4.71 (m, 2H), 4.64 (d, J = 4.8 Hz, 1H), 4.32 (dd, J = 10.1, 4.5 Hz, 2H), 3.85 – 3.70 (m, 3H), 3.67 – 3.34 (m, 4H).

Thiophenyl 2-O-benzoyl-3-O-(2-naphthyl)-4,6-O-(2-naphthylidene)-β-D-glucopyranoside (59). Acetal 53 (550 mg, 1 equiv) and dibutyl tin oxide (502 mg, 1.5 equiv) were dissolved in toluene (15 mL). The reaction was heated to reflux and when the reaction mixture was homogeneous, the reaction was cooled to rt. The solvent was removed under reduced pressure and the residue was azeotroped three times with toluene to afford the crude stannylene acetal.

The stannylene acetal intermediate was dissolved in THF and DMF (10:1, 30 mL). 2-Nap-Br (582 mg, 2 equiv), CsF (298 mg, 1.5 equiv) and TBAI (45 mg, 10 mol%) were added. The reaction was stirred at rt o/n. The reaction mixture was then filtered through a pad of Celite and concentrated to afford desired 3-O-PMB ether. The crude ether was treated with benzoic chloride in pyridine and purified by column
chromatography to afford 598 mg (81% over 3 steps) of glycoside 59 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.97 (d, $J = 1.4$ Hz, 1H), 7.90 – 7.72 (m, 10H), 7.68 – 7.27 (m, 17H), 5.72 (s, 1H), 5.15 – 4.92 (m, 2H), 4.83 (d, $J = 5.1$ Hz, 2H), 4.64 (d, $J = 9.7$ Hz, 1H), 4.42 (dd, $J = 10.5$, 4.9 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.78 – 3.70 (m, 2H), 3.57 (tdd, $J = 10.9$, 8.5, 3.6 Hz, 2H), 2.90 (d, $J = 2.6$ Hz, 1H).

**Thiophenyl 2-O-benzoyl-3,4-di-O-(2-naphthyl)-β-D-glucopyranoside (60).** Glycoside 59 (1.83 g, 1 equiv) was dissolved in BH$_3$•THF (1 M in THF, 15 mL, 5 equiv) and cooled to 0 °C. Bu$_2$BOTf (1 M in toluene, 3 mL, 1.1 equiv) was added dropwise and the reaction was stirred at 0 °C for 2 hours. The reaction was cooled to −78 °C and quenched with triethylamine (1.5 equiv) and methanol. It was warmed slowly to room temperature. The reaction mixture was concentrated by rotary evaporation to afford the crude 4-O-PMB ether. The residue was dissolved in methanol and concentrated three times. The residue was then purified by column chromatography (20% to 30% EtOAc in hexane) to afford 1.46 g (80%) of 4-O-Nap ether 60 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.01 (dd, $J = 8.4$, 1.4 Hz, 2H), 7.88 – 7.65 (m, 6H), 7.63 – 7.35 (m, 15H), 7.35 – 7.22 (m, 5H), 5.35 (dd, $J = 10.1$, 9.0 Hz, 1H), 5.09 – 4.79 (m, 5H), 3.97 (t, $J = 9.0$ Hz, 2H), 3.81 (t, $J = 9.3$ Hz, 2H), 3.58 (ddd, $J = 9.7$, 4.7, 2.5 Hz, 1H).

**Thiophenyl 2-O-benzoyl-3,4-di-O-(2-naphthyl)-6-O-p-nitrobenzoyl-β-D-glucopyranoside (61).** Alcohol 60 (1.46 g, 1 equiv) and $p$-nitrobenzoyl chloride (778 mg, 1.5 equiv) were dissolved in DCM (30 mL); then catalytic DMAP and triethylamine (800 µL, 2 equiv) were added. The reaction was stirred at rt o/n. The reaction was quenched with sat. aq. NaHCO$_3$ and extracted with DCM. The organic extracts were dried with
sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10–30% EtOAc in hexane) to afford 1.81 g (80%) of donor 56.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.33 – 8.17 (m, 2H), 8.06 (ddd, J = 17.9, 7.7, 1.7 Hz, 4H), 7.89 – 7.81 (m, 2H), 7.75 – 7.52 (m, 10H), 7.39 (ddddd, J = 14.0, 9.4, 5.5, 2.3 Hz, 11H), 7.33 – 7.18 (m, 5H), 7.12 (dd, J = 8.2, 6.6 Hz, 2H), 5.31 (d, J = 7.4 Hz, 3H), 5.08 – 4.78 (m, 6H), 4.67 (dd, J = 12.0, 1.5 Hz, 1H), 4.52 – 4.40 (m, 2H), 4.08 – 3.98 (m, 1H), 3.86 – 3.71 (m, 3H), 3.52 – 3.37 (m, 1H).

2-O-benzoyl-3,4-O-(2-naphthyl)-6-O-p-nitrobenzoyl-β(1,4)-D-glucopyranosyl-(4-(1H,1H,2H,2H-perfluorodecyl)-beznyl)-2-azido-3-O-(2-trimethylsilylthoxy)methyl-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (62). GlcN donor 61 (103 mg, 1 equiv) and GlcA acceptor 51 (240 mg, 1.5 equiv) were carefully azeotroped with toluene, dried on a high vacuum line, and then dissolved in dry DCM (2.5 mL). 4 Å MS (100 mg) were added and the reaction was stirred at room temperature for 30 minutes. NIS (90 mg, 2 equiv) was added and the reaction mixture was cooled to 0 °C. TfOH (1 µL, 0.1 equiv) was added and the reaction was stirred at 0 °C until TLC indicates consumption of donor. Upon completion, the reaction was quenched with diisopropylethylamine, filtered through a pad of Celite, and concentrated. The residue was purified by column chromatography to afford 104 mg (41%) of disaccharide 62 as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.10 – 8.03 (m, 2H), 7.87 (dd, J = 8.9, 1.9 Hz, 2H), 7.80 – 7.53 (m, 17H), 7.51 – 7.11 (m, 27H), 7.03 – 6.95 (m, 2H), 5.34 (t, J = 8.6 Hz, 1H), 5.10 – 4.77 (m, 8H), 4.75 – 4.65 (m, 1H), 4.61 (d, J = 7.2 Hz, 1H), 4.55 (d, J = 2.8 Hz, 2H), 4.48 – 4.36 (m, 3H), 4.02 (dd, J = 12.4, 9.6 Hz, 2H), 3.94 – 3.81 (m, 3H), 3.73 (d, J = 10.7 Hz, 2H),
3.68 – 3.58 (m, 2H), 3.50 – 3.40 (m, 2H), 3.36 (s, 1H), 3.29 (d, J = 9.3 Hz, 1H), 3.18 (dt, 
J = 11.2, 8.1 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.85 – 2.72 (m, 2H), 2.25 (d, J = 19.0 Hz, 
3H), 1.98 – 1.82 (m, 2H), 1.05 (s, 9H), 0.96 – 0.84 (m, 2H), -0.12 (d, J = 1.8 Hz, 9H).
2.7 References


CHAPTER III – SYNTHESIS AND TESTING OF LITHIUM-ION BATTERY ADDITIVES WITH PERFLUOROALKYL CHAINS

3.1 Introduction

3.1.1 Importance of Lithium-Ion Batteries

Rechargeable lithium-ion batteries (LIBs) have quickly become an important energy source and storage medium for electronics in recent years. Current use for lithium ion batteries includes electronics, but target applications for lithium-ion technologies include high-power demand applications, such as transportation. Recent advances in electrode materials chemistry has increase the capacity and power that LIBs are able to deliver in these applications. However a number of challenges must be addressed before LIBs are a viable energy storage solution in high capacity, high power applications. In particular, the ability of a battery to cycle repeatedly with high capacity and discharge rates. As batteries age over many cycles, a number of changes in the internal chemistry occurs which ultimately reduces performance.

LIBs function by shuttling lithium ions from the cathode to the anode for charge storage (Figure 3.1). As current is drawn from the battery, the lithium ions move from the anode back to the cathode. LIB cathodes and anodes are constructed from a lithium mixed metal oxide composite and a graphitic composite respectively; these are physically separated from each other by an ion-permeable polymer membrane and both placed in an
electrolyte solution. The most common electrolytes are simple organic carbonates, such as dimethyl carbonate, ethyl methyl carbonate, or ethylene carbonate. These solvents are compatible with the lithium-ion source, which is typically lithium hexafluorophosphate (LiPF$_6$).

![Electron flow schematic](image)

**Figure 3.1 Schematic of Lithium-ion Battery.**

3.1.2 Challenges in Improving LIB Performance

There are a number of barriers limiting the performance of lithium-ion batteries. An ever-present challenge is increasing the battery life, which is the number of times a battery can be charged and discharged. In addition to reusability, other aspects of LIB performance to be optimized include: energy density, power, durability, safety, and cost. Cell capacity loss occurs primarily at the anode forming a solid-electrolyte interface (SEI), while cell impedance rise occurs primarily due to thin film formation at the cathode surface. Many efforts have been focused on designing more robust electrode
materials, and numerous advances have been made in this regard. However, degradation of LIB performance over many cycle numbers remains an issue. One area that has seen relatively few developments is the electrolyte itself. Organic carbonates are relatively inert to the voltages used in LIBs, but can still decompose at cathode or anode surfaces at high cell potential over multiple cycles. Electrolyte degradation can affect battery performance in various ways, such as decreasing the amount of free lithium ion present in the electrolyte (cell capacity fade), or by decreasing the mobility of lithium ions to migrate between cathode and anode (cell impedance rise).

3.1.3 Additive Approach to Improving LIB Performance

The use of additives in electrolyte formulations is a simple and practical method to enhance the stability and performance of LIB electrodes. Additives have been developed with diverse objectives in mind, including control over SEI formation, stabilization of the cathode structure, stabilizing anions and salts, fire retardants, and overcharge protection. Recent advancements in cathode materials have made cathode protection a priority. In this regard, our collaborators at Argonne National Laboratory have tested numerous additive compounds in their high-performance lithium-ion batteries, but have not observed any performance enhancement using known, commercially-available compounds. This indicates a need for novel additives that can enhance LIB performance by protecting the battery electrodes through controlled SEI formation.
3.1.4 Perfluoroalkyl-Substituted Additives for LIBs

Perfluoroalkyl-modified materials are ideal candidates as additives designed to protect LIB cathodes. First, perfluoroalkyl groups are chemically robust due to the chemical stability of the C–F bond and their low polarizability. This feature allows perfluoroalkyl groups to withstand the high cell potentials found in lithium-ion batteries. Second, perfluoroalkyl groups have unique material and self-assembly properties. Due to their low polarizability, perfluoroalkyl groups are difficult to solvate in most normal organic solvents. For this reason perfluoroalkyl chains tend to self-assemble into supramolecular structures, such as micelles, vesicles or bilayers. The ability of these molecules to self-assemble is an attractive feature for protecting battery electrode surfaces. Ideally, the perfluoroalkyl-modified additives would be sacrificially oxidized at the surface of the metal-oxide cathode at high voltages, and become chemically grafted to the surface. This can initiate the deposition of more perfluoroalkylated compounds onto the cathode surface, resulting in a self-assembled but chemically reactive thin film. The oxidized layer of additive serves as a solvophobic passivating layer that can prevent further oxidation of electrolyte at the cathode surface (Figure 3.2). A similar surface modification can be envisioned at the graphitic anode, if desired.
With the above design in mind (Figure 3.2), we plan to synthesize a number of perfluoroalkyl-functionalized additives. The additives will consist of an electroactive headgroup, which will be oxidized at lower potentials than the carbonate solvent that comprises the electrolyte solution. The headgroup will either directly react with the electrode surface or polymerize on the surface to produce a stable coating. The additives will also feature a perfluoroalkyl group to promote self-assembly into larger structures as well as provide a solvophobic barrier at the electrode surface.

### 3.2 (2-Perfluorooctyl)Ethyl Vinyl Sulfone

(2-Perfluorooctyl)ethyl vinyl sulfone 63 was synthesized in two steps. Photochemical addition of perfluorooctyl iodide to divinyl sulfone was completed using 300 nm irradiation to produce a single PFO chain per molecule of divinyl sulfone. This intermediate, after workup, was dehalogenated using indium hydride generated in situ to afford the desired (2-perfluorooctyl)ethyl vinyl sulfone 63 in 33% yield over 2 steps (Figure 3.3).
(2-perfluorooctyl)ethyl vinyl sulfone 63 was evaluated as an additive in a LIB at 1–2% w/v in “Gen2” electrolyte, which consists of 1.2 M LiPF$_6$ in 7:3 ethylene carbonate:ethyl methyl carbonate. 1 wt% of 63 shows significant degradation of cell cycle performance (Figure 3.4), whereas no detriment or improvement to cell cycle performance (data not shown) occurred when 2 wt% of 63 was used. This was attributed to the reduction of the vinyl sulfone on the LIB anode, preventing the intercalation of lithium ions into the graphitic electrode.
3.3 The Perfluoroalkyl Ethylene Carbonate Series

Perfluoroalkyl-substituted ethylene carbonates (PFA-ECs) were investigated as fluorous analogues of ethylene carbonate, the primary solvent present in lithium-ion batteries. These compounds could easily be prepared from common perfluorinated starting materials, although the presence of the PFA group was not expected to promote oxidative degradation on the LIB cathode. Perfluoroalkyl ethylenes were dihydroxylated using KMnO₄ under biphasic conditions.⁹ These 1,2-diols 64a-d were then treated with triphosgene to afford PFA-ECs 65a-d in good yields (Figure 3.5).¹⁰
PFA-ECs 65a-d were tested as previously described in the “Gen2” electrolyte mixture in LIB coin cells. Discharge capacity versus cycle number data for 65a, 65b, and 65c are shown in Figures 3.6, 3.7, and 3.8 respectively; Perfluorodecyl-EC 65d was insufficiently soluble in “Gen2” electrolyte to allow for accurate measurements. The control experiment with unadulterated “Gen2” electrolyte showed a 14.5% capacity loss over 25 cycles, whereas the capacity losses were 13.2%, 16.3% and 8.9% for 65a, 65b, and 65c respectively, at 0.5 wt% additive loading. Similar trends were also noted for loadings of 1 wt%.
Figure 3.6 Cycle versus discharge capacity, with and without perfluorobutyl-EC (PFB-EC) 65a.

Figure 3.7 Cycle versus discharge capacity, with and without perfluorohexyl-EC (PFH-EC) 65b.
Of the three PFA-EC derivatives tested, only 65c exhibited significant reduction in capacitive loss in the LIB coin cell system. With this promising lead in hand, cell discharge capacity was extended to 200 cycles (Figure 3.9). The comparison between the “Gen2” and 0.5 wt% 65c was striking. The “Gen2” control retains only 27% of its discharge capacity after 200 cycles, as compared to the cell containing 0.5 wt% 65c, which retained 66% of its discharge capacity.
Additionally, 65c exhibited improved performance with respect to impedance in the LIB coin cell system. Prior to cycling, there is no difference in impedance between the control cell and the cell that contained 0.5 wt% 65c (data not shown). However when after 200 cycles, 0.5 wt% 65c produced significantly lower impedance rise relative to the “Gen2” control cell (Figure 3.10).
3.4 Perfluoroctyl-Substituted Thiophenes

Thiophenes are polymerizable under oxidative conditions, and are candidate additives for protecting the cathode of lithium-ion batteries. Thiophene structures polymerize at the cathode to produce a more robust cathode-electrolyte interface, which extends cycling lifetime and reduces cell impedance increase.\textsuperscript{11} Methyl 2-carboxy-3-aminothiophene was oxidized into diazonium tetrafluoroborate salt \textit{66} using amyl nitrite and BF\textsubscript{3}•Et\textsubscript{2}O, then subjected to Heck coupling with perfluoroctyl ethylene and Pd(OAc)\textsubscript{2} to afford fluorous conjugated thiophene \textit{67} in excellent yield. The ester was saponified and decarboxylated under Hunsdiecker conditions\textsuperscript{12} to afford vinyl PFO-substituted thiophene \textit{68} in good yield. The intermediate Heck product was also reduced using palladium on carbon under hydrogen to afford the reduced thiophene ester \textit{69}. 

Figure 3.10 AC impedance spectra, with and without PFO-EC (\textit{65c}), after cell cycling.
Saponification and protodecarboxylation afforded the reduced PFO-functionalized thiophene 70 (Figure 3.11).

![Chemical reactions and structures](image)

Figure 3.11 Synthesis of perfluoroctyl(vinyl) thiophene (68) and perfluoroctyl(ethyl) thiophene (70).

Thiophene derivatives 68 and 70 were tested as electrolyte additives in LIB coin cells as previously described. Compound 68 was shown to have no significant effect on cycle performance at 0.5 wt% or 2 wt% concentrations versus control with no additive (Figure 3.12). Additional half-cell experiments were conducted to determine which electrode was reacting with the additive; in the case, thiophene preferentially reduced at the anode, rather than oxidized at the cathode (data not shown). We attribute this to the susceptibility of the vinylene linkage in 68 to electrochemical reduction under charge/discharge conditions.
We then tested PFO-ethylene thiophene \textit{70} as an electroactive additive under similar conditions. Again, there was no significant improvement in performance at either 0.5 or 1 wt\% versus unadulterated electrolyte (Figure 3.13). It is worth noting that neither \textit{68} nor \textit{70} caused any detriment to the battery system, \textit{68} or \textit{70} which may be a useful factor when modifying other battery properties.
Figure 3.13 Cycle versus discharge capacity, with and without 3-(PFO-ethylene) thiophene (70).

3.5 \( p \)-(Perfluorooctylphenyl) Diphenylphosphine Oxide

Phosphines and phosphine oxides are also candidates as LIB additives. Phosphines are more prone to oxidation than the carbonate electrolyte solutions and thus are sacrificially oxidized at the cathode as opposed to the carbonate electrolyte. A layer may result preventing further electrolyte decomposition products from depositing on the cathode surface.\(^{13}\) Perfluorooctyl iodide was coupled with \( p \)-(iodophenyl)diphenylphosphine oxide to PFO-substituted triphenylphosphine oxide 71 in good yield (Figure 3.14). Compound 71 was tested as an electrolyte additive in a LIB coin cell as previously described, but did not result in improved cycling performance (data not shown).
3.6 Boronic Esters of 2-(Perfluoroalkyl)ethylene Glycols

With successful tests with the PFA-EC derivatives in hand, we sought to explore other structures utilizing the PFA ethylene glycol moiety. Perfluorodecyl ethylene glycol \(62d\) was condensed with benzene boronic acid to afford phenylboronic ester \(72\) in good yield (Figure 3.14). Phenylboronic ester \(72\) was tested in coin cells as previously described, but solubility in the “Gen2” electrolyte was poor, due to the perfluorodecyl group present. Shorter perfluoroalkyl derivatives may be synthesized in the future that would allow the study of their phenyl boronic esters as electrolyte additives.

3.7 Conclusions

A number of novel molecules were synthesized with perfluoroalkyl tails and their performance as LIB additives were tested. Many molecules tested did not have beneficial effects on LIB performance, or protect the cathode, and some were preferentially reactive
at the anode. Perfluorooctyl ethylene carbonate (PFO-EC) 65c was identified early as a promising additive in LIB performance testing, and a series of PFA-EC derivatives was prepared to probe the role of perfluoroalkyl chain length. However, performance evaluation of derivatives with longer or shorter perfluoroalkyl chains showed no benefit. Investigations of other PFA derivatives with different headgroups were also initiated, some of which merit further study.

3.8 General Methods and Experimentals

All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents were freshly distilled prior to use. $^{1}H$ NMR spectra were recorded at 300 or 400 MHz; $^{13}C$ NMR spectra were recorded at 75 or 100 MHz. $^{19}F$ NMR spectra were recorded at 282 MHz. $^{31}P$ NMR spectra were recorded at 121 MHz. Chemical shifts were referenced to the solvent used ($\delta$ 7.27 and 77.00 for CDCl$_3$, $\delta$ 3.31 and 49.15 for CD$_3$OD, and $\delta$ 4.80 in D$_2$O). Mass spectra were acquired using either a Hewlett-Packard 5989B or a Finnigan 40000 mass spectrometer.

(2-Perfluorooctyl)ethyl vinyl sulfone (63). Divinyl sulfone (1 eq, 240 mg, 2.0 mmol) and perfluoroctyl iodide (1.1 eq, 600 µL, 2.3 mmol) were dissolved in 5 mL of DCM in a quartz reaction tube. The reaction mixture was irradiated with 300 nm UV light for 6 hours. The reaction mixture was concentrated by rotary evaporation to afford an off-white solid and was used without further purification in the next step.

InCl$_3$ (6 mg, 20 mol%) and triethylsilane (100 µL, 4 eq) were dissolved in THF and stirred at rt for 10 minutes. The crude PFO intermediate iodide was added to the THF
solution, followed by the addition of triethylborane (50 µL, 1M in hexane, 20 mol%). The reaction mixture was stirred at rt for 4 hours until TLC determined reaction complete. The reaction was quenched with water and extracted with diethyl ether. Extracts were dried over sodium sulfate and concentrated by rotary evaporation. The crude solid was dissolved in refluxing hexane and allowed to crash out at rt to afford pure (2-Perfluoroocyt)ethyl vinyl sulfone \(63\) as a white solid (534 mg, 33% over 2 steps). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.01 (dd, \(J = 16.6, 9.9\) Hz, 1H), 6.43 (d, \(J = 16.6\) Hz, 1H), 6.36 (d, \(J = 9.9\) Hz, 1H), 3.52 – 3.40 (m, 2H), 2.81 – 2.60 (m, 2H).

2-((Perfluoroocyt)ethylene glycol (64c). Cetyltrimethylammonium bromide (350 mg, 0.96 mmol) and \(1H,1H,2H\)-perfluorodecene (1.05 mL, 3.95 mmol) were dissolved in dichloromethane (50 mL). A 6.8% aqueous solution of potassium permanganate (100 mL) was added, and the reaction was stirred vigorously for 3 hours. The biphasic mixture was filtered through a pad of Celite and separated; the organic phase was washed with brine, dried over sodium sulfate, and concentrated to dryness. The residue was redissolved in acetone and passed through a short silica plug, then concentrated to dryness to afford glycol \(64c\) as a white solid (0.94 g, 50%). \(^1\)H NMR (300 MHz, acetone-\(d_6\)): \(\delta\) 4.28 (m, 1H), 4.02–3.67 (m, 2H). \(^{13}\)C NMR (75 MHz, acetone-\(d_6\)): \(\delta\) 122.7-108.3 (8C), 71.49 (1C), 61.09 (1C).

2-((Perfluorobutyl)ethylene glycol (64a). (Perfluorobutyl)ethylene glycol was prepared in the same manner as above in 70% yield. \(^1\)H NMR (300 MHz, acetone-\(d_6\)) \(\delta\) 5.27 (s, 2H), 4.45 – 4.12 (m, 1H), 4.01 – 3.63 (m, 2H).
2-(Perfluorohexyl)ethylene glycol (64b). (Perfluorohexyl)ethylene glycol was prepared in the same manner as above in 66% yield. $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 5.96 (s, 1H), 4.95 (s, 1H), 4.31 (m, 1H), 3.96 – 3.71 (m, 2H).

2-(Perfluorodecyl)ethylene glycol (64d). (Perfluorodecyl)ethylene glycol was prepared in the same manner as above in 46% yield. $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 4.38 – 4.19 (m, 1H), 3.93 – 3.70 (m, 2H).

2-(Perfluoroctyl)ethylene carbonate (65c). Diol 64c (940 mg, 1.96 mmol) was dissolved in tetrahydrofuran (20 mL) and stirred at 0 °C, then treated sequentially with triethylamine (600 µL, 4.31 mmol) and triphosgene (210 mg, 0.71 mmol). The reaction mixture was warmed to rt over 2 hours with stirring, and then neutralized with saturated aqueous NaHCO$_3$. The product was extracted with diethyl ether, dried over sodium sulfate and concentrated, then recrystallized from chloroform to afford 2-(Perfluoroctyl)ethylene carbonate 65c a white solid (785 mg, 79%). $^1$H NMR (300 MHz, acetone-$d_6$): $\delta$ 5.74 (m, 1H), 5.16 – 4.75 (m, 2H). $^{13}$C NMR (101 MHz, acetone-$d_6$) $\delta$ 153.66 (1C), 122.7-108.3 (8C), 72.01 (1C), 64.41 (1C).

2-(Perfluorobutyl)ethylene carbonate (65a). 2-(Perfluorobutyl)ethylene carbonate 65a was prepared in the same manner as above in 48% yield (560 mg). $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 5.82-5.65 (m, 1H), 5.00 (dd, $J = 9.7$, 8.7 Hz, 1H), 4.88 (dd, $J = 9.7$, 4.7 Hz, 1H). $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 153.81 (1C), 122.8-108.1 (4C), 72.06 (1C), 64.53 (1C).
2-(Perfluorohexyl)ethylene carbonate (65b). 2-(Perfluorobutyl)ethylene carbonate 65b was prepared in the same manner as above in 62% yield (630 mg). $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 5.83 – 5.65 (m, 1H), 4.99 (dd, $J = 9.6$, 8.8 Hz, 1H), 4.87 (dd, $J = 9.6$, 4.7, 1H). $^{13}$C NMR (101 MHz, acetone-$d_6$) $\delta$ 153.64 (1C), 122.6-108.4 (6C), 72.01 (1C), 64.40 (1C).

2-(Perfluorodecyl)ethylene carbonate (65d). 2-(Perfluorobutyl)ethylene carbonate 65d was prepared in the same manner as above in 82% yield (1.26 g). $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 5.73 (m, 1H), 4.99 (t, $J = 9.2$ Hz, 1H), 4.87 (dd, $J = 9.8$, 4.7 Hz, 1H). $^{13}$C NMR (101 MHz, acetone-$d_6$) $\delta$ 153.65 (1C), 122.9-108.3 (10C), 72.00 (1C), 64.40 (1C).

Methyl 1-carboxylate-2-(perfluorooctyl)vinyl thiophene (67). Methyl 3-amino-2-carboxythiophene (622 mg, 4.0 mmol, 1 eq) was dissolved in 20 mL THF and cooled to –40 °C. Amyl nitrite (1.0 mL, 8.0 mmol, 2 eq) and BF$_3$-Et$_2$O (1.5 mL, 12.0 mmol, 3 eq) were added sequentially. The reaction was allowed to warm to rt. The product was precipitated out of solution by adding diethyl ether (20 mL) and filtered to obtain diazonium salt 66 as a white solid in quantitative yield (1022 mg). This solid was used without further purification.

The diazonium intermediate (242 mg, 0.95 mmol) was suspended in 10 mL methanol and degassed under a stream of argon. Perfluorooctylethylene (300 µL, 1.1 mmol, 1.1 eq) and Pd(OAc)$_2$ (40 mg, 0.19 mmol, 20 mol%) were added. The reaction was carefully heated to 50 °C, which generated copious amounts of gas. When effervescence ceased, the reaction mixture was cooled and concentrated. Then was
passed through a silica gel plug to afford PFO-substituted thiophene 67 as a white solid in 80% yield (460 mg). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.13 (dt, \(J = 16.3, 2.4\) Hz, 1H), 7.50 (dd, \(J = 5.3, 0.7\) Hz, 1H), 7.33 (d, \(J = 5.3\) Hz, 1H), 6.33 – 6.05 (m, 1H), 3.92 (s, 3H).

**2-(Perfluorooctyl)vinyl thiophene (68).** Methyl 1-carboxylate-2-(perfluorooctyl)vinyl thiophene 67 (460 mg, 0.79 mmol, 1 eq) was dissolved in 9:1 ethanol:water (10 mL) and treated with lithium hydroxide (40 mg, 2 eq). The reaction mixture was heated for 4 hours at reflux, then cooled to rt. Extracted with diethyl ether and concentrated to afford 427 mg (95% yield) of the free carboxylic acid, which was used without purification.

Free carboxylic acid prepared above (427 mg, 0.90 mmol, 1 eq) was dissolved in DMSO and treated with 10% Ag\(_2\)CO\(_3\) (25 mg) and 5% HOAc (3 \(\mu\)L). The reaction mixture was heated at 120 °C for 2.5 hours. The reaction was extracted with diethyl ether, washed with brine three times, dried over sodium sulfate and concentrated by rotary evaporation to afford PFO-substituted thiophene 68 as a colorless oil in 89% yield (350 mg). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.57 – 7.07 (m, 4H), 6.05 (dt, \(J = 16.0, 12.2\) Hz, 1H).

**Methyl 1-carboxylate-2-(perfluorooctyl)ethyl thiophene (69).** Methyl 1-carboxylate-2-(perfluorooctyl)vinyl thiophene 67 (1860 mg, 3.17 mmol, 1 eq) was dissolved in 1:1 methanol:ethyl acetate (25 mL) and treated with Pd/C (50 mg) under a hydrogen atmosphere at rt o/n. The reaction mixture was filtered through Celite to remove Pd/C and concentrated to afford reduced thiophene 69 as a colorless oil in 98% yield (1819
mg). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.47 (d, J = 5.2 Hz, 1H), 6.98 (d, J = 5.1 Hz, 1H), 3.89 (s, 3H), 3.37 – 3.20 (m, 2H), 2.43 (m, 2H).

2-(Perfluorooctyl)ethyl thiophene (70). 2-(perfluorooctyl)ethyl thiophene was prepared in the same manner as 68. Thiophene 70 was obtained as a pale yellow liquid in 70% yield over two steps (1.12 grams). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31 (ddd, J = 4.7, 3.0, 1.1 Hz, 1H), 7.03 (dt, J = 2.7, 1.2 Hz, 1H), 6.97 (dd, J = 5.0, 1.3 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.40 (ddt, J = 26.6, 17.9, 8.5 Hz, 2H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -82.31 (t, J = 10.1 Hz), -116.34 (m), -122.79 – -123.85 (m), -124.30 (d, J = 19.8 Hz), -124.71 – -125.52 (m), -127.16 – -128.08 (m).

Perfluorooctyl(phenyl) diphenylphosphine oxide (71). 4-(iodophenyl)diphenylphosphine oxide (808 mg, 2.0 mmol), which was prepared according to literature procedure$^{14}$, was then dissolved in DMSO (20 mL). Cu dust (545 mg, 10 mmol, 5 eq) and perfluorooctyl iodide (900 µL, 3.5 mmol, 1.5 eq) were added. The reaction mixture was degassed by bubbling argon for 10 minutes, then heated at 90 °C for 12 hours, then the reaction was cooled and filtered through Celite, then was diluted with 100 mL of diethyl ether and washed with brine (3x 100 mL) to remove DMSO. The organic extracts were dried over sodium sulfate, filtered, concentrated by rotary evaporation, then was purified by column chromatography using 0–10% of ethyl acetate in hexane to afford PFO-substituted phosphine oxide 71 as a white solid in 51% yield (710 mg). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.83 (dd, J = 11.4, 7.9 Hz, 2H), 7.76 – 7.40 (m, 12H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.01, 136.67, 132.27, 132.14, 131.96, 131.83, 130.71, 128.69, 128.52,
126.92, 126.84, 126.76, 120–105 (8C). $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -82.50, -112.86, -122.87, -123.23, -123.55, -124.39, -127.81. $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 29.06.

**Perfluorodecyl ethylene glycol benzene boronic ester (72).** 2-Perfluorodecyl ethylene glycol 64d (1.11g, 1.83 mmol) was dissolved in trifluorotoluene (20 mL) and treated with benzene boronic acid (228 mg, 1.88 mmol, 1.03 eq). The reaction mixture was heated at 90 °C for 12 hours. The reaction was concentrated by rotary evaporation and was subjected to silica gel chromatography using 20–30% ethyl acetate in hexane to afford boronic ester 72 as a white solid in 85% yield (1.09 g). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.90 – 7.72 (m, 2H), 7.60 – 7.47 (m, 1H), 7.47 – 7.35 (m, 2H), 5.07 (m, 1H), 4.67 – 4.48 (m, 2H).
3.9 References


VITA
VITA

Matt was born on December 24th, 1981 in Bloomington, Illinois. Growing up on a farm and surrounded by the natural world, Matt has always been interested in science. He graduated from University High School (Normal, Illinois) in 2000. He attended the University of Illinois at Urbana–Champaign from 2000 to 2005 where he obtained a B.S. in chemistry. Shortly after graduation, he decided that yet more studies in chemistry were necessary, and enrolled at Purdue University in 2006. He joined Professor Alexander Wei’s research group shortly after. In Dr. Wei’s group, he worked on a variety of projects, but focused on the synthesis of heparan sulfate-like carbohydrates via fluorous methodology and synthesis of fluorous molecules for novel application in lithium ion batteries. He defended his Ph.D. work in November 2013.
PUBLICATION
Perfluoroalkyl-substituted ethylene carbonates: Novel electrolyte additives for high-voltage lithium-ion batteries

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Highlights
• A new family of perfluoroalkyl-substituted electrolyte additives is synthesized.
• Perfluorooctyl-substituted ethylene carbonate (PFO-EC) shows best improvements.
• PFO-EC improves capacity retention and lowers impedance rise in high voltage LIBs.
• PFO-EC shows beneficial effects on both positive and negative electrodes.
• LSV, XPS, and Raman spectroscopy are used to obtain diagnostic data.

Abstract
A new family of polyfluoroalkyl-substituted ethylene carbonates is synthesized and tested as additives in lithium-ion cells containing EC:EMC+LiPF₆-based electrolyte. The influence of these compounds is investigated in Li₁₁₂Ni₀₁₅Mn₀₅₅Co₀₁₀O₂/graphite cells via a combination of galvanostatic cycling and electrochemical impedance spectroscopy (EIS) tests. Among the four additives studied in this work (4-(trifluoromethyl)-1,3-dioxolan-2-one (TFM-EC), 4-(perfluorobutyl)-1,3-dioxolan-2-one (PFB-EC), 4-(perfluorohexyl)-1,3-dioxolan-2-one (PFH-EC), and 4-(perfluoroctyl)-1,3-dioxolan-2-one (PFO-EC)), small amounts (0.5 wt%) of PFO-EC is found to be most effective in lessening cell performance degradation during extended cycling. Linear sweep voltammetry (LSV), X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy are used to further characterize the effects of PFO-EC on the positive and negative electrodes. LSV data from the electrolyte, and XPS analyses of electrodes harvested after cycling, suggest that PFO-EC is oxidized on the cathode forming surface films that slow electrode/cell impedance rise. Differential capacity (dQ/dV) plots from graphite/Li cells suggest that PFO-EC is involved in solid electrolyte interphase (SEI) formation. Raman data from anodes after cycling suggest that structural disordering of graphite is reduced by the addition of PFO-EC, which may explain the improved cell capacity retention.

1. Introduction
High-capacity lithium- and manganese-rich metal oxides are gaining increased attention because of their ability to deliver high rechargeable capacities; when cycled between 2.0 and 4.7 V vs. Li, a rechargeable capacity of 270 mAh-g⁻¹ can be routinely...
obtained [1]. Hence lithium-ion cells containing the LiMnO$_2$-stabilized Li$_2$MnO$_3$ (M = Mn, Ni, Co) positive electrodes, graphite negative electrodes and EC:EMC (3:7 by wt.) + 1.2 M LiPF$_6$-based electrolyte (henceforth referred as Gen2 electrolyte) can be designed to meet the target cell specific capacity of 300 Wh kg$^{-1}$ for transportation applications [2,3]. However, the target battery cycle life of up to 1000 charge–discharge cycles at 80% depth of discharge (DOD) can only be achieved through new electrolyte formulations because these cells show significant performance degradation on extended cycling [4]. Extensive diagnostic studies indicate that cell impedance rise mainly arises at the positive electrode, and cell capacity fade mainly results from lithium trapping in the solid electrolyte interphase (SEI) at the negative electrode [4–6]. During electrochemical aging, both electrodes undergo a cycle of surface film formation, decomposition, dissolution, and redeposition; this process results in the continuous consumption of lithium ions, thereby reducing cell capacity and often increasing cell impedance [7–9].

Electrolyte additives are known to be an effective and economic approach to improving the stability of electrode surface films [10]. In the past two decades, many organic and inorganic compounds have been identified as effective electrolyte additives: examples include vinylene carbonate (VC) [11,12], ethylene sulfite (ES) [13], vinyl ethylene carbonate (VEC) [14,15], and fluoroethylene carbonate (FEC) [16]. In recent years, with the emergence of many high-voltage cathode materials, the anodic stability of common electrolytes is recognized as the main bottleneck limiting the calendar- and cycle-life of high-energy lithium-ion cells [17]. Therefore, more attention has been devoted to improving stability of the cathode–electrolyte interface [6,18–25]. As part of DOE’s Advanced Battery Research (ABR) program, we have been examining ways to mitigate performance degradation of cells containing Li$_2$MnO$_3$:LiMnO$_2$-0.5Li$_x$Mn$_{0.5}$Co$_{0.5}$O$_2$-0.5Li$_{0.5}$Mn$_{0.5}$Ni$_{0.5}$O$_2$ (LMP-NMC) that are cycled at voltages beyond 4.5 V versus Li. Initial studies indicate that common electrolyte additives such as VC, VEC, and FEC are not effective at enhancing long-term cycling performance of these cells, i.e. stable electrode passivation could not be achieved with traditional SEI-forming additives. This observation underscores the need for new electrolyte additives that effectively form stable electrode passivation films in high-energy and high-voltage lithium-ion cells.

Polyfluoroalkyl (PFA) compounds are well known for their high chemical stabilities, and exhibit both hydrophobic and lipophobic behaviors. Upon dispersing in organic solvents, lipophobic PFAs tend to aggregate and form micelles in solution [26]. These types of compounds have been extensively used as fluorosurfactants, and are especially valuable as additives in stain repellents [27]. In light of these facts, we envision that compounds containing PFAs could serve as a new type of electrolyte additive, forming double-layered passivating layers that reduce both electrode surface degradation and electrolyte decomposition. In our design, the PFA additive has two components: (i) a reactive headgroup for attachment onto electrode surfaces via either reductive or oxidative decomposition, so that it becomes an integral part of the surface layer (inner layer); (ii) a polyfluoroalkyl chain that self-assembles on this inner layer as a lipophobic outer layer (outer layer) that is highly stable and impermeable to the electrolyte solvent. A schematic representation of this idea is shown in Scheme 1.

To explore this novel idea, we synthesized a series of PFA-substituted ethylene carbonates (PFO-EC) and studied them as electrolyte additives in our lithium-ion cells. Cell performance was characterized using a combination of galvanostatic cycling and electrochemical impedance spectroscopy (EIS) techniques, and supplemented by linear sweep voltammetry (LSV), X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy data. Of the various PFA-EC compounds studied, we determined that perfluoroctyl-substituted ethylene carbonate (PFO-EC) most significantly improves the long-term cycling performance of our cells.

2. Experimental

2.1. Materials and synthesis

All chemicals used in the synthesis of polyfluoroalkyl compounds were purchased from commercial suppliers and used without further purification. 4-(trifluoromethyl)-2,3-dioxolan-2-one (TFM-EC) was purchased from Synquest Laboratories, Inc. (United States); all other polyfluoroalkyl-ECs were synthesized by a two-step reaction sequence (Scheme 2). Newly synthesized compounds were characterized by $^1$H, $^{13}$C, and $^{19}$F NMR spectroscopy, using a 300- or 400-MHz spectrometer. All chemical shift values (δ) are reported in ppm, referenced relative to TMS ($^1$H and $^{13}$C) or CFCl$_3$ ($^{19}$F).

Scheme 1. Schematic representation illustrating the formation of double-layer passivation films via (i) decomposition of the headgroup on electrode surface forming an inner layer; (ii) self-assembly of tails on these inner layers forming a lipophobic outer layer.

Scheme 2. Synthesis of polyfluoroalkyl (PFA)-substituted ethylene carbonates.
The NMR characterization data for these two compounds are as follows:

- Dissolved in tetrahydrofuran (20 mL) and stirred at 0°C for 3 h, then filtered through a pad of Celite and separated. The organic phase was washed with brine, dried over sodium sulfate, and concentrated. The residue was redissolved in acetone and passed through a silica gel plug, then concentrated to dryness to obtain 1H,1H,2H-perfluorodecane-1,2-diol as a white solid (0.94 g, 50%).
- NMR characterization data for this compound are as follows: 1H NMR (400 MHz, acetone-d6): δ 4.28 (m, 1H), 4.62−4.67 (m, 2H). 13C NMR (100 MHz, acetone-d6): δ 127.7−108.3 (m), 71.40 (s), J = 22.6 Hz, 61.1 (s).

1H,1H,2H-perfluorodecane-1,2-diol (940 mg, 1.96 mmol) was dissolved in tetrahydrofuran (20 mL) and stirred at 0°C, then treated sequentially with triethylamine (600 μL, 4.31 mmol) and triphenylphosphine (210 mg, 0.71 mmol). The reaction mixture was warmed to room temperature over 2 h with stirring, then neutralized with saturated aqueous NaHCO3. The product was extracted with diethyl ether, dried over sodium sulfate and concentrated, then recrystallized from chloroform to obtain PFO-EC as a white solid (785 mg, 79%).

The NMR characterization data for this compound are as follows: 1H NMR (400 MHz, acetone-d6): δ 4.28 (m, 1H), 4.62−4.67 (m, 2H). 13C NMR (100 MHz, acetone-d6): δ 153.6 (s), 122.7−108.3 (m), 71.40 (s), J = 22.6 Hz, 61.1 (s).

In a typical synthesis, cetyltrimethylammonium bromide (350 mg, 0.96 mmol) and 1H,1H,2H-perfluorodecene (1.05 mL, 3.95 mmol) were dissolved in dichloromethane (50 mL), then treated with a 6.88 aqueous solution of potassium permanganate (100 mL). The biphasic reaction mixture was stirred vigorously for 3 h, then filtered through a pad of Celite and separated. The organic phase was washed with brine, dried over sodium sulfate, and concentrated. The residue was redissolved in acetone and passed through a silica gel plug, then concentrated to dryness to obtain 1H,1H,2H-perfluorodecane-1,2-diol as a white solid (0.94 g, 50%). The NMR characterization data for this compound are as follows: 1H NMR (400 MHz, acetone-d6): δ 4.28 (m, 1H), 4.62−4.67 (m, 2H). 13C NMR (100 MHz, acetone-d6): δ 127.7−108.3 (m), 71.40 (s), J = 22.6 Hz, 61.1 (s).

Perfluorobutyl (PFB)- and perfluoroethyl (PFH)-substituted ECs were synthesized in a similar fashion from 1H,1H,2H-perfluorohexene and 1-octene respectively, in 48% and 62% overall yield.

The NMR characterization data for these two compounds are as follows: 1H NMR (300 MHz, acetone-d6): δ 5.82−5.95 (m, 1H), 5.00 (dd, 1H, J = 8.7, 9.7 Hz), 4.88 (dd, 1H, J = 4.7, 9.7 Hz). 13C NMR (75 MHz, acetone-d6): δ 153.81 (s), 122.8−108.1 (m), 72.11 (dd, J = 22.3, 33.6 Hz), 64.5 (s). PFH-EC: 1H NMR (400 MHz, acetone-d6): δ 5.82−5.95 (m, 1H), 4.99 (dd, 1H, J = 8.8, 9.7 Hz), 4.87 (dd, 1H, J = 4.7, 9.6 Hz). 13C NMR (100 MHz, acetone-d6): δ 153.64 (s), 122.6−108.4 (m), 72.0 (dd, J = 22.3, 33.7 Hz), 64.4 (s).

### Table 1

<table>
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<tr>
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<th>Discharge capacity (mAh g(^{-1}))</th>
<th>Capacity fade (mAh g(^{-1}) per cycle)</th>
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<tr>
<td>Initial</td>
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<td>Gen2</td>
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<tr>
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<td>PFO-EC</td>
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</tr>
<tr>
<td></td>
<td>1 wt%</td>
<td>263.9</td>
</tr>
</tbody>
</table>

* Cells were cycled between 2.2 and 4.6 V at 30°C; the 15 mAh g\(^{-1}\) current cycle data provide a good measure of "true capacity," as a low current minimizes ohmic polarization effects in capacity–voltage profiles.

The electrochemical anodic stability of electrolytes is examined by linear sweep voltammetry (LSV) using a three-electrode system. Platinum is used as the working electrode, and lithium metal as the counter and reference electrodes. LSV data are obtained at room temperature (23°C) using a scan rate of 20 mV s\(^{-1}\) from the open circuit voltage (OCV) (ca. 3 V) to 5.5 V. The reduction behavior of electrolytes is investigated in graphite//Li coin cells. The onset potential of the reduction reaction, determined from the differential capacity curve (dQ/dV vs. V), is defined as the reduction potential.

Electrochemical cycling experiments are conducted in 2032-type coin cells, which are galvanostatically cycled at a constant temperature of 30°C. The electrodes are weighed on an analytical balance (Mettler Toledo, XS105; 0.1 mg resolution) to confirm the active material loading. Formation cycling of full cells is conducted using a two-step protocol: three cycles between 2.2 and 4.1 V to enable complete wetting of the electrochemically active surfaces, followed by two cycles between 2.2 and 4.6 V to "activate" the oxide material; a 0.16 mA (~15 mA) current is used in both steps. Extended cycling in the 2.2−4.6 V voltage range is conducted with a higher current (0.8 mA, ~C/10 rate) current is used in both steps. Extended cycling in the 2.2−4.6 V voltage range is conducted with a higher current (0.8 mA, ~C/10 rate) current is used in both steps.

Electrochemical cycling results are obtained periodically with an EG&G 273A potentiostat.
and a Solartron SI1260 frequency response analyzer controlled by ZPlot measurement software. The cells are charged to 3.75 V and held for 4 h before data are collected in the potentiostatic mode, at 30 °C in the 100 kHz to 10 mHz frequency range, with a 10 mV perturbation around 3.75 V [28].

After the extended cycling, cells are discharged to, and held at, 2 V for 24 h before disassembly in an Ar-atmosphere glove box. The harvested electrodes are then examined by various electrochemical and physicochemical characterization tests. X-ray photoelectron spectroscopy (XPS) spectra on positive electrode samples are obtained with a Kratos Axis Ultra X-ray photoelectron spectrometer under ultrahigh vacuum (10⁻⁹ Torr) conditions and with monochromatic Al Kα (1486.6 eV) radiation as the primary excitation source. Survey spectra are collected at a constant pass energy of 160 eV from a ~1.0 mm² area of the sample. High-resolution spectra of the C1s, O1s, F1s, Li1s, P2p, and Mn2p core levels are performed using the Shirley background correction and Gaussian–Lorentzian curve synthesis. The energy scale is adjusted based on the graphite peak in the C1s spectrum at 284.5 eV. Raman spectra on negative electrode samples were obtained on a Renishaw InVia Raman microscope using a 10-mW He–Ne laser (632 nm excitation). The power of the laser beam is adjusted to 1 mW at the sample. The acquired data are from a depth of ~1 μm from the electrode surface. The harvested electrodes are thoroughly rinsed in DMC and dried in the glove box prior to Raman measurements; this rinsing minimizes background fluorescence from electrolyte residue and electrode surface films.

3. Results and discussion

3.1. Cycling performance of Li1.2Ni1.5Mn0.5Co0.5O2/graphite full cells

During our cycling tests, cell to cell variations are always observed. These variations arise from various factors that include (i) small differences in active material weight between similar electrodes, (ii) small differences in the glove box environment when assembling the cells, (iii) differing amount of impurities in the electrolytes, additives, etc. However, the overall data trends observed across multiple cells are consistent. Therefore, only representative data and trends are reported here.

Table 1 summarizes the cycling performance of Li1.2Ni1.5Mn0.5Co0.5O2/graphite full cells with various PFA-substituted ethylene carbonates (the corresponding capacity vs. cycle number plots can be found in the Supporting Information). No obvious correlation is observed between cell cycling performance and PFA chain length. After 25 cycles, the capacity fade trends are as follows: PFO-EC > Gen2 > PFH-EC > TFM-EC > PFH-EC. That is, relative to the baseline electrolyte, cells with the PFO-EC and PFH-EC additives show the best and worst capacity retention, respectively. Cell capacity retention shows a small but consistent correlation with the additive concentrations. TFM-EC cells with 1 wt% additive perform slightly better than those with 0.5 wt% additive, but cells with 0.5 wt% PFB-EC, PFH-EC and PFO-EC perform somewhat better than those with 1 wt% additive. Additional cells containing 0.5 wt% of each additive were tested to 50 cycles; the capacity fade data shown in Fig. 1 are consistent with the trend reported above.

AC impedance data of Li1.2Ni1.5Mn0.5Co0.5O2/graphite full cells, without and with 0.5 wt% of each additive in the baseline electrolytes, are shown in Figs. 2a–2e. Fig. 2a shows the AC impedance data of Gen2 electrolyte. After 50 cycles, the Gen2 electrolyte data are consistent with the trend reported above. The AC impedance data of Gen2 electrolyte containing 0.1, 0.5, and 2 wt% PFO-EC are shown in Fig. 2b. Low current (15 mA g⁻¹) cycles produce and follow the rapid (75 mA g⁻¹) aging cycles.
electrolyte, are shown in Fig. 2. The data for various cells are very similar after the initial formation cycling. After 50 cycles, however, cell impedances are significantly different and show the following trend: TFM-EC > PFH-EC > PFB-EC > Gen2 > PFO-EC. That is, cells with 0.5 wt% TFM-EC and 0.5 wt% PFO-EC show the highest and lowest impedances, respectively.

Of all the additives tested, cells with PFO-EC provided the best performance, which we attribute to a more solvophobic barrier and better protection of the electrode surfaces. In fact, PFO-EC is the least soluble in the Gen2 electrolyte; the maximum additive

![Fig. 4. Capacity–voltage plots for full cells containing the Gen2 electrolyte and Gen2 + 0.5 wt% PFO-EC electrolyte. The data were acquired with a 15 mA g\(^{-1}\) current in the 2.2–4.6 V voltage window at 30 °C. The initial cycle data are similar for cells with and without the additive.](image)

![Fig. 5. AC impedance spectra of Li\(_{1.2}\)Ni\(_{0.15}\)Mn\(_{0.55}\)Co\(_{0.1}\)O\(_2\)//graphite full cells, with and without 0.5 wt% PFO-EC, after (a) formation cycles, (b) 200 cycles at 30 °C.](image)

![Fig. 6. Oxidation behavior of Gen2 electrolyte (1.2 M LiPF\(_6\) in 3:7 EC:EMC by wt.), with and without PFO-EC, determined by linear sweep voltammetry (LSV) at a Pt working electrode. The inset contains an expanded view of the data.](image)

![Fig. 7. Differential capacity plots from first cycle lithiation data of graphite/Li cells in Gen2 electrolyte with and without PFO-EC. (a) The X-axis voltage range is from 2 to 0.3 V, which highlights electrolyte reduction processes; (b) the X-axis voltage range is from 0.3 to 0 V, which shows the main graphite lithiation peaks.](image)
loading is ca. 2 wt%, whereas loadings of PFH-EC, PFB-EC and TFM-EC could be as high as 5 wt%. The lower solubility of PFO-EC suggests that its decomposition products may also be less soluble in the electrolyte, which would lend greater stability to the electrode surface films. In contrast, electrode surface films arising from PFH-EC, PFB-EC and TFM-EC are less stable (or more soluble), and hence less beneficial to cell performance.

It should be noted that variation in molecular weights of the PFA-EC additives give rise to large differences in molar ratios for a given wt.% loading; for example, the molar equivalents of PFO-EC, PFH-EC, PFB-EC, and TFM-EC are 1.00, 1.25, 1.65, and 3.25, respectively. The improved capacity retention of TFM-EC cells might thus relate to an effectively higher molarity; previous work has shown that TFM-EC forms an effective SEI on a graphite anode [29]. Indeed, when the concentration of TFM-EC is reduced to 0.25 wt% (a closer molar ratio to 0.5 wt% PFO-EC), a faster cell capacity fade is observed (data not shown).

A systematic study was further conducted to determine the concentration of PFO-EC that provide the best performance. Fig. 3 shows that Li$_{1.2}$Ni$_{0.15}$Mn$_{0.55}$Co$_{0.1}$O$_2$//graphite full cells with 0.5 wt % PFO-EC provide the best capacity retention. Cells with 2 wt% PFO-EC show a faster capacity fade, whereas performance of cells with 0.1 wt% PFO-EC is similar to that of the baseline cell. After 200 cycles, the discharge capacity of cells with 0.5 wt% PFO-EC is 172 mAh-g$^{-1}$, which is 66% of its initial discharge capacity (260 mAh-g$^{-1}$). In contrast, the discharge capacity of the baseline (Gen2 only) cells is 70 mAh-g$^{-1}$, which is 27% of its initial discharge capacity (258 mAh-g$^{-1}$). The enhanced capacity retention resulting from the additive is also clearly seen in Fig. 4, which contains capacity-electrode data from the full cells. The PFO-EC additive is also effective at inhibiting cell impedance rise during long-term cycling.

![Fig. 3](image-url)

**Fig. 3.** LSV plots for a Pt electrode in Gen2 electrolyte, with and without PFO-EC. For the baseline electrolyte, accelerated current increase is seen only at voltages greater than 4.8 V, whereas the PFO-EC bearing electrolyte shows an oxidation current increase starting near ~4.3 V. The higher oxidation current suggests that the PFO-EC has a lower oxidation potential than Gen2 electrolyte and could be sacrificially oxidized on the positive electrode.

Differential capacity (dQ/dV) plots for the first lithiation cycle of graphite//Li cells were obtained to study electrolyte reduction behavior, without or with 0.5 wt% PFO-EC in the electrolyte (Fig. 7). The dQ/dV plots were quite similar regardless of PFO-EC, and additional reduction peaks at higher voltages (>1 V vs Li$^+$/Li) were not observed (Fig. 7a). Increasing the PFO-EC concentration to 2 wt % yielded similar results (data not shown). The PFO-EC cells showed a larger peak at ~0.75 V vs Li$^+$/Li and a smaller peak at ~0.65 V vs Li$^+$/Li, compared to the Gen2 cells, which suggests that the additive modifies electrolyte reduction behavior. This may be due in part to the sacrificial reduction of PFO-EC on the graphite anode surface, at...
a similar reduction potential as EC [30]; however, the data does not provide unequivocal proof, as the PFO-EC carbonyl is relatively more electrophilic and may also be involved in SEI formation through some chemical reactions. In particular, it is possible that PFO-EC can preferentially react with various nucleophiles generated from EC reduction (alkoxides, carbonates, etc.), contributing to SEI formation via anionic polymerizations [31]. The resulting SEI, composed of PFO-EC reaction products, could be considered as a "functionalized" passivation film with low solvent permeability, which may improve the SEI layer stability and cell capacity retention. Moreover, this SEI does not affect the overpotential for lithium ion reduction and intercalation compared to the SEI formed in the additive-free electrolyte (Fig. 7b).

3.3. XPS spectra from fresh and harvested positive electrodes

XPS spectra from the pristine positive electrode, and from positive electrodes harvested from formed and aged full cells with and without 0.5 wt% PFO-EC, are shown in Fig. 8. The harvested electrodes were lightly rinsed with anhydrous DMC to remove residual electrolyte. Element concentrations (at.%) calculated from the data are shown in Table 2.

![Image](image.png)

Table 2: Element concentrations (at.%) calculated from XPS spectra of the fresh positive electrode and from positive electrode samples harvested from cells that were formed and aged in the Gen2 and PFO-EC electrolytes.

<table>
<thead>
<tr>
<th></th>
<th>C1s</th>
<th>P 1s</th>
<th>O 1s</th>
<th>Li 1s</th>
<th>Mn 2p</th>
<th>P 2p</th>
</tr>
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<tbody>
<tr>
<td>Fresh</td>
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<td>26.5</td>
<td>9.7</td>
<td>3.3</td>
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<td>0</td>
</tr>
<tr>
<td>Formed_Gen2</td>
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<td>22.7</td>
<td>11.6</td>
<td>9.3</td>
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<td>Aged_Gen2</td>
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<td>15.7</td>
<td>3.8</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
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<td>24.8</td>
<td>10.4</td>
<td>14.6</td>
<td>0.94</td>
<td>1.4</td>
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<tr>
<td>Aged_PFO-EC</td>
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<td>20.8</td>
<td>17.9</td>
<td>1.7</td>
<td>0.98</td>
<td>2.5</td>
</tr>
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</table>

Fig. 9. Raman spectra from graphite electrodes, before and after exposure to Gen2 electrolyte or Gen2 + 0.5 wt% PFO-EC (a and b, respectively). Electrodes were harvested from cells cycled between 2.2 and 4.6 V, either after formation cycling ("formed") or after 200 cycles ("aged”). Band intensities are normalized to the G-band.

3.4. Raman spectra from fresh and harvested negative electrodes

The graphite anodes were examined by Raman spectroscopy, a standard tool for characterizing carbonaceous materials [32,33]. Fig. 9 shows representative Raman data from pristine and harvested negative electrodes; in all spectra, three peaks appear between 1000 and 2000 cm⁻¹, assignable as the D, G, and D' bands (~1350, ~1580, and ~1620 cm⁻¹ respectively). The G band is a commonly accepted signature of graphitic carbon, whereas the D and D' bands are associated with defects and disorder within the films.
graphite; the ratio of the D and G band areas ($I_D/I_G$) correlates with increased carbon disorder.

Fig. 9a shows the Raman spectra for graphite electrodes harvested from cells cycled in Gen2 electrolyte. The $I_D/I_G$ for the pristine graphite electrode is 0.56, which is higher than that expected for pure graphite ($I_D/I_G = 0$) due to the presence of granular carbons ($I_D/I_G = 2.47$). The D and G peak shapes change noticeably for anode samples after formation cycling ($I_D/I_G = 0.92$) and even more after another 200 cycles ($I_D/I_G = 1.35$), with a substantial increase in the size of the D peak and a broadening of the G peak. These data suggest structural disordering at the graphite surface, which exposes new graphitic edges and fragments of graphite planes that catalyze reductive decomposition of the electrolyte. Continued structural disordering upon prolonged cycling contributes toward increased electrolyte reduction and SEI reformation, leading to gradual transfer of lithium from the cathode to the anode SEI and eventually degrading cell capacity. Fig. 9b shows Raman spectra for the fresh graphite electrode and for harvested electrodes from cells cycled in the PFO-EC electrolyte; the $I_D/I_G$ is 0.73 after formation cycling and 0.84 after 200 cycles. These data suggest that the PFO-EC additive reduces disordering of the graphite surface, both after formation cycling and after extended cycling, which results in less Li$^+$ trapping and improved cell capacity retention.

4. Conclusions

A new family of polyfluoroalkyl-substituted ECs is examined as electrolyte additives in full cells using Li$_{1-x}$Ni$_x$O$_{2}$/Mn$_{0.5}$Co$_{0.5}$O$_2$-based cathodes and graphite anodes. Addition of 0.5 wt% 4-(perfluoroalkyl)-1,3-dioxolan-2-one (PFO-EC) to a standardized electrolyte solution, Gen 2 (1.2 M LiPF$_6$ in EC:EMC), is found to improve capacity retention and reduce impedance rise in full cells cycled between 2.2 and 4.6 V. The LSV and XPS data suggest that PFO-EC is sacrificially oxidized on the positive electrode; the dQ/dV plots from the first lithiation of graphite/Li cells also suggest that PFO-EC is involved in SEI formation.

Improvements in cell performance from the PFO-EC additive can be attributed to synergistic effects of the performance on both electrodes. The sacrificial oxidation of PFO-EC at the cathode forms surface films that reduce cell impedance rise; PFO-EC also reacts at the anode to generate a more stable SEI. The two mechanisms are synergistic in their actions: the cathode protection not only reduces electrolyte oxidation and slows down cell impedance rise, but also reduces the dissolution of transition metal from the oxide, and ultimately helps to improve SEI stability at the negative electrode. At the anode, PFO-EC stabilization of the SEI lessens electrolyte reduction and lithium trapping, which helps to maintain electrolyte integrity and reduce cell impedance rise. Further mechanistic studies on additive oxidation–reduction reactions are currently underway, and will be discussed in due course.

The data presented here validates our hypothesis of using polyfluoroalkyl-ECs as novel functional electrolyte additives, and opens up possibilities for developing other PFA-substituted additives that may provide further performance improvements. These PFA-substituted compounds may also be useful additives in other lithium-ion cells, including those based on the 5 V spinel-based positive electrodes.

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Appendix A. Supplementary data

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.jpowsour.2013.07.070.

References